PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:	)	Confirmation No. **2093**
EVANS et al.	)	
Application No.: **10/872,784**	)	Group Art Unit: **1617**
Filed: **June 22, 2004**	)	Examiner: **Hui, San-Ming R**
FOR: **FORMULATION**	)	

DECLARATION UNDER 35 U.S.C. § 1.132
OF PAUL RICHARD GELLERT

PAUL RICHARD GELLERT of AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK declares:

1. I graduated from the University of Oxford in Chemistry in 1984. I undertook postgraduate research with Professor Brian Howard in the Physical Chemistry Laboratory at the University of Oxford leading to the award of a D.Phil in 1988. From February 1988 until the present I have been employed by AstraZeneca, (formerly Zeneca and ICI) initially as a Senior Research Scientist and subsequently as a Team Leader/Manager, Principal Scientist and, since 2004, a Senior Principal Scientist.

2. I have worked in the formulation and drug delivery area throughout my career with AstraZeneca, where my research and development work has covered a range of formulation types including sustained released injections, including fulvestrant.

3. During the course of my study of the subject application (hereinafter "the Evans Application") and the underlying data, I have become aware of several transcription or other errors between certain disclosures of the subject application and the underlying laboratory notebook data. One purpose of this Declaration is to point out the existence

and nature of these errors and to report further testing that has been carried out under my guidance to obtain additional data (paragraphs 4-10 below and Attachments A-D). A further purpose of this Declaration is to set out and document the manner in which an experienced formulator would likely have approached the task of developing a sustained release injectable formulation suitable for human use for a steroidal compound such as fulvestrant in about early 2000, which I understand is when the priority applications supporting the Evans Application were filed (paragraphs 11 - 25 below and Attachment E). Citations to literature and patent references in this Declaration will be in the format Lead Author (Date), and the full citations are given in the Table of References at the end of this Declaration. A copy of each cited reference (or cited portions of the longer references) is included in Attachment F under the Tab number noted in the Table of References.

4. In Table 2 of the Evans Application, the solubility of fulvestrant in castor oil appears to have been transcribed incorrectly from the original source, the laboratory notebook. The value in the latter is 24.5 mg/ml and not 20 mg/ml. In other experiments to determine the solubility of fulvestrant in castor oil and also in benzyl benzoate, some variability was observed.

5. In Table 3 of the Evans Application, the given solubility values were generated at 4°C and not at 25°C as is stated in the title of Table 3. For fulvestrant formulations, it is preferable that the fulvestrant remains completely in solution at both 4°C and 25°C. The 4°C temperature corresponds to the storage temperature (2°C to 8°C in the FDA approved label for Faslodex), and the 25°C temperature corresponds to the administration temperature (ambient temperature). In addition, the specified solubility values on this Table 3 are mean values calculated from analysis of replicate samples from one or more trials. The individual values are shown in handwriting in the amended version of Table 3 in Attachment A. In addition, it appears that the mean values for the last three compositions have been incorrectly calculated. The corrected mean values, together with the correction of the temperature from "25°C" to read "4°C", are also shown in handwriting in the amended version of Table 3 in Attachment A.

6. I have evaluated the transcription and other errors against the original application disclosures and conclude that these do not change the ultimate conclusions made from the data as originally reported. The addition of 15% w/v benzyl benzoate to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20% and 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

7. An additional set of experiments has been conducted at 25°C under my guidance to obtain consistent data with reduced variability from a single set of rigorously controlled solubility experiments and to demonstrate that the unexpected increase of solubility of fulvestrant by adding benzyl benzoate into compositions containing ethanol, benzyl alcohol and castor oil, is present across the broader range of composition encompassed by the claims being presented with this Declaration. The solubility of fulvestrant in benzyl benzoate and in castor oil was also measured in the same set of experiments using the same batch of benzyl benzoate and the same batch of castor oil as were used to make up the compositions. The Experimental Test Procedure is described in Attachment B.

8. The results from these solubility experiments are shown in the table in Attachment C. These results show that the solubility of fulvestrant in castor oil alone (21.4 mg/ml) is significantly greater than the solubility of fulvestrant in benzyl benzoate alone (3.8 mg/ml) and demonstrate the unexpected increase in fulvestrant solubility on the addition of 10, 15 and 25% w/v benzyl benzoate, in place of an equivalent amount of castor oil, to compositions having total alcohol concentrations in castor oil of 10%, 15%, 20%, 25% and 30% w/v.

9. Thus, the results that were obtained from experiments conducted under rigorously controlled conditions and with an expanded range of compositions, as shown in Attachment C, confirm the ultimate conclusions drawn from the results shown in Table 3 of the original application disclosure, namely that the addition of 10% to 25% w/v benzyl

benzoate to compositions having total alcohol concentrations in castor oil of between 10% to 30% w/v unexpectedly provides a positive effect on fulvestrant solubility, significantly increasing the solubility of fulvestrant in the compositions despite fulvestrant having a lower solubility in benzyl benzoate than in either alcohol or castor oil.

10. During the course of my study of the Evans Application and the underlying source materials it was drawn to my attention that some of the composition data given for Delestrogen and Delalutin somehow had been shifted one column to the right. Thus, for Delestrogen, the 78% and 58% figures shown under the BzBz column should have been under the OIL column; the 20% and 40% figures shown under the BzOH column should have been under the BzBz column; and the 2% figures shown under EtOH should have been under the BzOH column. Similarly for Delalutin, the "up to 2%" shown under the EtOH column should have been under the BzOH column. This table reports that the source of this data was J.Pharm.Sci (1964) 53(8) 891, which is Riffkin (1964) elsewhere referred to in this Declaration, and I have also verified the corrected data from the entries for Delalutin and Delestrogen in PDR (1973). A copy of Table 1 from the Evans Application is reproduced as Attachment D, on which these corrections have been made in handwriting, and I have additionally more correctly noted that Delalutin is 17-hydroxy progesterone *caproate*, and that the "COMP" designation for Delalutin should be "BMS" (Bristol-Myers Squibb). Attachment D also includes a one page explanation of the corrections to this Table 1.

11. In about early 2000, a person responsible for developing a sustained release injectable formulation suitable for administration to humans for a new steroidal compound such as fulvestrant, would have had specialized training and experience in developing pharmaceutical formulations and methods for their administration. In developing such a formulation for fulvestrant, the objective would have been to formulate an intramuscular (IM) injection that would provide for the satisfactory sustained release of fulvestrant over a period of at least two weeks and preferably over a period of at least four weeks to reduce the frequency of administration, and would have a target fulvestrant content of at

least 45 mg/mL so as to provide a fulvestrant dose of at least 250 mg in a single 5-6 mL injection. From my personal experience and knowledge of the literature at about that time, I believe that such an experienced formulator would likely have approached the task of developing a formulation for fulvestrant in about the following manner.

12. Given the foregoing objective, the experienced formulator would have appreciated that the traditional administration options to explore were intramuscular (IM) injection of a sustained release aqueous or oil suspension or an oil-based solution (depot) containing at least 250 mg of fulvestrant in a volume of vehicle that is tolerable for injection, *i.e.*, no more than 5 or 6 mL.

13. Because of the extremely low solubility of fulvestrant in water, a reasonable starting point would have been to investigate intramuscular injection of an aqueous or oil suspension of fulvestrant. However, the formulator would have found that injection of an aqueous suspension of fulvestrant resulted in extensive local tissue irritation at the injection site as well as a poor release profile, such as reported in paragraph [0042] of the Evans Application. Since suspensions thus were not an acceptable option for fulvestrant, the experienced formulator would have moved on to further explore whether 250 mg of fulvestrant could be solubilised in no more than 5-6 mL of an oil-based vehicle, *i.e.*, to achieve the target fulvestrant concentration of at least 45 mg/mL.

14. In the preformulation phase, the experienced formulator would have conducted a literature review or otherwise would have become familiar with commercially marketed injectable formulations, particularly injectable sustained release formulations of steroids or other relatively insoluble compounds such as those listed in Table 1 of the Evans Application, with the objective of identifying potential oil vehicles, co-solvents and other excipients that already had been found to be tolerated and/or to have passed through regulatory review, and which might be candidates for further consideration and testing for the fulvestrant formulation. This review also would have provided guidance with respect to concentration levels of such co-solvents and other excipients that generally had been found acceptable in sustained release oil-based intramuscular injections administered to

humans. This objective is confirmed, for example, in Nema (1997) at page 166:

> Generally, a knowledge of which excipients have been deemed safe by the FDA or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their new drug product. ... Regulatory bodies may view an excipient previously approved in an injectable dosage form favorably, and will frequently require less safety data.

The purpose of this Nema paper was thus "to present the various excipients that have been included in the formulation of injectable products marketed in the USA."[1] Similar objectives were intended to be served by the compilations of commercial formulations in Strickley I (1999), Strickley II (2000) and Strickley III (2000):

> This compilation will also be useful for those interested in knowing what additives are currently used in injectable products and at what concentrations they are administered in practice. This compilation only focuses on marketed formulations and does not delve into the subject of preclinical or drug discovery formulations associated with early-stages pharmacokinetics or proof-of-concept pharmacodynamics, where the formulation scientist is not bound by regulatory constraints.

(Strickley I (1999) at 324).

Powell (1998) similarly states at page 238 with respect to its compilation of commercially used excipients:

> Thus, the formulation scientist is often faced with a dilemma -- which excipients are truly available for use (based on what has been used previously), and which are not? ... And at what concentrations, and by what route? ...
>
> Herein are listed the excipients found in most of the approved and marketed parenteral formulations, given systematically by excipient name. In this format it is easy to determine what concentrations were used, the route of administration, the main rationale for addition of that excipient, the drug that was formulated, the manufacturer, brand name, etc.

15. From the literature review, the formulator would have noted reference to a number of intramuscular injectable sustained release oil-based steroidal formulations that had been

[1] Nema (1997) does caution, however, that there is no guarantee that the new drug product will be safe as excipients are combined with other additives and/or with a new drug, creating unforeseen potentiation or synergistic toxic effects.

commercially marketed:

- Strickley I (1999), Table VII:

  Haloperidol Decanoate/Haldol decanoate (50-100 mg/mL in sesame oil, benzyl alcohol 1.2%);

  Testosterone Enanthate/Delatestryl (200 mg/mL in sesame oil, chlorobutanol 5 mg/mL);

- PDR (1973) at pages 1277-1278

  Proluton/progesterone (50 mg/mL in sesame oil, 150 mg/ml benzyl benzoate, 5 mg/ml benzyl alcohol, 1 mg/ml propylparaben);

- PDR (1973) at pages 1349-1354

  Deladumone/Testosterone Enanthate & Estradiol Valerate (90 & 4 mg/mL in sesame oil, 0.5% chlorobutanol);

  Deladumone OB/Testosterone Enanthate & Estradiol Valerate (180 & 8 mg/mL in sesame oil, 2% benzyl alcohol);

  Delalutin/hydroxyprogesterone caproate (250 mg/mL in 52% castor oil, 46% benzyl benzoate, 2% benzyl alcohol);

  Delestrogen/estradiol valerate (20 mg/mL in 78% castor oil, 20% benzyl benzoate, 2% benzyl alcohol and 40 mg/mL in 58% castor oil, 40% benzyl benzoate, 2% benzyl alcohol);

  Delatestryl/Testosterone Enanthate (200 mg/mL in sesame oil, 0.5% chlorobutanol);

  Delaluteval 2X/hydroxyprogesterone caproate & estradiol valerate (250 mg/mL & 5 mg/mL in castor oil, 45% benzyl benzoate, 1.6% benzyl alcohol);

- PDR (1973) at pages 1391-1392

  Prolixin Enanthate/FluphenazineEnanthate (25 mg/mL in sesame oil, 1.5% benzyl alcohol);

- Wang (1980):

  Depo-Testosterone/testosterone cypionate (100 mg/mL in 87.4% cottonseed oil, 0.1 mL benzyl benzoate, 9.45 mg benzyl alcohol as a preservative);

- Mackey (1995):

  Testoviron Depot/testosterone enanthate (250 mg/mL in castor oil and benzyl

benzoate);

as well as a number of other commercialized oil based long-acting IM injectable formulations reported on Table 1 of the Evans Application.

16. As a further part of the preformulation phase, the experienced formulator would have conducted a preformulation solubility screen, separately measuring the solubility of fulvestrant in a range of pure solvents, including the potential oil and co-solvent candidates that had been identified in the above literature review as being suitable for inclusion in intramuscular injection formulations. See, for example, Gupta (1999), Chapter 17 at page 402, under the heading "Formulation Development":

> The activities necessary to develop a parenteral product can be placed into the following three broad areas: preformulation, formulation, and scale-up. While there are alternative development perspectives, all development ultimately needs to accomplish the same activities. Preformulation includes the characteristics of the bulk drug plus initial screening for excipient compatibility with the drug.

"Preformulation studies" are said to "provide fundamental data and experience necessary to develop formulations for a specific compound" including, as item 8.1 in the outline of areas of specific interest, a determination of "solubility" in "selected solvents" (at 403). "Significant formulation activities begin with initial preformulation data and knowledge of the specific route of administration" (at 405), which "formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous or co-solvent system) ..." (at 404). It is further noted that "injection volume is one of the most important considerations in the formulation development of a commercial product" (at 405). When carrying out such a preformulation solubility screen with fulvestrant, the formulator would have found that fulvestrant had extremely low solubility in water, low solubility in most oils (but highest in castor oil), low solubility in benzyl benzoate, and the highest solubility in ethanol and benzyl alcohol, such as reported in Table 2 of the Evans Application.

17. With the information on prior commercialized formulations and the fulvestrant solubility data from the preformulation screen (such as reported in Table 2 of the Evans

Application), the experienced formulator would have selected castor oil as the oil vehicle because of the higher solubility of fulvestrant in castor oil relative to the other oils tested. Nevertheless, he would have appreciated that the target fulvestrant concentration of at least 45 mg/mL could not be achieved with castor oil alone, and that a co-solvent would be required.

18. A number of the commercialized formulations that would have been identified in the literature review (including the castor oil-based formulations) have a substantial benzyl benzoate component, which may be present as a co-solvent. See, for example, Delalutin noted in paragraph 15 above, which is reported in PDR (1973) and noted in Table I of the Evans Application, and is one of the formulations discussed in Riffkin (1964), "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones" (see Riffkin n. 6). Delalutin is 250 mg/mL 17-hydroxyprogesterone caproate dissolved in 52% castor oil, 46% benzyl benzoate and 2% benzyl alcohol. However, Riffkin Table II reports that the solubility of 17-hydoxyprogesterone caproate in castor oil alone is only 55.6 mg/mL, but the solutility of 17-hydroxyprogesterone caproate in benzyl benzoate is substantially higher, being at least 250 mg/mL (see example 4 of Huber (US '520) and Attachment E discussed below). Even if not needed as a cosolvent, Riffkin (1964) notes that "the addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favorable viscosity, making it easier to inject" (paragraph bridging pages 893-894).

19. However, the skilled formulator would have appreciated from the fulvestrant solubility data generated in the preformulation screen that fulvestrant had very different solubility characteristics relative to the steroids of previous commercial formulations. Attachment E is a compilation showing the chemical structures and relative solubilities in castor oil and sesame oil of the compounds named in Riffkin (1964) Table II compared to the structure and the solubility of fulvestrant in these oils. It can be seen that the solubility of fulvestrant in castor oil and in sesame oil (20 mg/mL and 0.58 mg/mL, respectively, from Table 2 of the Evans Application) is appreciably lower than the solubility of the other steroids in these oils (taken from Table II of Riffkin (1964)). The second page of Attachment E tabulates the concentration in benzyl benzoate of five named steroids, taken

from Examples 1-5 of Huber (US '520), ranging from 200 to 400 mg/ml.[2] By comparison, the solubility of fulvestrant in benzyl benzoate is reported in Table 2 of the Evans Application as being only 6.15 mg/mL, and only 3.8 mg/mL as determined in the recently conducted tests reported in Attachment C.

20. The experienced formulator thus would have expected that benzyl benzoate would *not* act as a co-solvent for fulvestrant in castor oil because the solubility of fulvestrant in benzyl benzoate was significantly lower than its solubility in castor oil. The addition of benzyl benzoate to castor oil, for whatever reason, would have been expected to *decrease, rather than increase*, the solubility of fulvestrant in the resulting castor oil/benzyl benzoate mixture. This is confirmed in Table 4 of the Evans Application, which reports a fulvestrant solubility of only 12.6 mg/mL in the castor oil vehicle containing only 15% benzyl benzoate, compared to the 20 mg/mL solubility of fulvestrant in castor oil alone as reported in Table 2.[3]

21. Based on the solubility data determined in the preformulation screen (such as reported in Table 2 of the Evans Application), ethanol and/or benzyl alcohol would have been seen as the best co-solvent candidates for raising the fulvestrant solubility to the 45 mg/mL target in the castor oil vehicle, and would also function to lower the viscosity of the resulting formulation and make it easier to inject. Consistent with this solubility data, Dukes (US '814) added 40% w/v benzyl *alcohol* in order to dissolve 50 mg/mL fulvestrant in the castor oil-based formulation used in the experimental rat studies of his Example 3. It thus would have been apparent that 40% w/v benzyl alcohol could function as a co-solvent in castor oil to achieve the target fulvestrant concentration. Nevertheless, the skilled formulator would have been concerned with using such a high alcohol content in intramuscular injectable formulations for administration to a human.

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[2] Data taken from the Examples of Huber (US '520); these are concentrations used in the examples and not necessarily the actual maximum solubility of each steroid in benzyl benzoate, which may be higher. Huber was a co-author on Riffkin (1964).

[3] It should be noted that in the further tests that were recently conducted under my guidance (paragraphs 7-9 above and Attachments B and C hereto), the solubility of fulvestrant in castor oil alone was again tested and found to be 21.4 mg/mL, and the solubility of fulvestrant in benzyl benzoate alone was again tested and found to be only 3.8 mg/mL, which further confirms that benzyl benzoate would not be expected to act as a cosolvent for fulvestrant in castor oil.

22. First of all, the experienced formulator would want to minimize the amount of co-solvents and excipients in any injectable formulation. For example, as stated in Gupta (1999), Chapter 17, "Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parental Products" at page 414:

> Cosolvents are commonly used to enhance drug solubility and stability. Cosolvents may include ethanol, propylene glycol, polyethylene glycols, and glycerine. These components have intrinsic effects on biologic tissue and can alter the properties of other excipients, thus influencing the tissue damage or pain caused by a product. There is a dearth of literature on the pain caused by cosolvents, but there is also a growing body of knowledge on the tissue damage that they can cause. It is not certain that tissue damage is always directly correlated with the injection pain, but minimization of both pain on injection and potential for tissue damage should be included in the product development plan.

See also Gupta (1999), Chapter 11, titled Cosolvent Use in Injectable Formulations, page 217:

> Ideally, it is best to select and use solvents that would maximize the solubility of the compound. Maximizing the solubility of a compound in a particular cosolvent system would result in lower total levels of the non-aqueous solvent(s) being administered to the patient, thereby lowering the chance for potential side effects.

This objective would have applied to aqueous and oil-based systems alike, in that the precedent of commercialized formulations identified in the literature review would have confirmed that fixed oils, such as castor oil, have long been commercially used and accepted as the major component of oil-based sustained release intramuscular injectable steroidal formulations. On the other hand, co-solvents such as ethanol or benzyl alcohol have generally been used only in far lesser concentrations, as discussed in the following paragraph.

23. Thus, use of such a high content of either benzyl alcohol or ethanol would have been contrary to precedent as shown from the review of commercialized oil-based intramuscular injectable sustained release formulations. The literature review as of early 2000 would have shown that any benzyl alcohol in such formulations was almost always

present as a preservative in a concentration of about 2% or less, occasionally at a concentration of up to 5%, but only rarely at higher concentrations. With respect to benzyl alcohol see, for example:

- Gupta (1999), Chapter 11 at page 229 stating that benzyl alcohol "is typically used in concentrations of up to 2 percent as a preservative and up to 5 present as a solvent," and then discussing reported toxicities.
- Nema (1997), Table V at page 168, reporting that benzyl alcohol was present as an antimicrobial preservative in 74 injectable formulations (not limited to oil-based IM formulations) at concentrations of from 0.75-5% (note that benzyl alcohol is not included at all in Nema Table I, "Solvents and Co-solvents";
- Powell (1998), the benzyl alcohol listing at pages 244-246, particularly those indicated as being used in IM formulations;
- Strickley I (1999) at page 329 notes the inclusion of 2% benzyl alcohol in an IM lorazapam formulation in a propylene glycol vehicle, but does not include benzyl alcohol at all in Table VI listing "Cosolvents Used in Parenteral Formulations;"
- Lopatin (1972) noting in Table 3 at page 727 opposite Benzyl alcohol, "Toxic. Used in concentration of not over 3%. Has irritant action in concentration of 5%;"
- Cornelius (US '863), col. 1, lines 30-35 stating, "It is known that the solubility of steroids in vegetable or animal oils can be increased by the addition of excipients such as benzyl alcohol and benzyl benzoate. An objection to the use of such excipients, and specifically benzyl alcohol in somewhat higher concentrations, is that these agents may irritate the tissues."

The literature review as of early 2000 also would have shown that, with few exceptions, ethanol was not included in such formulations in excess of about 10%. See, for example:

- Gupta (1999), Chapter 11 at page 225 noting that ethanol has been used at levels up to 50 percent, but these levels typically are associated with pain on injection;
- Strickley I (1999), Table VI, "List of Cosolvents Used in Parenteral Formulations" more specifically lists the ethanol content in IM formulations for specifically identified drugs, which concentrations range only from 2.5 to 10%; an IM/IV lorazapam formulation in a propylene glycol vehicle is noted at page 329 as having 18% alcohol, but is not included with the IM formulations in Table VI;

- Nema (1997), Table I, "Solvents and Co-solvents" at page 167, lists ethanol as being in 24 formulations with a concentration range of 0.6-80% (for Prograf); note that this is misleading, however, since Prograf is a *concentrate* for intravenous infusion only, and is to be diluted 250 to 1000 times before administration;
- Powell (1998), lists "alcohol" at page 242 and "ethyl alcohol" at page 255, wherein the ethanol concentration for IM formulations ranges from 0.61-10%.

24. Thus, even though Dukes (US '814) had demonstrated that the target 45 mg/mL fulvestrant concentration could be achieved by adding 40% benzyl alcohol to the castor oil vehicle, the precedent of commercialized IM oil-based systems would have motivated the experienced formulator to substantially reduce the benzyl alcohol content of the formulation intended for human use, and this commercial precedent would have made him very reluctant to replace benzyl alcohol with the substantial amount of ethanol that would be needed to maintain the target fulvestrant concentration. Benzyl benzoate clearly would not be considered to solve this dilemma, but rather would be expected to have a negative effect on fulvestrant solubility since fulvestrant was even less soluble in benzyl benzoate than in castor oil, that is, one would have expected that adding benzyl benzoate would require still *more* alcohol to maintain the target fulvestrant concentration.[4]

25. Under these circumstances, the discovery by Evans *et al.*, that the addition of benzyl benzoate to the castor oil/alcohol mixture actually increases the solubility of fulvestrant such that more fulvestrant could be dissolved in a given volume of formulation, was unexpected and truly surprising. This positive benzyl benzoate effect on fulvestrant solubility in the resulting formulation is shown in Table 3 of the specification (and is not changed by the above-noted corrections), and is confirmed and demonstrated over a broader range of formulation composition by the additional set of experiments conducted under my guidance and discussed in paragraphs 7-9 above, the results of which are reported in Attachments C.

[4] It should be noted that even apart from this solubility issue, there would have been no motivation to add benzyl benzoate for viscosity reduction since the significant quantity of alcohol would serve the dual function of acting as a co-solvent as well as reducing the injection viscosity and making it easier to inject, whereas the benzyl benzoate would be expected to have a negative effect on the fulvestrant solubility.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punished by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

Signature: P. R. Mukt.

Date: 8th August 2008.

TABLE OF REFERENCES

Tab	Author/Inventor	Reference Citation/Patent
1	Cornelius (US '863)	US Patent 4,212,863
2	Dukes (EP '014)	EP 0 346 014 A1 (corresponds to US Patent 5,183,814)
3	Dukes (US '814)	US Patent 5,183,814 (corresponds to EP 0 346 013 A1)
4	Gupta (1999)	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
5	Huber (US '520)	US Patent 3,164,520
6	Lopatin (1972)	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
7	Mackey (1995)	M.A. Mackey, A.J. Conway and D.J. Handelsman. Tolerability of intramuscular injections of testosterone ester in oil vehicle. *Hum. Reprod.* **10**: 862-865 (1995)
8	Nema (1997)	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
9	PDR (1973)	*Physicians' Desk Reference (27th edition).* 1277-1278, 1350-1354, 1391-1392 Medical Economics Company, Oradell, NJ (1973)
10	Powell (1998)	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 (1998)
11	Riffkin (1964)	C. Riffkin, R. Huber and C.H. Keysser. Castor oil as a vehicle for parenteral adminstation of steroid hormones. *J.Pharm.Sci.* **53**: 891-5 (1964)
12	Strickley I (1999)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) -Part I. *PDA J. Pharm. Sci. Technol.* **53**:324–349 (1999)
13	Strickley II (2000)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part II *PDA J. Pharm. Sci. Technol.* **54**:69–96 (2000)
14	Strickley III (2000)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
15	Wang (1980)	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

ATTACHMENT A

TABLE 3

EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT ~~25°C~~ 4°C.

		% w/v							
	Ethanol (96%)	5	5	10	10	10	10	15	15
	Benzyl Alcohol	5	5	5	5	10	10	15	15
	Benzyl Benzoate		15		15		15		15
	Castor Oil	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100
Mean	Fulvestrant Solubility [mgml^{-1}]	27	36	46	54	45	~~68~~ 64	~~78~~ 77	~~102~~ 103
	Individual values [mgml^{-1}]	27.8	35.5	54.0	64.1	48.4	62.9	65.8	80.6
		25.8	36.1	38.6	47.3	41.7	60.8	76.9	101.9
					53.0		63.2	90.0	121.6
					50.3		72.9	73.4	107.4

ATTACHMENT B:

Experimental Test Procedure for measuring the solubility of fulvestrant in different solvent vehicles at 25°C

1. Solvent vehicles for the solubility experiments were prepared by weighing the required amount of benzyl benzoate, benzyl alcohol and ethanol into a 20 ml volumetric flask and then diluting to volume with castor oil.
2. For each solvent vehicle in which the solubility of fulvestrant was to be determined, 1.0-1.5g of fulvestrant was weighed into each of 3 separate vials (2 dram size) and 5mls of the solvent vehicle was added to each vial, except for the pure castor oil vehicle, where 80mg of fulvestrant were weighed into each of the 3 separate vials and 2mls of the castor oil added to each vial. The reduced amount of fulvestrant and lower volume of solvent vehicle was needed to maintain stirring and achieve adequate mixing with the pure castor oil vehicle due to the combination of its higher viscosity and lower fulvestrant solubility/higher undissolved fulvestrant levels compared to the other solvent vehicles.
3. A magnetic stirrer bar was placed into each vial and the vials were capped and then placed on a magnetic stirrer block maintained at 25 ± 0.5°C.
4. After 5 days of stirring at 25 ± 0.5°C, an aliquot of each fulvestrant/solvent vehicle mixture was removed from each vial and placed into an Eppendorf tube which was then centrifuged at 12000 rpm for 5 minutes at ambient temperature.
5. For all but the fulvestrant/castor oil mixture, 1 ml of the supernatant was then removed from the Eppendorf tube and pipetted into a 10ml or 20ml volumetric flask and then diluted to volume with methanol and mixed to give a sample for analysis. The choice of whether to use a 10ml or 20ml volumetric flask for a particular sample was dependent on the likely concentration of fulvestrant in the sample and the quantifiable concentration range of the HPLC assay method used. For the fulvestrant/castor oil mixture, 100µl of the supernatant was removed from the Eppendorf tube and pipetted into a 1ml volumetric flask and then diluted to volume with methanol and mixed to give a sample for analysis.
6. Step 5 was repeated to give a duplicate sample for analysis. Thus, this gave 2 samples for each of the 3 vials, giving a total of 6 samples for analysis for each solvent vehicle tested.
7. The resultant samples were analysed for fulvestrant content by reverse phase High

Performance Liquid Chromatography (HPLC). The HPLC method that was used is described below at point 9. The fulvestrant content obtained for each sample was used to calculate a value for the concentration of fulvestrant dissolved in the corresponding solvent vehicle after stirring for 5 days at 25°C.

8. The mean solubility of fulvestrant for each different solvent vehicle tested was calculated as the arithmetic mean of the 6 individual values for the concentration of fulvestrant dissolved in the corresponding solvent vehicle.
9. HPLC Method details:

Gradient HPLC Method

Eluent A : 27% Methanol / 32% Acetonitrile / 41% Water

Eluent B : 41% Methanol / 49% Acetonitrile / 10% Water

Column : 15cm 3.5um Symmetry C8 4.6mm i.d.

Detection wavelength : 225 nm

Flow rate : 2 mL min-1

Temperature : 40°C

Injection volume : 10 µL

Gradient programme :

Time (min)	Eluent A (%)	Eluent B (%)
0	100	0
25	100	0
55	0	100
65	0	100
66	100	0
70	100	0

Retention time of fulvestrant: 21minutes approximately

ATTACHMENT C: EFFECT OF BENZYL BENZOATE ON FULVESTRANT SOLUBILITY IN CASTOR OIL AT 25°C

	% w/v																					
Ethanol (96%)	0	0	5	5	5	5	10	10	10	10	10	10	10	10	12.5	12.5	12.5	12.5	15	15	15	15
Benzyl Alcohol	0	0	5	5	5	5	5	5	5	5	10	10	10	10	12.5	12.5	12.5	12.5	15	15	15	15
Benzyl Benzoate	0	100		10	15	25		10	15	25		10	15	25		10	15	25		10	15	25
Castor oil	100	0	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100	to 100
Mean Fulvestrant solubility [mgml^{-1}]	**21.4**	**3.8**	**27.6**	**29.2**	**43.3**	**47.5**	**64.6**	**71.6**	**84.2**	**94.0**	**68.1**	**87.2**	**93.4**	**118.9**	**96.6**	**107.7**	**116.1**	**139.6**	**121.3**	**144.6**	**143.8**	**166.2**
Individual values [mgml^{-1}]	23.2	3.9	29.5	31.2	43.9	48.3	64.2	76.2	83.8	95.2	68.6	90.0	92.5	122.1	104.1	106.1	115.5	138.9	110.0	129.8	148.2	163.3
	17.8	4.0	28.3	26.3	45.1	50.7	66.8	72.1	81.9	97.8	68.9	84.9	92.1	120.3	74.0	86.6	117.9	141.0	120.0	133.5	147.1	164.8
	21.5	3.9	24.5	31.5	44.3	45.4	61.2	66.2	93.2	95.6	71.6	87.6	93.9	120.4	102.0	112.6	118.8	139.4	124.4	150.1	144.4	168.5
	21.8	3.8	26.6	29.3	45.4	45.2	66.0	65.7	84.6	96.1	67.6	88.1	93.0	118.3	98.6	117.9	116.1	142.1	125.6	151.7	144.4	169.7
	22.2	4.0	27.0	29.1	36.9	47.6	65.8	75.4	82.4	88.2	67.0	90.7	93.8	116.8	102.1	107.9	117.0	138.7	123.3	151.2	139.5	165.5
	22.0	3.2	29.6	27.8	44.3	47.6	63.6	73.9	79.1	91.0	64.8	82.1	95.3	115.7	98.4	115.1	111.5	137.9	124.6	151.1	139.1	165.5

ATTACHMENT D

TABLE I

OIL BASED LONG-ACTING INTRAMUSCULAR INJECTIONS

PRODUCT NAME	STEROID	DOSE	TYPE	COMP'.	SOURCE	OIL	Soln	BzOH	EtOH	DOSE	DOSING
SUSTANON 100	Testosterone propionate	30 mg	Androgen	Organon	AHPI Data Sheet Comp. 1999	Arachis		0.1 ml		1 ml	3 weeks
	Testosterone phenyl-propionate	60 mg									
	Testosterone isocaproate	40 mg									
	Testosterone decanoate	100 mg									
PROLUTON DEPOT	Hydroxy progesterone hexanoate	250 mg/ml	Progestogen	Schering BC	AHPI Data Sheet Comp. 1999	Castor	up to 46%			2 or 2 ml	1 week
TOCOGESTAN	Hydroxy progesterone enanthate	300 mg	Progestogen	Theramex	Dict. Vidal 1999	Ethyl oleate	40%			2 ml	<1 week
	Progesterone or Tocopherol	50 mg 250 mg									
TROPICDIOLONE	Estroprogestate	2.5 mg	Mixed	Theramex	Dict. Vidal 1997	Olive	45%			1 ml	15 to 30 days
	Nandrolone undecanoate	50 mg									
	Hydroxy-progesterone heptanoate	80 mg									
NORISTERAT	Norethisterone enanthate	200 mg	Contra-ceptive	Schering BC	AHPI Data Sheet Comp. 1999	Castor	YES			1 ml	8 weeks
BENZO-GYNOESTRYL	Estradiol benzhydro-benzoate	5 mg	Estradiol	Roussel	Dict. Vidal 1999	Arachis				1 ml	1 week
PROGESTERONE-RETARD	Hydroxy progesterone caproate	250 mg/ml	Progestogen	Fournier	Dict. Vidal 1999	Castor	YES			1 or 2 ml	1 week
GRAVIBINAN	Estradiol 17-β-valerate	5 mg/ml	Mixed	Schering	Dict. Vidal	Castor	YES			1 or	1-2
	Hydroxy-progesterone caproate	250 mg/ml		BC	1995					2 ml	weeks
PARABOLAN	Trenbolone	76 mg	Androgen	Negma	Dict. Vidal 1997	Arachis		75 mg	45 mg	2.5 ml	2 weeks
DELESTROGEN	Estradiol valerate	20 mg/ml 40 mg/ml	Estradiol	BMS	J Pharm. Sci (1964) 53(8) 891	Castor	70% 58% 40% 5%	20% 40% 10% 2%	5% 2%		
OHLALUTIN	17-Hydroxy progesterone caproate	250 mg/ml	Progestogen	~~Duphar~~ BMS	J Pharm. Sci.(1964) 53(8) 891	Castor	YES	YES up to 2%	5% 2%		

Bzlle = benzylbenzoate
BzOH = benzylalcohol
EtOH = ethanol. Dict.
Vidal = Dictionnaire Vidal % are w/v and
*approximate as measured directly from a single sample

Corrections to Table 1

In Table 1, the given values for the benzyl benzoate, benzyl alcohol and ethanol levels for the Delestrogen and Delalutin products have been incorrectly entered into the wrong columns. The entries are shown in their correct form in the attached corrected version of Table 1. The error is apparent from a review of the reference J.Pharm Sci (1964) 53 (8) 891 (Riffkin) which is stated in Table 1 as being the Source of the information for the Delestrogen and Delalutin products:

- In the Summary on page 895 of Riffkin, Delestrogen and Delalutin are identified as castor oil based commercially available products containing estradiol valerate at 20 & 40 mg/ml and 17-hydroxy-progesterone caproate at 250 mg/ml respectively.
- Furthermore, details of particular vehicle compositions for estradiol valerate and 17-hydroxy-progesterone caproate are given in Tables V and VI
    - In Table VI, the only 20 mg/ml formulation of estradiol valerate, also referred to as commercially available, has the composition castor oil 78%, benzyl benzoate 20% and benzyl alcohol 2%.
    - In Table VI, the only 40 mg/ml castor oil based formulation of estradiol valerate, has the composition castor oil 58%, benzyl benzoate 40% and benzyl alcohol 2%.
    - In Table V, there are three 250/mg/ml castor oil based formulations of 17-hydroxy-progesterone caproate that all contain benzyl benzoate. Two of these formulations also contain 2% benzyl alcohol and the other formulation does not contain benzyl alcohol ie they all contain up to 2% benzyl alcohol.

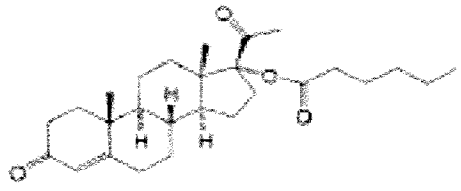
- None of the vehicle compositions disclosed in Tables V and VI in Riffkin contain ethanol. Therefore the entries in the Ethanol column of Table 1 for the Delestrogen and Delalutin products must have been incorrectly entered in the wrong column and should have been entered into the Benzyl Alcohol column.
- It is also apparent from Table VI that the 78% and 58% entries in the Benzyl Benzoate column of Table 1 for the Delestrogen products should have been entered into the Oil column and the 20% and 40% entries in the Benzyl Alcohol column should have been entered into the Benzyl Benzoate column
- The exact compositions for the Delestrogen and Delalutin products are confirmed in the Physicians Desk Reference (Edition 27, 1973) on page 1352.

In addition, the name of the steroid given in Table 1 for the Delalutin product should have been 17-hydroxy-progesterone caproate and not just 17-hydroxy-progesterone. Also the entry under the Company column for the same product should read BMS rather than DMS.

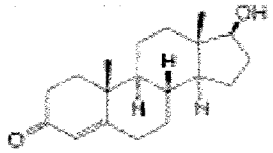
ATTACHMENT E

Structure of compounds disclosed in Riffkin et al.

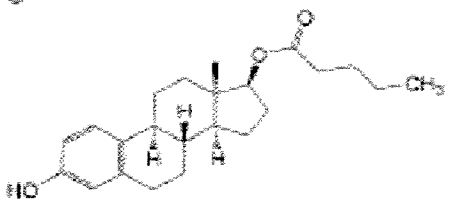
17-Hydroxyprogesterone caproate:



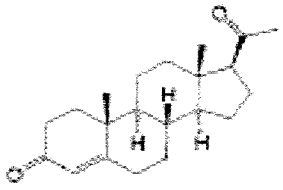
Testosterone:



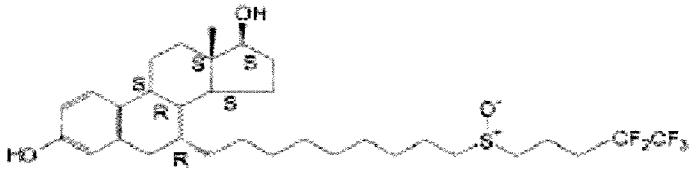
Estradiol valerate:



Progesterone:



On the other hand, fulvestrant has the following structure:



From Riffkin et al. Table II:

Steroid	Solubility [mg/ml] at 25°C	
	Castor oil	Sesame oil
Fulvestrant	20	0.58
17-Hydroxyprogesterone caproate	55.5	23.4
Testosterone	38.6	5.4
Estradiol valerate	60.6	16.1
Progesterone	52.0	22.9

Tabulation of data from Examples of Huber, 3,164,520:

Example	Steroid	Steroid concentration in benzyl benzoate (mg/ml)
1	16,17-dihydroxyprogesterone	200
2	testosterone palmitate	200
3	progesterone	250
4	Progesterone + 17-hydroxyprogesterone caproate	250 + 250
5	Testosterone enanthate	400

ATTACHMENT F

TABLE OF REFERENCES

Tab	Author/Inventor	Reference Citation/Patent
1	Cornelius (US '863)	US Patent 4,212,863
2	Dukes (EP '014)	EP 0 346 014 A1 (corresponds to US Patent 5,183,814)
3	Dukes (US '814)	US Patent 5,183,814 (corresponds to EP 0 346 013 A1)
4	Gupta (1999)	P.K. Gupta and G.A. Brazeau (eds). *Injectable Drug Development:Techniques to Reduce Pain and Irritation.* Chapters 11 & 17 Interpharm Press, Denver, Colorado (1999)
5	Huber (US '520)	US Patent 3,164,520
6	Lopatin (1972)	P.V. Lopatin, V. P. Safonov, T. P. Litvinova and L. M. Yakimenko. Use of nonaqueous solvents to prepare injection solutions. *Pharm. Chem. J.* ***6***:724-733 (1972)
7	Mackey (1995)	M.A. Mackey, A.J. Conway and D.J. Handelsman. Tolerability of intramuscular injections of testosterone ester in oil vehicle. *Hum. Reprod.***10**: 862-865 (1995)
8	Nema (1997)	S. Nema, R.J. Washkuhn, and R.J. Brendel. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* **51**:166-71 (1997)
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10	Powell (1998)	M. F. Powell, T. Nguyen, and L. Baloian. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* **52**:238–311 [pages 238-255 provided] (1998)
11	Riffkin (1964)	C. Riffkin, R. Huber and C.H. Keysser. Castor oil as a vehicle for parenteral adminstation of steroid hormones. *J.Pharm.Sci.* **53**: 891-5 (1964)
12	Strickley I (1999)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) -Part I. *PDA J. Pharm. Sci. Technol.* **53**:324–349 (1999)
13	Strickley II (2000)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part II *PDA J. Pharm. Sci. Technol.* **54**:69–96 (2000)
14	Strickley III (2000)	R. G. Strickley. Parenteral formulations of small molecule therapeutics marketed in the United States (1999) - Part III. *PDA J. Pharm. Sci. Technol.* **54**:152–169 (2000)
15	Wang (1980)	Y.C. J. Wang and R. R. Kowal. Review of excipients and pH's for parenteral products used in the United States. *J. Parenteral Drug Assoc.* **34**:452–462 (1980).

ATTACHMENT F

ATTACHMENT F - COMPILATION

TAB 1

United States Patent [19]

Cornelius

[11] **4,212,863**

[45] **Jul. 15, 1980**

[54] **HIGHLY CONCENTRATED PHARMACEUTICAL FORMULATIONS OF STEROIDS AND PROCESSES FOR THEIR PREPARATION**

[75] Inventor: **Lammert Cornelius**, Boxmeer, Netherlands

[73] Assignee: **Akzo N.V.**, Arnhem, Netherlands

[21] Appl. No.: **953,877**

[22] Filed: **Oct. 23, 1978**

[30] **Foreign Application Priority Data**

Oct. 29, 1977 [NL] Netherlands 7711916

[51] **Int. Cl.**[2] **A61K 31/56**

[52] **U.S. Cl.** **424/240**

[58] **Field of Search** 424/240, 284

[56] **References Cited**

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Chemical Abstracts, vol. 82, No. 4 (1975) Paragraph 21, 826(g).

Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Stevens, Davis, Miller & Mosher

[57] **ABSTRACT**

The invention relates to highly concentrated liquid pharmaceutical formulations of steroids of the oestrane, androstane and (19-nor-)pregnane series comprising tocol or a derivative thereof that is fluid at normal temperature, or mixtures thereof, in an amount of at least 10% by weight of the formulation, and optionally one or more of the usual fluid carriers, such as vegetable oil, benzyl benzoate and/or benzyl alcohol.

10 Claims, No Drawings

HIGHLY CONCENTRATED PHARMACEUTICAL FORMULATIONS OF STEROIDS AND PROCESSES FOR THEIR PREPARATION

The invention relates to highly concentrated pharmaceutical formulations of steroids of the oestrane, androstane and (19-nor-)pregnane series, the said formulations being fluid at normal temperature, and to processes for their preparation.

Injection preparations of steroids are known. Such preparations usually consist of solutions of the steroids in oily carriers, such as arachis oil, sesame oil, olive oil and similar carriers, to which yet other excipients may, if desired, be added, such as benzyl alcohol and benzyl benzoate. Such fluid preparations may be injected almost without damage to tissues, and absorption of the active substance by the organism takes place from the subcutaneous or intramuscular depot thus obtained. The extent and the duration of the absorption depends on various factors including the dosage and concentration of the steroid and the physical properties of the steroid, such as lipophilicity. The upper limit of the concentration is naturally governed by the solubility of the steroid in the carrier. If this solubility is not very great, achievement of the desired effect will necessitate repeating injections at shorter intervals or injecting larger volumes, and there are of course objections to both of these procedures.

It is known that the solubility of steroids in vegetable or animal oils can be increased by the addition of excipients such as benzyl alcohol and benzyl benzoate. An objection to the use of such excipients, and specifically benzyl alcohol in somewhat higher concentration, is that these agents may irritate the tissues.

Other ways of administration to give higher concentrations in the subcutaneous or intramuscular depot are the injection of crystal suspensions or the implantation of solid formulations. The preparation of stable crystal suspensions may give rise to problems, while the surgical intervention, though minor, constitutes an objection to the implantation.

When the preparation and use of a highly concentrated long-acting injection preparation of steroids is therefore desired, for example an injection preparation for the inhibition of ovulation in animals or man, one or more of the above-noted objections will be valid to a greater or lesser extent.

The administration of steroids in solution, for example a solution in oil, by the oral route is also known; see for example the Dutch Patent Application No. 7402689.(=British Pat. No. 1,500,374).

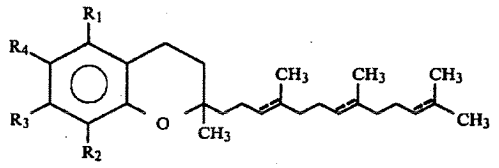
The administration of fluid pharmaceutical preparations by the oral route may be realized in various ways. The prescribed quantity, for example a number of drops or ml, may be taken per spoon, on a sugar lump or together with food. The solution may also be taken "sealed" in a soft gelatine capsule or in microcapsules.

With the oral administration of certain steroids in solution, for example testosterone and esters thereof, the problem may also arise that the solubility (and therefore the amount of active agent per dosage unit) in the known solvents is relatively low, so that either more or larger dosage units must be administered on each occasion or the administration of the preparation must be repeated at shorter intervals. There are objections to both procedures. In such cases there is an obvious need for solutions with greater concentrations.

It has now surprisingly been found that highly concentrated formulations of steroids, said formulations being fluid at normal temperature, and said steroids being of the oestrane, androstane and (19-nor-)pregnane series, may be prepared by dissolving the steroids in tocol or in a derivative thereof which is liquid at normal temperature (15°–30° C.), or in a mixture of two or more of these derivatives whereby the quantity of tocol or derivative thereof in the formulation is at least 10% by weight.

Hence, the invention relates to the highly concentrated steroid formulations thus obtained, and to the processes for their preparation.

Tocol and the derivatives liquid at normal temperature may be represented by the general formula:



where

R_1=H, CH_3 or C_2H_5;

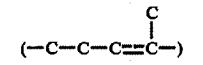
R_2=H, CH_3 or C_2H_5;

R_3=H, CH_3 or C_2H_5;

R_4=H, OH, O-acyl (1–2 atoms) or O-alkyl (1–2 C-atoms); and

the dotted lines denote the optional presence of a carbon-carbon double bond.

The compounds in which the side-chain in the formula given above contain one or two isoprene residues



less than indicated are also included amongst the tocol derivatives noted above.

For tocol itself, R_1=R_2=R_3=H, R_4=OH and the side-chain is saturated. Examples of tocol derivatives are: 5-methyltocol, 7-methyltocol, 8-methyltocol, 5,7-dimethyltocol, 5,8-dimethyltocol, 7,8-dimethyltocol, 5,7,8-trimethyltocol, 8-methyltocotrienol, 7,8-dimethyltocotrienol, 5,8-dimethyltocotrienol, 5,7,8-trimethyltocotrienol, 5,7-di-ethyltocol, 5,7-dimethyl-8-ethyltocol, 5,7-di-ethyl-8-methyltocol, the formates and acetates, as well as the methyl and ethyl esters of these compounds, and 6-desoxytocol. Use is preferably made of tocol, 5,7,8-trimethyltocol(α-tocopherol) or 8-methyltocol(δ-tocopherol). In practice use is generally made of the racemates dl-tocol, dl-α-tocopherol and dl-δ-tocopherol.

During the preparation of a formulation according to the invention, excipients such as benzyl alcohol or benzyl benzoate may optionally also be used, or a quantity of an oily carrier such as arachis oil or sesame oil may be added. Such a use or addition may be desirable in the preparation of injection formulations in order to lower the viscosity and in this way make the preparation easier to inject; in other words, to enable the formulation to be injected through a needle of the desired bore.

The amount of tocol or derivative thereof in the preparation is preferably at least 25% w/w, which means that at least 100 mg and preferably 250 mg tocol

or derivative thereof is present in a milliliter (about 1000 mg) of solution. The upper limit of the quantity of tocol or derivative thereof is of course determined by the amount of steroid which can be dissolved in the carrier, and depends to some extent on both the steroid and the carrier; it lies between 50 and 90% w/w and is generally between 60 and 80% w/w. This means that the maximum amount of steroid per ml solution (about 1000 mg), again depending on the steroid and the carrier, will be between 100 and 500 mg and generally may be 200–400 mg.

The process offers particular advantages for steroids of the oestrane, androstane and (19-nor-) pregnane series containing at least a 3-oxo-Δ^4-group and an optionally esterified hydroxy group at position 17 and/or 21 (if present), since with these steroids much higher concentrations can be achieved than is possible with the known solvents and concentrations of 100 to 400 mg in the absolute sense are furthermore possible; for certain steroids with the characteristics noted, even concentrations up to 500 mg per ml tocol or derivative thereof are possible.

Examples of oestrane, androstane and (19-nor-) pregnane compounds with at least a 3-oxo-Δ^4-group and an optionally esterified hydroxy group at position 17 and/or 21 (when present) are: testosterone, 19-nor-testosterone (nandrolone), progesterone, 19-nor-progesterone, 17α-hydroxyprogesterone, 17α-hydroxy-19-nor-progesterone, 21-hydroxy-progesterone, 21-hydroxy-19-nor-progesterone, 16α-ethyl-21-hydroxy-progesterone, 16α-ethyl-21-hydroxy-19-nor-progesterone, 16-methylene-17α-hydroxy-progesterone, corticosterone, desoxycorticosterone, cortisone, hydrocortisone, prednisolone, aldosterone and the 17 and/or 21 esters of these steroids derived from organic mono- or di-carboxylic acids with 1 or 2, respectively, to 18 carbon atoms.

Examples of such organic mono- and di- carboxylic acids are aliphatic carboxylic acids such as propionic acid, butyric acid, isocaproic acid, decanoic acid, α-methyldecanoic acid, lauric acid, myristic acid, oleic acid, palmitic acid, trimethylacetic acid, undecenoic acid, malonic acid, succinic acid, glutaric acid and tartaric acid, cyclo-aliphatic carboxylic acids, such as cyclohexane-carboxylic acid, cyclopentylpropionic acid and cyclohexylbutyric acid, araliphatic carboxylic acids such as phenylacetic acid and phenylpropionic acid, and aromatic carboxylic acids such as benzoic acid.

The steroids named may also be further substituted at positions 6, 7 and/or 11, for example by a methyl, ethyl or methylene group, and/or may contain a further double bond, for example a Δ^6 bond.

The preparations obtained according to the invention, depending on the steroid present, may be used for various indications. Preparations based on testosterone and esters thereof may be used as androgenically active preparations in substitution therapy. Preparations based on oestrogens may be used in cases of oestrogen deficiency. Preparations containing nandrolone or esters thereof can find use as anabolic preparations or ovulation-inhibiting preparations. Preparations based on progesterone or progesterone derivatives may be used as progestagenic preparations, not only for the maintenance of a pregnancy but also for prevention of pregnancy (ovulation inhibiting action) and they may furthermore be used for the treatment of endometrial carcinoma. For use as ovulation inhibitors, long-acting esters of 17α-hydroxy-progesterone, such as for example, 17α-hydroxy-progesterone caproate and medroxyprogesterone acetate, are used. Preparations containing corticosteroids may be used in those cases in which mineralocorticoid, glucocorticoid, anti-inflammatory, anti-allergic, anti-shock or analgesic activity is desired.

An interesting application of those preparations according to the invention based on nandrolone esters, in particular nandrolone esters derived from organic carboxylic acids with more than 7 carbon atoms, for example nandrolone phenylpropionate, is the use as an injection preparation for the regulation of oestrus in animals. Such an injection preparation offers particular advantages for the suppression of oestrus in domestic animals such as dogs. Since it is possible, in accordance with the invention, to prepare injection formulations containing well over 300 mg nandrolone ester, for example nandrolone palmitate, per ml, it is possible to suppress oestrus in dogs for more than 3 months with a single injection of 1 ml. Only concentrations of 50 to 100 mg per ml can be obtained with the known solvents such as arachis oil, while the addition of benzyl benzoate and/or benzyl alcohol enables concentrations of 100 to 200 mg per ml to be reached with certain nandrolone esters, for example nandrolone palmitate. For the suppression of oestrus, therefore, either a larger volume (2 to 5 ml) would have to be injected, or the injection would have to be repeated at an earlier date, and there are objections to both these procedures.

On using injection preparations according to the invention based on nandrolone esters for the suppression of oestrus in animals it was furthermore shown that, specifically with the preparations based on nandrolone esters derived from aliphatic carboxylic acids with 9–18 carbon atoms, an additional depot effect (prolonged activity or sustained release effect) appears, so that the very high concentration in the depot, particularly during the initial phase, does not result in an undesirably high blood level; unwanted side-effects as a result of excessively high blood levels do not therefore occur.

Another interesting use of the preparations according to the invention is the oral administration in the form of soft gelatine capsules containing a highly concentrated solution of the steroids in tocol or a derivative thereof. This use is specifically of importance for the oral administration of testosterone and nandrolone, in particular the esters of these steroids derived from organic carboxylic acids.

The activity of both testosterone and nandrolone is much lower on oral administration than on parenteral administration. It is true that this difference proves to be smaller for the esters of these compounds, but it may nevertheless still constitute an adequate reason for choosing the parenteral administration form in preference to the oral form, particularly in those cases where the doses to be administered are relatively high, as, for example, in androgen substitution therapy, and a large number of dosage units or a relatively large dosage unit (swallowing problem!) have or has, respectively, to be given on each occasion or alternatively the dosage has to be repeated at shorter intervals. In such cases, use of the highly concentrated solutions according to the invention can weigh the scales in favour of the medically and technically easier oral dosage form, such as the soft gelatine capsule containing the concentrated solution of, for example, a testosterone or nandrolone ester. Such an oral administration form furthermore offers the advantage that the active agent is made available to the organism in a lipoid solution, which has a favourable effect on the activity of the preparation. In this connec-

tion see the Belgian Patent Specifications Numbers 826086 and 845613.

It is known that certain tocol derivatives possess vitamin E activity. For many applications, such as suppression of oestrus in animals, this is not objectionable, but for applications in the human sector the vitamin E activity of a preparation according to the invention may be a drawback. It is however known that the various tocols possess differing vitamin E activities, and that tocol itself and certain derivatives, for example 5,7-diethyltocol and 6-desoxytocol, possess little or no vitamin E activity, so that a formulation with the desired low vitamin E activity or a formulation devoid of vitamin E activity can be prepared according to the choice of carrier.

The invention is illustrated by means of the following examples.

EXAMPLE I

Saturated solutions of a number of steroids in 5,7,8-trimethyltocol (α-tocopherol) were prepared at 21° C. The concentration of steroid in mg per ml solution is given in column a of Table A. Column b gives the concentration of steroid in mg per ml in a saturated solution in a solvent comprising equal parts by volume of α-tocopherol and arachis oil, while for comparison column c shows the concentration of steroid in mg per ml in a standard solution in arachis oil.

Table A

Steroid	a	6	c
testosterone	100	40	5
corticosterone	40	2	1
16α-ethyl-21-hydroxy-progesterone-21-decanoate	500	200	50
16α-ethyl-21-hydroxy-progesterone-21-heptanoate	>225	>225	140
dinandrolone oxydiacetate	120	20	10
dinandrolone adipate	180	85	2
testosterone undecanoate	>225	>225	85
nandrolone palmitate	400	200	75

EXAMPLE II

300 g nandrolone palmitate and 250 g α-tocopherol were added to a mixture of 100 g benzyl alcohol and 250 g benzyl benzoate which had been warmed to 70° C. After stirring for a while, a clear solution was obtained. The solution was cooled to room temperature after which the volume was adjusted to 1000 ml by addition, with stirring, of arachis oil (about 100 g). The solution thus obtained was filled into 1000 vials in a volume of 1 ml solution each, after which the vials were closed with oil-resistant rubber stoppers and so-called open "Ciliatto" capsules. The vials were finally heated at 121° C. for 30 minutes in an autoclave.

In a similar way, but using tocol instead of α-tocopherol, and in another batch δ-tocopherol instead of α-tocopherol, solutions were prepared and vials were filled with 1 ml solution containing 300 mg nandrolone palmitate.

The injection preparations thus obtained proved to be eminently suitable for use in the suppression of oestrus in dogs, a single injection of 1 ml made using a syringe fitted with a 19 G needle giving suppression of oestrus lasting at least 3 months.

EXAMPLE III

A sterile solution of testosterone undecanoate in tocol, containing 208.35 g per liter, was made. In the way usual in the pharmaceutical technique, this solution was encapsulated under aseptic conditions in soft gelatine capsules with a volume (contents) of 0.24 ml, so that the testosterone undecanoate content was 50 mg per capsule. The capsule wall (113 mg) consisted of gelatine (77 mg), glycerine (17.5 mg), sorbitol (15.5 mg), parabens (0.5 mg), TiO_2 (0.6 mg) and Cochineal Red A (1.9 mg; dye).

A number of other steroids were dissolved in tocol and encapsulated in soft gelatine capsules in a similar way. Details are given in Table B.

Table B

Steroid	Capsule content (ml)	mg steroid per capsule
Testosterone α-methyldecanoate	0.12	25
Nandrolone decanoate	0.18	50
Nandrolone α-methyl-β-cyclohexylpropionate	0.08	20
Dinandrolone oxydiacetate	0.24	25

EXAMPLE IV

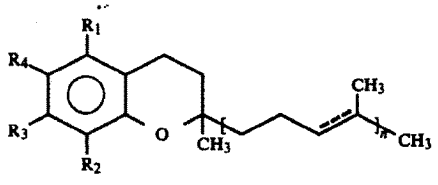
Injection formulations of a number of steroids in a solution based on tocol, benzyl alcohol, benzyl benzoate and arachis oil (50:5:20:25) were prepared in the usual way (see Example II) and filled into 1 ml capsules. The steroids are given in Table C, together with their concentrations in mg per ml solution.

Table C

Steroid	mg per ml
Nandrolone phenylpropionate	200
16α-ethyl-21-hydroxyprogesterone-21-decanoate	350
Dinandrolone oxydiacetate	75
Oestradiol phenylpropionate	50
17α-hydroxyprogesterone caproate	150
Nandrolone palmitate/laurate (2:1)	300

I claim:

1. A highly concentrated liquid pharmaceutical steroid formulation comprising (1) at least one steroid of the oestrane, androstane or (19-nor-)pregnane series containing at least a 3-oxo-Δ^4-group and an hydroxy group at position 17 and or 21 (if present) and (2) a solvent for said steroid comprising at least one of tocol or a derivative thereof that is fluid at normal temperatures and of the formula:



where

R_1=H, CH_3, or C_2H_5;
R_2=H, CH_3, or C_2H_5;
R_3=H, CH_3, or C_2H_5;
R_4=H, OH, O-C_{1-2} acyl, OCH_3, or C_2H_5; and
n=1, 2, or 3;

the dotted lines indicate the optional presence of a carbon atom double bond, with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

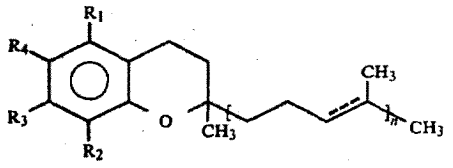
2. The formulation of claim 1, wherein said tocol or derivative thereof is selected from the group consisting of tocol, α-tocopherol and δ-tocopherol.

3. The formulation of claims 1 or 2, wherein said tocol or derivative thereof constitutes at least 25% by weight of said formulation.

4. The steroid formulation of claim 1 where the hydroxy group of the steroid is esterified.

5. The steroid formulation of claim 1 further containing at least one fluid carrier selected from the group consisting of vegetable oils, benzyl benzoate, and benzyl alcohol with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

6. A process for preparing a highly concentrated pharmaceutical steroid formulation comprising dissolving at least one steroid of the oestrane, androstane, or (19-nor-) pregnane series containing at least a 3-oxo-Δ^4-group and an hydroxy group at position 17 and or 21 (if present) in at least one of tocol or a derivative thereof that is liquid at normal temperatures and of the formula:



where

R_1=H, CH_3, or C_2H_5;
R_2=H, CH_3, or C_2H_5;
R_3=H, CH_3, or C_2H_5;
R_4=H, OH, O-C_{1-2} acyl, or C_2H_5; and
n=1, 2, or 3;

the dotted lines indicate the optional presence of a carbon atom double bond, with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

7. Process according to claim 6, characterized in that said tocol or derivative thereof is selected from the group consisting of tocol, α-tocopherol and γ-tocopherol.

8. The process of claim 6 wherein the hydroxy group of the steroid is esterified.

9. The process of claim 6 comprising further adding at least one fluid carrier selected from the group consisting of vegetable oils, benzyl benzoate, and benzyl alcohol to the formulation with the proviso that said tocol or derivative constitutes at least 10% by weight of said formulation.

10. Process according to claims 6, 7, 8 or 9, characterized in that said tocol or derivative thereof constitutes at least 25% by weight of said formulation.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,212,863

DATED : July 15, 1980

INVENTOR(S) : Lammert CORNELIUS

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Line 3 of the Abstract, change "comprising" to --containing--.

Column 2, line 51, change "esters" to --ethers--.

Column 6, line 63, in claim 1, change "C_2H_5" to read --OC_2H_5--.

Column 8, line 14, in claim 6, change "or C_2H_5" to read --OCH_3 or C_2H_5--.

Signed and Sealed this

Fourth Day of May 1982

[SEAL]

Attest:

GERALD J. MOSSINGHOFF

Attesting Officer *Commissioner of Patents and Trademarks*

UNITED STATES PATENT AND TRADEMARK OFFICE

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DATED : July 15, 1980

INVENTOR(S) : Lammert CORNELIUS

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 8, line 14, in claim 6, change "OCH_3 or C_2H_5" to read --OCH_3 or OC_2H_5--.

Signed and Sealed this

Twentieth Day of *July 1982*

[SEAL]

Attest:

GERALD J. MOSSINGHOFF

Attesting Officer *Commissioner of Patents and Trademarks*

ATTACHMENT F - COMPILATION

TAB 2

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 346 014 A1**

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(54) **Therapeutic product.**

(57) The invention relates to a therapeutic product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions; to a process for the manufacture of said product and to a pharmaceutical composition containing said product. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to a process for the manufacture of said composition.

EP 0 346 014 A1

THERAPEUTIC PRODUCT

This invention relates to a therapeutic product for use in a new method of medical treatment and, more particularly, it relates to a product comprising an oestrogen and a pure antioestrogen for use in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal conditions, particularly perimenopausal or postmenopausal osteoporosis. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to the use thereof in the manufacture of a new medicament for use in the treatment or prophylaxis of perimenopausal or postmenopausal conditions.

When a female animal, particularly a human female, enters the perimenopausal stage the animal's ovaries begin to secrete less of the female sex hormones, particularly oestradiol. Symptoms in women at this stage include the following: vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and distal urethra), psychosomatic complaints, changes in lipid metabolism and osteoporosis. The rate of decline of ovarian function and the severity of the above-mentioned symptoms are highly variable between individual women but in a substantial number of individuals the symptoms are sufficiently severe that treatment is required. Oestrogen replacement therapy has been used in women and it is generally recognised to be effective in combatting the typical perimenopausal and post-menopausal symptoms (British Medical Journal, 1987, 295, 914; American Journal of Obstet. and Gynecol., 1987, 156, 1298 and 1347). However oestrogen replacement therapy can also cause uterine hyperplasia, irregular vaginal menstruation and, in a small proportion of women, endometrial cancer (American Journal of Obstet. and Gynecol., 1987, 156, 1313).

To combat the continuous unopposed stimulation of oestrogen-responsive tissues an oestrogen and a progestogen are normally co-administered for part of each treatment period thereby causing regular vaginal menstruation. (American Journal of Obstet. and Gynecol., 1987, 156, 1304). However the continuation of menstrual periods is unattractive to many postmenopausal women and, in addition, progestogens can cause side effects, for example oedema, premenstrual irritability and breast tenderness.

Alternative therapies are therefore required.

It has recently been shown that compounds demonstrating a mixture of oestrogenic and antioestrogenic properties in warm-blooded animals, including humans, may be of use in the treatment of postmenopausal conditions (European Patent Specification No. 0178862). Particular compounds stated to have such activity include clomiphene and tamoxifen. Comprehensive reviews of the clinical usage of these compounds are available, for example a review of clomiphene by Clark et al. in Pharmacology and Therapeutics, 1982, Volume 15, pages 467 to 519, and a review of tamoxifen by Furr et al. in Pharmacology and Therapeutics, 1984, Volume 25, pages 127-205.

It has also recently been shown that a treatment regime comprising the dosing of a small amount of an oestrogen, for example oestrone sulphate or natural conjugated oestrogens, followed by the dosing of an antioestrogen, for example tamoxifen or clomiphene led to the partial inhibition of the maximum oestrogen-induced stimulation of uterine endometrial tissue (A. Kauppila et al., Gynecol. obstet. Invest., 1988, 25, 58 and Arch. Gynecol., 1983, 234, 49).

It has now been found that administration of an oestrogen and a pure antioestrogen, whether simultaneously, sequentially or separately, results in the oestrogen being selectively effective in some oestrogen-responsive tissues, for example bone, and being selectively opposed in other oestrogen-responsive tissues, for example the endometrium of the uterus, and this is the basis of the present invention.

A pure antioestrogen is a compound which possesses antioestrogenic activity and no oestrogenic activity. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate alone. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

It is disclosed in European Patent Specification No. 138504 that certain pr ferred steroidal antioestrogens are pure antioestrogens. It is also disclosed in European Patent No. 124369 that certain preferred non-steroidal antioestrogens are pure antioestrogens.

According to the present invention there is provided a product comprising an oestrogen and a pure antioestrogen for simultaneous, s quential or separate use in selective o strogen therapy of perimenopausal or postmenopausal conditions.

In a particular product of the invention the oestrogen component of a product of the invention is oestradiol, ethinyloestradiol, oestriol, oestron , natural conjugat d oestrogens, piperazine oestrone sulphate, mestranol, chlorotrianisene, dienoestrol, stilboestrol or hexoestrol or a pharmaceutically-acceptable ester thereof.

A pharmaceutically-acceptable ester of the o strogen component of a product of the invention is, for example, an alkyl or aryl ester each of up to 12 carbon atoms. It will be appreciated that an ester of a steroidal oestrogen may be formed at the 3-position, the 17-position or at both of these positions. It will also be appreciated that an ester may be formed at one or both of the phenolic groups in some non-steroidal oestrogens, for example stilboestrol and hexoestrol. A suitable alkyl ester of up to 12 carbon atoms is, for example, an acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, cyclopentylpropionate, nonanoate, decanoate, undecanoate or dodecanoate. A suitable aryl ester of up to 12 carbon atoms is, for example, a benzoate, toluate or naphthoate. A preferred pharmaceutically-acceptable ester of the oestrogen component of a product of the invention includes, for example, oestradiol benzoate, oestradiol cyclopentylpropionate, oestradiol dipropionate, oestradiol heptanoate, oestradiol undecanoate, oestradiol valerate and stilboestrol dipropionate.

In a further particular product of the invention the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

In a further particular product of the invention the pure antioestrogen is a compound of the formula:-
NU-A-X-R^1
wherein NU is 6-hydroxy-2-p-hydroxyphenylnapth-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_5-$(1,4-phenylene)$-(CH_2)_2-$;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnapth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_4-$(1,4-phenylene)$-(CH_2)_2-$;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_4-$(1,4-phenylene)$-(CH_2)_2-$;
and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, $-SOR^1$ or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

In a further particular product of the invention the pure antioestrogen is
N-n-butyl-, N-n-butyl-N-methyl-, N-n-pentyl, N-(1H,1H-heptafluorobutyl)-or N-(1H,1H-heptafluorobutyl)-N-methyl-3-p-[5-(6-hydroxy-2-p-hydroxyphenylnaphth-1-yl)pentyl]phenylpropionamide;
N-methyl-N-(1H,1H-heptafluorobutyl)-p-[4-[(1RS,2RS)-6-hydroxy-2-p-hydroxphenyl-2-methyl-1,2,3,4-tetrahydronaphth-1-yl]-butyl]phenylpropionamide;
(1RS,2RS)-1-[4-[p-(2-n-hexylthioethyl)phenyl]butyl]-2-p-hydroxyphenyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl, hexylsulphonyl or pentafluoropentylsulphinyl derivatives;
2-p-hydroxyphenyl-1-[5-[p-(2-n-hexylthioethyl)phenyl]pentyl]naphth-6-ol or the corresponding hexylsulphinyl derivative; or
(1RS,2RS)-1-[4[p-(2-n-hexylthioethyl)phentyl]butyl]-2-p-hydroxyphenyl-2-methyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl or pentafluoropentylsulphinyl derivative, or the corresponding (1RS,2SR) isomers of both the hexylthio and hexylsulphinyl derivatives.

A preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol or ethinyloestradiol, or a pharmaceutically-acceptable ester thereof, and the pure antioestrogen is 7α-[9-(4,4,5,5,5- pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol or (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

A particularly preferred product of the invention comprises an oestrogen and a pure antio strogen for use as stated abov wh rein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-

oestra-1,3,5(10)-triene-3,17β-diol.

According to a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

In a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing into admixture said oestrogen and said pure antioestrogen.

A product of the invention may be administered to a warm-blooded animal, including a human, in the form of a pharmaceutical composition. Thus according to a further feature of the present invention there is provided a pharmaceutical composition which comprises the product of the invention together with a pharmaceutically-acceptable diluent or carrier.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. It will be understood that there is no absolute requirement that the oestrogen and pure antioestrogen components of the product of the invention must be dosed simultaneously. Sequential or separate use of these components may also provide selective oestrogen therapy and such use is to be understood to fall within the definition of a product of the invention. Thus it will be appreciated that a pharmaceutical composition according to the present invention includes a composition comprising an oestrogen, a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. A pharmaceutical composition according to the present invention also includes separate compositions comprising a first composition comprising an oestrogen and a pharmaceutically-acceptable diluent or carrier, and a second composition comprising a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, capsules, aqueous or oily suspensions, emulsions or dispersible powders or granules), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions; for example for use within a transdermal patch), for parenteral administration (for example as a sterile aqueous or oily solution or suspension for intravenous, subcutaneous, intramuscular or intravascular dosing), or as a suppository for rectal dosing or as a pessary for vaginal dosing.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylen oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, castor oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as castor oil, soya bean oil or arachis oil, or a mineral oil, such as, for example, liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

The pharmaceutical compositions may also be in the form of sterile injectable aqueous or oily suspensions, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol, in a vegetable oil (such as arachis oil, castor oil or coconut oil) or in a mineral oil (such as liquid paraffin).

Conveniently the subcutaneous or intramuscular injection of an aqueous suspension or an oily solution or suspension of a pharmaceutical composition of the invention provides a depot of the active ingredients at the injection site from which those ingredients may leach out over a period of time to provide the sustained release thereof.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

According to a further feature of the invention there is provided a process for the manufacture of a pharmaceutical composition as defined above which comprises bringing into admixture a product as defined above together with a pharmaceutically-acceptable diluent or carrier.

The invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering simultaneously, sequentially or separately to a warm-blooded animal an effective amount of a product as defined above. The invention also provides the use of a product as defined above for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

It will be appreciated that the definition of the product of the invention and the pharmaceutical composition of the invention includes only those products or compositions which are useful in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal condition. Pharmaceutical compositions comprising an oestrogen and a pure antioestrogen, together with a pharmaceutically-acceptable diluent or carrier, are novel. In European Patent Sepcifications Nos. 138504 and 124369 it is disclosed that the antioestrogenic activity of the compounds disclosed therein may be demonstrated by the co-administration of a test compound and oestradiol benzoate to an immature female rat. Antioestrogenic activity is demonstrated by antagonism of the increase in weight of the uterus of the rat which is produced when oestradiol benzoate alone is administered to said rat. It is to be noted that, during those tests, the oestradiol benzoate was given by subcutaneous injection whereas the test compound was given separately either orally or subcutaneously.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this feature of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the are such as, for example, those disclosed above.

This aspect of the invention also provides a process for the manufacture of a pharmaceutical composition as defined immediately above which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

This aspect of the invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering to a warm-blooded animal an effective amount of a pharmaceutical composition as defined immediately above. The invention also provides the use of a pharmaceutical composition as defined immediately above for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

As stated above a product of the invention is of use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. Selective oestrogen therapy may be demonstrated using the standard procedure set out below:-

a) an in vivo assay measuring the antioestrogenic activity of a compound and any oestrogenic activity possessed by that compound. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate without the pure antioestrogen. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

The oestrogenic activity of a compound may be demonstrated in rats by the effect of the compound when it is administered alone to said rat on the uterine weight of the animal.

b) An in vivo assay in mature rats measuring the antioestrogenic activity of a compound by the effect of the compound when dosed during a test period of 28 days in antagonising the protective effect on the animals' bone density of their endogenous oestrogens. The bone density of a group of ovariectomised rats in which endogenous oestrogen levels are much reduced serves as a control for the effect expected to be produced by a fully effective antioestrogen.

The antioestrogenic activity of the compound in mature rats can also be measured in the same assay by measuring the effect of the compound in antagonising the effect of the animals' endogenous oestrogens which serve to increase the weight of their uteri.

A comparison of the potencies of the antioestrogenic effects of a compound as measured by its effects on the animals' bone density and uterine weights allows the selectivity of the antioestrogenic effects of the compound to be measured.

Although the pharmacological properties of a product of the invention vary with the structures of the oestrogenic and antioestrogenic components and with the route of administration, in general a product of the invention comprises:-

(i) an oestrogen which possesses oestrogenic activity in the above test (a) at doses in the range, for example, 0.002-2.0 mg/kg orally or in the range, for example, 0.0001-0.1 mg/kg subcutaneously;

(ii) a pure antioestrogen which possesses antioestrogenic activity in the above tests (a) and (b) at doses in the range, for example, in test (a): ED_{50} 0.05-5 mg/kg orally or ED_{50} 0.01-1.0 mg/kg subcutaneously;
in test (b): antiuterotrophic effect:- ED_{50} < 20 mg/kg/day orally, < 2 mg/kg/day subcutaneously or intramuscularly and < 10 mg/kg/injection when dosed as an intramuscular depot injection; reduction in bone density:- ED_{50} > 20 mg/kg/day orally, > 5 mg/kg/day subcutaneously or intramuscularly and > 10 mg/kg/injection when dosed as an intramuscular depot injection.

A product of the invention is thereby seen to be surprisingly selective as the activity of the pure antioestrogen component is expressed to a high degree within uterine tissue but to a lesser degree on bone.

The size of the dose, for therapeutic or prophylatic purposes, of a product of the invention as defined above will naturally vary according to the nature and severity of the conditions presented, the age and menopausal state of the animal and the route of administration.

In general the minimum quantity of the oestrogenic component of a product of the inv ntion as defined above will be chosen so as to provide a beneficial effect with regard to th nature and severity of the conditions presented. The quantity of the pure antioestrogenic compon nt is then chosen to antagonis to a substantial degree the effect of the oestrogenic component on th uterine tissue. Methods of evaluating the

condition of uterine tissue are well known to the man skilled in the art, for example, by examination of a specimen of endometrial tissue taken by, for example, suction or, for example, by way of a biopsy.

So far as the oestrogenic component of a product of the invention as defined above is concerned the size of the dose and routes of administration conventionally utilised in oestrogen replacement therapy may be used. Thus, for example, a tablet containing, for example, 0.5 to 2 mg of oestradiol, oestradiol benzoate, natural conjugated oestrogens or oestradiol valerate may be administered daily. Alternatively a tablet containing 10 to 100 μg of ethinyloestradiol may be administered daily. Alternatively the oestrogenic component may be administered by, for example, intramuscular injection utilising, for example, 1 to 10 mg of oestradiol benzoate dissolved in an oil such as ethyl oleate; for example, transdermal means utilising, for example, 10-100 μg of oestradiol contained within a transdermal patch; or, for example, vaginal application utilising, for example, daily application of 0.5 to 2 mg of natural conjugated oestrogens contained within 0.5 to 5 ml of a cream.

So far as the antioestrogenic component of a product of the invention as defined above is concerned the size of the dose is chosen such that the effect of the oestrogenic component on uterine tissue is antagonised to a substantial degree whereas the beneficial effect of the oestrogenic component on bone is substantially unopposed.Thus, for example, the antioestrogenic component may be formulated in like manner to the oestrogenic component, for example as a tablet, an oily solution suitable for intramuscular injection, within a transdermal patch, or within a cream suitable for vaginal application. The daily administration of one or more tablets containing conveniently 50 mg to 5 g, and preferably 50 mg to 500 mg, of a pure antioestrogen may be used. Preferably the pure antioestrogen may be administered by the periodic intramuscular injection of, for example, an aqueous suspension or an oily solution or suspension containing 50 mg to 5 g of the pure antioestrogen. Preferably an oily solution, for example a solution containing arachis or castor oil, an alcohol such as benzyl alcohol and 50 mg to 500 mg of the pure antioestrogen is employed. Such an injection provides a depot of the pure antioestrogen which thereafter leaches out from the injection site to provide a selective antioestrogenic effect for a period of, for example, one to six weeks.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. As previously mentioned perimenopausal and postmenopausal conditions include, for example, vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and the distal urethra), psychosomatic complaints, changes in the lipid metabolism and oesteoporosis. The selective antioestrogenic effect of the pure antioestrogenic component of a product of the invention, as demonstrated by a greater antioestrogenic effect on the uterus of a rat than on the bone of the rat, allows the beneficial effect of the oestrogenic component of the product of the invention to be selectively applied to the bone and prevents the detrimental effect of an unopposed oestrogenic effect on the uterus. The utero-selective effect of the pure antioestrogenic component of a product of the invention will allow the beneficial effect of the oestrogenic component of a product of the invention to be applied to other oestrogen-responsive tissues, for example those causing vasomotor disturbances, pyschosomatic complaints and changes in lipid metabolism.

The invention will now be illustrated in the following non-limiting Examples.

Example 1

Assay in Mature Rats of the Selective Antioestrogenic Activity of a Pure Antioestrogen

The pure antioestrogen used was (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

The compound was given subcutaneously as a solution in arachis oil at doses of 2 mg/kg/day and 10 mg/kg/day to two groups of 5 mature rats for a total of 28 days. Further groups of 5 mature rats served as an untreated control group. A further group of 5 mature rats was ovariectomised to serve as another control group. At the end of the treatment period the weights of the uteri of the test and control groups of rats were determined. In addition the femurs were dissected, weighed and their volumes were determined using Archimedes Principle. The femurs were then burned and the residual ash was weighed. From these data, gross femur density and bone mineral density were calculated as follows:-

Gross Femur Density = Femur Weight/Femur Volume

Bon Mineral Density = Femur Ash Weight/Femur Volume

The results shown below in Tables I and II demonstrate that at a dose of 2 mg/kg/day subcutaneously

the test compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri (90% inhibition of uterine weight) whereas there was no significant inhibition of either bone mineral density or of gross femur density.

TABLE I

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	382 ± 34	
Ovariectomised Controls	111 ± 14	
Test Compound at 2 mg/kg/day s.c.	135 ± 8	91%
Untreated Controls	369 ± 47	
Ovariectomised Controls	99 ± 5	
Test Compound at 10 mg/kg/day s.c.	125 ± 4	90%

TABLE II

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition	Bone Mineral Density (g/ml)	Calculated Inhibition
Untreated Controls	1.612 ± 0.010		0.742 ± 0.009	
Ovariectomised Controls	1.569 ± 0.010		0.685 ± 0.010	
Test Compound at 2 mg/kg/day s.c.	1.604 ± 0.006	19%*	0.730 ± 0.007	21% *
Untreated Controls	1.629 ± 0.014		0.766 ± 0.005	
Ovariectomised Controls	1.571 ± 0.007		0.704 ± 0.005	
Test Compound at 10 mg/kg/day s.c.	1.580 ± 0.004	84%	0.727 ± 0.005	63%

* This level of inhibition was not statistically significant.

Example 2

The experiment described in Example 1 was repeated except that the pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. This compound was given at a series of doses as a daily intramuscular injection, the compound having been dissolved in a mixture of propylene glycol: ethanol: water: poloxamer 407. The formulation contained 25 mg of test compound, 100 mg of ethanol (96%), 100 mg of water, 20 mg of poloxamer 407 and sufficient propylene glycol to bring the solution to a volume of 1 ml.

The results shown below in Tables III and IV demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas there was no significant inhibition of gross femur density.

TABLE III

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	302 ± 36	
Ovariectomised Controls	70 ± 1.3	
Test Compound (mg/kg)		
0.1	208 ± 17	41
0.3	174 ± 16	55
1	94 ± 9	90
3	103 ± 2	86

TABLE IV

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Untreated Controls	1.523 ± 0.008	
Ovariectomised Controls	1.491 ± 0.006	
Test Compound at (mg/kg)		
0.1	1.528 ± 0.005	0%
0.3	1.528 ± 0.008	0%
1	1.532 ± 0.005	0%
3	1.533 ± 0.005	0%

Example 3

The pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Each of a series of selected doses of this compound was dissolved in a mixture of castor oil and benzyl alcohol and given by intramuscular injection to a group of 5 mature rats. The formulation contained 50 mg of the test compound, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. In each case a second dose was administered two weeks after the first dose. Two weeks after the second dose the weights of the uteri of the test groups of rats were determined. In addition the femurs were dissected and analysed for Gross Femur Density as in Example 1.

A further group of rats, given two injections of castor oil separated by a two week period, served as an intact control group. A further group of rats was ovariectomised to serve as another control group.

The results shown below in Tables V and VI demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas at the two higher test doses there was no significant inhibition of gross femur density.

TABLE V

Treatm nt	Uterine Weight (mg)	Calculated Inhibition
Intact Controls	318 ± 31	
Ovariectomised Controls	76 ± 4	
Test Compound (mg/rat/dose)		
0.75	202 ± 23	48
1.25	180 ± 15	57
2.5	123 ± 12	81

TABLE VI

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Intact Controls	1.584 ± 0.007	
Ovariectomised Controls	1.521 ± 0.005	
Test Compound (mg/rat/dose)		
0.75	1.562 ± 0.004	35
1.25	1.576 ± 0.004	13*
2.5	1.569 ± 0.007	23*

* This level of inhibition was not statistically significant.

Claims

1. A product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

2. A product as claimed in claim 1 wherein the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)-triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

3. A product as claimed in claim 1 wherein the pure antioestrogen is a compound of the formula:-
NU-A-X-R¹
wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$ or $-(CH_2)_3-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or$-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;

and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

4. A product as claimed in claim 1 wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)-nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

5. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

6. A pharmaceutical composition comprising a product as claimed in any one of claims 1 to 4 together with a pharmaceutically-acceptable diluent or carrier.

7. The use of a product as claimed in any one of claims 1 to 4 for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

8. A pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

9. A process for the manufacture of a pharmaceutical composition as claimed in claim 8 which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

10. The use of a pharmaceutical composition as claimed in claim 8 for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

Claims for the following Contracting States: GR, ES.

1. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal condition, which process is characterised by bringing together said oestrogen and said pure antioestrogen.

2. A process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process is characterised by bringing into admixture said oestrogen and said pure antioestrogen.

3. A process as claimed in claim 1 or claim 2 wherein the pure antioestrogen is
N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl- or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;
N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]-phenylpropionamide;
7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)-triene-3,17β-diol; or
7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

4. A process as claimed in claim 1 or 2 wherein the pure antioestrogen is a compound of the formula:-
NU-A-X-R^1
wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$, or $-(CH_2)_5-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;
or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $-(CH_2)_{10}-$, $-(CH_2)_{11}-$or $-(CH_2)_4-(1,4\text{-phenylene})-(CH_2)_2-$;
and wherein XR^1 is $-CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

5. A process as claimed in claim 1 or claim 2 wherein th oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

6. A process for the manufacture of a pharmaceutical composition which comprises bringing into admixture a product as defined in any one of claims 1 to 5 together with a pharmaceutically-acceptable diluent or carrier.

7. A process for the manufacture of a pharmaceutical composition which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 5563

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X	EP-A-0 124 369 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Page 15, lines 4-6 *	1-10	A 61 K 31/565// (A 61 K 31/565 A 61 K 31:165)
D,X	EP-A-0 138 504 (IMPERIAL CHEMICAL INDUSTRIES PLC) * Page 14, lines 2-5 *	1-10	
A	CHEMICAL ABSTRACTS, vol. 109, no. 3, 18th July 1988, page 73, abstract no. 17199p, Columbus, Ohio, US; N. FROEHLANDER et al.: "Growth hormone and somatomedin C during post-menopausal replacement therapy with estrogen alone and in combination with an antiestrogen", & MATURITAS 1988, 9(4), 297-302 * Abstract *	1-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-09-1989	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

ATTACHMENT F - COMPILATION

TAB 3

US005183814A

United States Patent [19]

Dukes

[11] Patent Number: 5,183,814

[45] Date of Patent: Feb. 2, 1993

[54] SELECTIVE OESTROGEN THERAPY FOR PERIMENOPAUSAL OR POSTMENOPAUSAL CONDITIONS

[75] Inventor: **Michael Dukes**, Wilmslow, United Kingdom

[73] Assignee: **Imperial Chemical Industries PLC**, London, England

[21] Appl. No.: **362,043**

[22] Filed: **Jun. 6, 1989**

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[57] **ABSTRACT**

The invention relates to a therapeutic product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions; to a process for the manufacture of said product and to a pharmaceutical composition containing said product. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to a process for the manufacture of said composition.

4 Claims, No Drawings

SELECTIVE OESTROGEN THERAPY FOR PERIMENOPAUSAL OR POSTMENOPAUSAL CONDITIONS

This invention relates to a therapeutic product for use in a new method of medical treatment and, more particularly, it relates to a product comprising an oestrogen and a pure antioestrogen for use in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal conditions, particularly perimenopausal or postmenopausal osteoporosis. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to the use thereof in the manufacture of a new medicament for use in the treatment or prophylaxis of perimenopausal or postmenopausal conditions.

When a female animal, particularly a human female, enters the perimenopausal stage the animal's ovaries begin to secrete less of the female sex hormones, particularly oestradiol. Symptoms in women at this stage include the following: vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and distal urethra), psychosomatic complaints, changes in lipid metabolism and osteoporosis. The rate of decline of ovarian function and the severity of the above-mentioned symptoms are highly variable between individual women but in a substantial number of individuals the symptoms are sufficiently severe that treatment is required. Oestrogen replacement therapy has been used in women and it is generally recognised to be effective in combatting the typical perimenopausal and post-menopausal symptoms (*British Medical Journal*, 1987, 295, 914; *American Journal of Obstet. and Gynecol.*, 1987, 156, 1298 and 1347). However oestrogen replacement therapy can also cause uterine hyperplasia, irregular vaginal menstruation and, in a small proportion of women, endometrial cancer (*American Journal of Obstet. and Gynecol.*, 1987, 156, 1313).

To combat the continuous unopposed stimulation of oestrogen-responsive tissues an oestrogen and a progestogen are normally co-administered for part of each treatment period thereby causing regular vaginal menstruation. (*American Journal of Obstet. and Gynecol.*, 1987, 156, 1304). However the continuation of menstrual periods is unattractive to many postmenopausal women and, in addition, progestogens can cause side effects, for example oedema, premenstrual irritability and breast tenderness.

Alternative therapies are therefore required.

It has recently been shown that compounds demonstrating a mixture of oestrogenic and antioestrogenic properties in warm-blooded animals, including humans, may be of use in the treatment of postmenopausal conditions (European Patent Specification No. 0178862). Particular compounds stated to have such activity include clomiphene and tamoxifen. Comprehensive reviews of the clinical usage of these compounds are available. for example a review of clomiphene by Clark et al. in *Pharmacology and Therapeutics*, 1982, Volume 15, pages 467 to 519, and a review of tamoxifen by Furr et al. in *Pharmacology and Therapeutics*, 1984, Volume 25, pages 127–205.

It has also recently been shown that a treatment regime comprising the dosing of a small amount of an oestrogen, for example oestrone sulphate or natural conjugated oestrogens, followed by the dosing of an antioestrogen, for example tamoxifen or clomiphene led to the partial inhibition of the maximum oestrogen-induced stimulation of uterine endometrial tissue (A. Kauppila et al., *Gynecol. obstet. Invest.*, 1988, 25, 58 and *Arch. Gynecol.*, 1983, 234, 49).

It has now been found that administration of an oestrogen and a pure antioestrogen, whether simultaneously, sequentially or separately, results in the oestrogen being selectively effective in some oestrogen-responsive tissues, for example bone, and being selectively opposed in other oestrogen-responsive tissues, for example the endometrium of the uterus, and this is the basis of the present invention.

A pure antioestrogen is a compound which possesses antioestrogenic activity and no oestrogenic activity. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate alone. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

It is disclosed in European Patent Specification No. 138504 that certain preferred steroidal antioestrogens are pure antioestrogens. It is also disclosed in European Patent No. 124369 that certain preferred non-steroidal antioestrogens are pure antioestrogens.

According to the present invention there is provided a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

In a particular product of the invention the oestrogen component of a product of the invention is oestradiol, ethinyloestradiol, oestriol, oestrone, natural conjugated oestrogens, piperazine oestrone sulphate, mestranol, chlorotrianisene, dienoestrol, stilboestrol or hexoestrol or a pharmaceutically-acceptable ester thereof.

A pharmaceutically-acceptable ester of the oestrogen component of a product of the invention is, for example, an alkyl or aryl ester each of up to 12 carbon atoms. It will be appreciated that an ester of a steroidal oestrogen may be formed at the 3-position, the 17-position or at both of these positions. It will also be appreciated that an ester may be formed at one or both of the phenolic groups in some non-steroidal oestrogens, for example stilboestrol and hexoestrol. A suitable alkyl ester of up to 12 carbon atoms is, for example, an acetate, propionate, butyrate, valerate, hexanoate, heptanoate, octanoate, cyclopentylpropionate, nonanoate, decanoate, undecanoate or dodecanoate. A suitable aryl ester of up to 12 carbon atoms is, for example, a benzoate, toluate or naphthoate. A preferred pharmaceutically-acceptable ester of the oestrogen component of a product of the invention includes, for example, oestroadiol benzoate, oestradiol cyclopentylpropionate, oestradiol dipropionate, oestradiol heptanoate, oestradiol undecanoate, oestradiol valerate and stilboestrol dipropionate.

In a further particular product of the invention the pure antioestrogen is

N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl-or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)trien-7α-yl)undecanamide;

N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-triene-7α-yl)butyl]-phenylpropionamide;

7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]-or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3,5(10)triene-3,17β-diol; or

7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

In a further particular product of the invention the pure antioestrogen is a compound of the formula:

$$NU—A—X—R^1$$

wherein NU is 6-hydroxy-2-p-hydroxyphenylnapth-1-yl and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_5$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnapth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$; and wherein XR^1 is $—CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $—SR^1$, $—SOR^1$ or $—SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H-heptafluorohexyl.

In a further particular product of the invention the pure antioestrogen is

N-n-butyl-, N-n-butyl-N-methyl-, N-n-pentyl, N-(1H,1H-heptafluorobutyl)-or N-(1H,1H-heptafluorobutyl)-N-methyl-3-p-[5-(6-hydroxy-2-p-hydroxyphenylnaphth-1-yl)pentyl]phenylpropionamide;

N-methyl-N-(1H,1H-heptafluorobutyl)-p-[4-[(1RS,2RS)-6-hydroxy-2-p-hydroxphenyl-2-methyl-1,2,3,4-tetrahydronaphth-1-yl]-butyl]phenylpropionamide; (1RS,2RS)-1-[4-[p-(2-n-hexylthioethyl)phenyl]-butyl]-2-p-hydroxyphenyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl, hexylsulphonyl or pentafluoropentylsulphinyl derivatives; 2-p-hydroxyphenyl-1-[5-[p-(2-n-hexylthioethyl)-phenyl]pentyl]naphth-6-ol or the corresponding hexylsulphinyl derivative; or (1RS,2RS)-1-[4[p-(2-n-hexylthioethyl)phentyl]butyl]-2-p-hydroxyphenyl-2-methyl-1,2,3,4-tetrahydronaphth-6-ol or the corresponding 4,4,5,5,5-pentafluoropentylthio derivative, or the corresponding hexylsulphinyl or pentafluoropentylsulphinyl derivative, or the corresponding (1RS,2SR) isomers of both the hexylthio and hexylsulphinyl derivatives.

A preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol or ethinyloestradiol, or a pharmaceutically-acceptable ester thereof, and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol or (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

A particularly preferred product of the invention comprises an oestrogen and a pure antioestrogen for use as stated above wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

According to a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing together said oestrogen and said pure antioestrogen.

In a further feature of the invention there is provided a process for the manufacture of a product comprising an oestrogen and a pure antioestrogen for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions, which process comprises bringing into admixture said oestrogen and said pure antioestrogen.

A product of the invention may be administered to a warm-blooded animal, including a human, in the form of a pharmaceutical composition. Thus according to a further feature of the present invention there is provided a pharmaceutical composition which comprises the product of the invention together with a pharmaceutically-acceptable diluent or carrier.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. It will be understood that there is no absolute requirement that the oestrogen and pure antioestrogen components of the product of the invention must be dosed simultaneously. Sequential or separate use of these components may also provide selective oestrogen therapy and such use is to be understood to fall within the definition of a product of the invention. Thus it will be appreciated that a pharmaceutical composition according to the present invention includes a composition comprising an oestrogen, a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for simultaneous use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. A pharmaceutical composition according to the present invention also includes separate compositions comprising a first composition comprising an oestrogen and a pharmaceutically-acceptable diluent or carrier, and a second composition comprising a pure antioestrogen and a pharmaceutically-acceptable diluent or carrier. Such a composition conveniently provides the product of the invention for sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, capsules, aqueous or oily suspensions, emulsions or dispersible powders or granules), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions; for example for use within a transdermal patch), for parenteral administration (for example as a sterile aqueous or oily solution or suspension for intravenous, subcutaneous, intramuscular or intravascular dosing), or as a suppository for rectal dosing or as a pessary for vaginal dosing.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, castor oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as castor oil, soya bean oil or arachis oil, or a mineral oil, such as, for example, liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

The pharmaceutical compositions may also be in the form of sterile injectable aqueous or oily suspensions, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol, in a vegetable oil (such as arachis oil, castor oil or coconut oil) or in a mineral oil (such as liquid paraffin).

Conveniently the subcutaneous or intramuscular injection of an aqueous suspension or an oily solution or suspension of a pharmaceutical composition of the invention provides a depot of the active ingredients at the injection site from which those ingredients may leach out over a period of time to provide the sustained release thereof.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

According to a further feature of the invention there is provided a process for the manufacture of a pharmaceutical composition as defined above which comprises bringing into admixture a product as defined above together with a pharmaceutically-acceptable diluent or carrier.

The invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering simultaneously, sequentially or separately to a warm-blooded animal an effective amount of a product as defined above. The invention also provides the use of a product as defined above for the manufacture of a new medicament for use simultaneously, sequentially or separately in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

It will be appreciated that the definition of the product of the invention and the pharmaceutical composition of the invention includes only those products or compositions which are useful in a new method for the treatment or prophylaxis of perimenopausal or postmenopausal condition. Pharmaceutical compositions comprising an oestrogen and a pure antioestrogen, together with a pharmaceutically-acceptable diluent or carrier, are novel. In European Patent Sepcifications Nos. 138504 and 124369 it is disclosed that the antioestrogenic activity of the compounds disclosed therein may be demonstrated by the co-administration of a test compound and oestradiol benzoate to an immature fe-

male rat. Antioestrogenic activity is demonstrated by antagonism of the increase in weight of the uterus of the rat which is produced when oestradiol benzoate alone is administered to said rat. It is to be noted that, during those tests, the oestradiol benzoate was given by subcutaneous injection whereas the test compound was given separately either orally or subcutaneously.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this feature of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the are such as, for example, those disclosed above.

This aspect of the invention also provides a process for the manufacture of a pharmaceutical composition as defined immediately above which comprises bringing into admixture an oestrogen and a pure antioestrogen together with a pharmaceutically-acceptable diluent or carrier.

This aspect of the invention also provides a method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering to a warm-blooded animal an effective amount of a pharmaceutical composition as defined immediately above. The invention also provides the use of a pharmaceutical composition as defined immediately above for the manufacture of a new medicament for use in selective oestrogen therapy of perimenopausal or postmenopausal conditions.

As stated above a product of the invention is of use in selective oestrogen therapy of perimenopausal or postmenopausal conditions. Selective oestrogen therapy may be demonstrated using the standard procedure set out below:

a) an in vivo assay measuring the antioestrogenic activity of a compound and any oestrogenic activity possessed by that compound. This may be demonstrated in rats by the effect of the compound in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when each of a pure antioestrogen and oestradiol benzoate are administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate without the pure antioestrogen. Unlike the known antioestrogens tamoxifen and clomiphene, when a pure antioestrogen is administered alone to a rat no increase in uterine weight whatsoever is observed.

The oestrogenic activity of a compound may be demonstrated in rats by the effect of the compound when it is administered alone to said rat on the uterine weight of the animal.

b) An in vivo assay in mature rats measuring the antioestrogenic activity of a compound by the effect of the compound when dosed during a test period of 28 days in antagonising the protective effect on the animals' bone density of their endogenous oestrogens. The bone density of a group of ovariectomised rats in which endogenous oestrogen levels are much reduced serves as a control for the effect expected to be produced by a fully effective antioestrogen.

The antioestrogenic activity of the compound in mature rats can also be measured in the same assay by measuring the effect of the compound in antagonising the effect of the animals' endogenous oestrogens which serve to increase the weight of their uteri.

A comparison of the potencies of the antioestrogenic effects of a compound as measured by its effects on the animals' bone density and uterine weights allows the selectivity of the antioestrogenic effects of the compound to be measured.

Although the pharmacological properties of a product of the invention vary with the structures of the oestrogenic and antioestrogenic components and with the route of administration, in general a product of the invention comprises:

(i) an oestrogen which possesses oestrogenic activity in the above test (a) at doses in the range, for example, 0.002–2.0 mg/kg orally or in the range, for example, 0.0001–0.1 mg/kg subcutaneously;

(ii) a pure antioestrogen which possesses antioestrogenic activity in the above tests (a) and (b) at doses in the range, for example, in test (a): ED_{50} 0.05–5 mg/kg orally or ED_{50} 0.01–1.0 mg/kg subcutaneously; in test (b): antiuterotrophic effect: $ED_{50} < 20$ mg/kg/day orally, < 2 mg/kg/day subcutaneously or intramuscularly and < 10 mg/kg/injection when dosed as an intramuscular depot injection; reduction in bone density: $ED_{50} > 20$ mg/kg/day orally, > 5 mg/kg/day subcutaneously or intramuscularly and > 10 mg/kg/injection when dosed as an intramuscular depot injection.

A product of the invention is thereby seen to be surprisingly selective as the activity of the pure antioestrogen component is expressed to a high degree within uterine tissue but to a lesser degree on bone.

The size of the dose, for therapeutic or prophylatic purposes, of a product of the invention as defined above will naturally vary according to the nature and severity of the conditions presented, the age and menopausal state of the animal and the route of administration.

In general the minimum quantity of the oestrogenic component of a product of the invention as defined above will be chosen so as to provide a beneficial effect with regard to the nature and severity of the conditions presented. The quantity of the pure antioestrogenic component is then chosen to antagonise to a substantial degree the effect of the oestrogenic component on the uterine tissue. Methods of evaluating the condition of uterine tissue are well known to the man skilled in the art, for example, by examination of a specimen of endometrial tissue taken by, for example, suction or, for example, by way of a biopsy.

So far as the oestrogenic component of a product of the invention as defined above is concerned the size of the dose and routes of administration conventionally utilised in oestrogen replacement therapy may be used. Thus, for example, a tablet containing, for example, 0.5 to 2 mg of oestradiol, oestradiol benzoate, natural conjugated oestrogens or oestradiol valerate may be administered daily. Alternatively a tablet containing 10 to 100 μg of ethinyloestradiol may be administered daily. Alternatively the oestrogenic component may be administered by, for example, intramuscular injection utilising, for example, 1 to 10 mg of oestradiol benzoate dissolved in an oil such as ethyl oleate; for example, transdermal means utilising, for example, 10–100 μg of oestradiol contained within a transdermal patch; or, for example, vaginal application utilising, for example, daily application of 0.5 to 2 mg of natural conjugated oestrogens contained within 0.5 to 5 ml of a cream.

So far as the antioestrogenic component of a product of the invention as defined above is concerned the size of the dose is chosen such that the effect of the oestrogenic component on uterine tissue is antagonised to a substantial degree whereas the beneficial effect of the oestrogenic component on bone is substantially unopposed. Thus, for example, the antioestrogenic component may be formulated in like manner to the oestrogenic component, for example as a tablet, an oily solution suitable for intramuscular injection, within a transdermal patch, or within a cream suitable for vaginal application. The daily administration of one or more tablets containing conveniently 50 mg to 5 g, and preferably 50 mg to 500 mg, of a pure antioestrogen may be used. Preferably the pure antioestrogen may be administered by the periodic intramuscular injection of, for example, an aqueous suspension or an oily solution or suspension containing 50 mg to 5 g of the pure antioestrogen. Preferably an oily solution, for example a solution containing arachis or castor oil, an alcohol such as benzyl alcohol and 50 mg to 500 mg of the pure antioestrogen is employed. Such an injection provides a depot of the pure antioestrogen which thereafter leaches out from the injection site to provide a selective antioestrogenic effect for a period of, for example, one to six weeks.

As mentioned above a product of the invention is useful for selective oestrogen therapy of perimenopausal or postmenopausal conditions. As previously mentioned perimenopausal and postmenopausal conditions include, for example, vasomotor disturbances (hot flushes), urogenital atrophy (particularly affecting the vagina and the distal urethra), psychosomatic complaints, changes in the lipid metabolism and oesteoporosis. The selective antioestrogenic effect of the pure antioestrogenic component of a product of the invention, as demonstrated by a greater antioestrogenic effect on the uterus of a rat than on the bone of the rat, allows the beneficial effect of the oestrogenic component of the product of the invention to be selectively applied to the bone and prevents the detrimental effect of an unopposed oestrogenic effect on the uterus. The utero-selective effect of the pure antioestrogenic component of a product of the invention will allow the beneficial effect of the oestrogenic component of a product of the invention to be applied to other oestrogen-responsive tissues, for example those causing vasomotor disturbances, pyschosomatic complaints and changes in lipid metabolism.

The invention will now be illustrated in the following nonlimiting Examples.

EXAMPLE 1

Assay in Mature Rats of the Selective Antioestrogenic Activity of a Pure Antioestrogen

The pure antioestrogen used was (1RS,2RS)-2-p-hydroxyphenyl-2-methyl-1-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-1,2,3,4-tetrahydronaphth-6-ol.

The compound was given subcutaneously as a solution in arachis oil at doses of 2 mg/kg/day and 10 mg/kg/day to two groups of 5 mature rats for a total of 28 days. Further groups of 5 mature rats served as an untreated control group. A further group of 5 mature rats was ovariectomised to serve as another control group. At the end of the treatment period the weights of the uteri of the test and control groups of rats were determined. In addition the femurs were dissected, weighed and their volumes were determined using Archimedes Principle. The femurs were then burned and the residual ash was weighed. From these data, gross femur density and bone mineral density were calculated as follows:

Gross Femur Density = Femur Weight/Femur Volume

Bone Mineral Density = Femur Ash Weight/Femur Volume

The results shown below in Tables I and II demonstrate that at a dose of 2 mg/kg/day subcutaneously the test compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri (90% inhibition of uterine weight) whereas there was no significant inhibition of either bone mineral density or of gross femur density.

TABLE I

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	382 ± 34	
Ovariectomised Controls	111 ± 14	
Test Compound at 2 mg/kg/day s.c.	135 ± 8	91%
Untreated Controls	369 ± 47	
Ovariectomised Controls	99 ± 5	
Test Compound at 10 mg/kg/day s.c.	125 ± 4	90%

EXAMPLE 2

The experiment described in Example 1 was repeated except that the pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol. This compound was given at a series of doses as a daily intramuscular injection, the compound having been dissolved in a mixture of propylene glycol: ethanol: water: poloxamer 407. The formulation contained 25 mg of test compound, 100 mg of ethanol (96%), 100 mg of water, 20 mg of poloxamer 407 and sufficient propylene glycol to bring the solution to a volume of 1 ml.

The results shown below in Tables III and IV demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas there was no significant inhibition of gross femur density.

TABLE III

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	302 ± 36	
Ovariectomised Controls	70 ± 1.3	
Test Compound (mg/kg)		
0.1	208 ± 17	41
0.3	174 ± 16	55
1	94 ± 9	90
3	103 ± 2	86

TABLE IV

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Untreated Controls	1.523 ± 0.008	
Ovariectomised Controls	1.491 ± 0.006	
Test Compound at (mg/kg)		
0.1	1.528 ± 0.005	0%
0.3	1.528 ± 0.008	0%
1	1.532 ± 0.005	0%
3	1.533 ± 0.005	0%

EXAMPLE 3

The pure antioestrogen used was 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]oestra-1,3,5(10)-triene-3,17β-diol.

Each of a series of selected doses of this compound was dissolved in a mixture of castor oil and benzyl alcohol and given by intramuscular injection to a group of 5 mature rats. The formulation contained 50 mg of the test compound, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. In each case a second dose was administered two weeks after the first dose. Two weeks after the second dose the weights of the uteri of the test groups of rats were determined. In addition the femurs were dissected and analysed for Gross Femur Density as in Example 1.

A further group of rats, given two injections of castor oil separated by a two week period, served as an intact control group. A further group of rats was ovariectomised to serve as another control group.

The results shown below in Tables V and VI demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas at the two higher test doses there was no significant inhibition of gross femur density.

TABLE V

Treatment	Uterine Weight (mg)	Calculated Inhibition
Intact Controls	318 ± 31	
Ovariectomised Controls	76 ± 4	
Test Compound (mg/rat/dose)		
0.75	202 ± 23	48
1.25	180 ± 15	57
2.5	123 ± 12	81

TABLE VI

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Intact Controls	1.584 ± 0.007	
Ovariectomised Controls	1.521 ± 0.005	
Test Compound (mg/rat/dose)		
0.75	1.562 ± 0.004	35
1.25	1.576 ± 0.004	13*
2.5	1.569 ± 0.007	23*

*This level of inhibition was not statistically significant.

What we claim is:

1. A method of selective oestrogen therapy of perimenopausal or postmenopausal conditions which comprises administering to a warm-blooded animal an oestrogen and a pure antioestrogen, the oestrogen and pure antioestrogen being present in amounts such that the oestrogen is effective only in selected oestrogen-responsive tissues and is selectively opposed in other oestrogen-responsive tissues.

2. The method as claimed in claim 1 wherein the pure antioestrogen is

N-n-butyl-N-methyl-, N-1H,1H-heptafluorobutyl-N-methyl-or N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecanamide;

N-n-butyl- or N-1H,1H-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]phenylpropionamide;

7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)decyl]- or 7α-[10-(p-chlorobenzylsulphinyl)decyl]-oestra-1,3-5(10)-triene-3,17β-diol; or 7α-(9-n-heptylsulphinylnonyl-)oestra-1,3,5(10)-triene-3,17β-diol.

3. The method as claimed in claim 1 wherein the pure antioestrogen is a compound of the formula:

NU—A—X—R'

wherein NU is 6-hydroxy-2-p-hydroxyphenylnaphth-1-yl and A is $—(CH_{12})_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_5$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenylnaphth-1-yl (either 1RS,2RS or 1RS,2SR isomer), or 1,2,3,4-tetrahydro-6-hydroxy-2-p-hydroxyphenyl-2-methylnaphth-1-yl (either the 1RS,2RS or 1RS,2SR isomer), and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$;

or NU is (1RS,2RS)-5-hydroxy-2-p-hydroxyphenylindan-1-yl or (1RS,2RS)-5-hydroxy-2-p-hydroxyphenyl-2-methylindan-1-yl and A is $—(CH_2)_{10}—$, $—(CH_2)_{11}—$ or $—(CH_2)_4$-(1,4-phenylene)-$(CH_2)_2—$;

and wherein XR^1 is $—CONR^1R^2$ wherein R^2 is hydrogen or methyl and R^1 is n-butyl, 1H,1H-heptafluorobutyl, n-pentyl or n-hexyl, or XR^1 is $-SR^1$, SOR^1 or $-SO_2R^1$ wherein R^1 is n-pentyl, n-hexyl, 4,4,5,5,5-pentafluoropentyl or 1H,1H,2H,2H,3H,3H,-heptafluorohexyl.

4. The method as claimed in claim 1, wherein the oestrogen is oestradiol, oestradiol benzoate, oestradiol valerate or oestradiol undecanoate and the pure antioestrogen is 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)-nonyl]oestra-1,3,5(10)triene-3,17β-diol.

* * * * *

ATTACHMENT F - COMPILATION

TAB 4

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INJECTABLE DRUG DEVELOPMENT

TECHNIQUES TO REDUCE PAIN AND IRRITATION

Edited by

Pramod K. Gupta

and

Gayle A. Brazeau

Contents

B: Methods to Assess Pain, Irritation, and Muscle Damage Following Injections

11

Cosolvent Use in Injectable Formulations

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Formulators today must routinely deal with progressively more water-insoluble compounds. This makes developing solution dosage forms particularly challenging. Identification and utilization of clinically acceptable excipients—as well as scalable methods to formulate solubilized compounds—has been, and continues to be, a subject of great importance to formulation scientists.

One of the most common approaches used in parenteral formulation of water-insoluble compounds is the use of organic cosolvent systems. These systems utilize certain organic solvents combined with physiologically compatible aqueous solutions. These systems are primarily used to provide higher solubility for poorly water-soluble compounds, which allows for these compounds to be administered in solution form. The ability to administer compounds in solution form by the parenteral route eliminates particle size considerations and dissolution barriers, generally providing for complete bioavailability of poorly absorbed and/or highly metabolized compounds by avoiding hepatic first-pass effects. Cosolvents may also be used to improve the chemical stability of compounds prone to hydrolytic or photolytic degradation, or occasionally to decrease the aqueous solubility of a given compound when administered intramuscularly. There are numerous products on the market for parenteral use that utilize cosolvent systems. Table 11.1 lists a number of these products with their cosolvent compositions (Trissel 1996).

Table 11.1. Cosolvent Composition of Selected Marketed and Investigational Parenteral Products (Trissel 1996)

General Name	Trade Name	Manufacturer	Route	Cosolvent Composition
Digoxin	Lanoxin®	Burroughs Wellcome	IM, IV	40% PG, 10% EtOH, pH 6.8
Trimethoprim-sulfamethoxazole	Septra®	Glaxo Wellcome	IV	40% PG, 10% EtOH, 0.3% diethanolamine, 1% BA
Phenytoin	Dilantin®	Parke-Davis	IV	40% PG, 10% EtOH, pH 12
Diazepam	Valium®	Roche	IM, IV	40% PG, 10% EtOH, 1.5% BA
Lorazepam	Ativan®	Wyeth-Ayerst	IV	41% PG, 9% PEG 400, 2% BA
Pentobarbital	Nembutal®	Abbott	IV	40% PG, 10% EtOH, pH 9.5
Chlordiazepoxide HCl	Librium®	Roche	IM	20% PG, 1.5% BA
Etoposide	VePesid®	Bristol-Myers Squibb	IV	65% PG, 30.5% EtOH, 8% Tween 80®, 3% BA
Miconazole	Monistat®	Janssen	IV	11.5% Cremophor® EL
Secobarbital sodium	Tubex® cartridge	Wyeth-Ayerst	IM, IV	50% PEG, pH 9.5-10.5
Nitroglycerin	Nitro-Bid®	Hoechst Marion Roussel, Abbott	IV	70% EtOH, 4.5% PG
Multivitamins	M.V.I.®-12	Astra	IV	30% PG, 1.6% Tween 80®, 0.028% Tween 20®
Investigational Compounds				
9-Amino-camptothecin			IV	2% DMA, 50% PEG 400
Bryostatin			IV	60% PEG 400, 30% dehydrated alcohol, 10% Tween 80®
Diaziqoune			IV	10% DMA, pH 6.5

Abbreviations: IV: Intravenous; IM: Intramuscular; PG: propylene glycol; PEG: polyethylene glycol; EtOH: ethanol; BA: benzyl alcohol; DMA: dimethylacetamide

In terms of solubility enhancement, the use of cosolvents is one of the most powerful methods available to formulators. The solubilizing potential of cosolvents compares very favorably to other generally accepted techniques used for solubilization of water-insoluble compounds, including micellar solubilization, complexation, prodrugs, and salt formation. In many instances, cosolvents may be the technique of choice for parenteral applications given that (1) micellarization using surface active agents could likely be problematic from an irritation/toxicity perspective, (2) suitable complexing agents may not be appropriate for the compound of interest, (3) formation of either prodrugs or salt forms may not be possible for a given compound, and (4) appropriate cosolvent vehicle selection may reduce tissue irritation.

Numerous factors must be considered before a cosolvent system is selected. Ideally, the water-miscible organic solvent must be nontoxic; should cause minimal or no hemolysis, irritation, or muscle damage on injection; and should be nonsensitizing. The solvent should also be devoid of any inherent pharmacological activity that may interfere with that of the drug itself. Obviously, the cosolvent formulation should provide the desired pharmaceutical/biopharmaceutical profiles and should allow for a reasonable shelf life following manufacture. These solvents are rarely used undiluted due in part to their inherent properties, for example, viscosity and tonicity. Therefore, the physicochemical properties of the cosolvent system must also be considered (viscosity, pH, lipophilicity), as well as the safety of the various solvents used. A summary of some of the physicochemical properties of common solvents used in parenteral formulations is given in Table 11.2.

Ideally, it is best to select and use solvents that would maximize the solubility of the compound. Maximizing the solubility of a compound in a particular cosolvent system would result in lower total levels of the nonaqueous solvent(s) being administered to the patient, thereby lowering the chance for potential side effects. This will also reduce the chance of precipitation of the solution on administration, which is a major concern when administering doses via the IV route. There are numerous reports in the literature regarding cosolvency theory, and potentially useful methods based on various physicochemical properties for predicting solubilities in various solvents and solvent mixtures, as well as the effects of cosolvent systems on the physicochemical properties of compounds solubilized in them (Hildebrand 1916, 1917, 1919; Hildebrand and Scott 1950; Higuchi et al. 1953; E monson and Goyan 1958; Moore 1958; Paruta et al. 1962, 1964; Gorman Hall 1964; Fedors 1974; Martin et al. 1980, 1982; Yalkowsky et al. 1976 tin and Miralles 1982; Yalkowsky and Roseman 1981; Rub Yalkowsky 1985, 1987; Yalkowsky and Rubino 1985; Rubino et al bino 1987, 1990; Rubino and Berryhill 1986; Rajagopalan et a son et al. 1993; Bendas et al. 1995; Darwish and Bloomfield 1995;

Table 11.2. Physicochemical Parameters for Commonly Used Organic Solvents (at 25°C)

Solvent	Molecular Weight (g)	Dielectric Constant, ε	Solubility Parameter, δ (cal/cm^3)	Density (g/mL)	Boiling Point (°C)	Interfacial Tension (dyne/cm)
DMF	73	36.7[a]	12.1[a]	0.94[b]	153[b]	6.9[a]
DMA	87	37.8[a]	10.8[a]	0.94[b]	165[b]	4.6[a]
PEG 400	380–420	13.6[a]	11.3[a]	1.13[c]	—	11.7[a]
EtOH	46	24.3[a]	12.7[a]	0.79[b]	78.5[b]	0.5[a]
PG	76	32.0[a](20°)	12.6[a]	1.04[b]	189[b]	12.4[a]
Benzyl alcohol	108	13.1[d]	—	1.04[b]	204.7[b]	—
Glycerin	92	42.5[a]	17.7[a]	1.26[b]	290[b] (dec)	32.7[a]
Water	18	78.5[a]	23.4[a]	1.00[b]	100[b]	45.6[a]
DMSO	78	46.7[a]	—	1.10[a]	189[a]	—

Dec: decomposition
a: Rubino and Yalkowsky (1987)
b: Budavari (1989)
c: Wade and Weller (1994)
d: Weast and Tuve (1967)

al. 1995). Therefore, this chapter focuses more on the conventional solvents and use levels encountered in parenteral dosage forms, safety/toxicity of these cosolvents, and ways in which to minimize cosolvent-related side effects.

Commonly Used Solvents

There are numerous solubilizing agents available to formulators, particularly for use in preclinical work. However, the solubilizers available to formulators for use in humans are considerably more limited, usually on the basis of available safety/toxicity data. The most common organic solvents encountered in cosolvent systems for human clinical/commercial use include PEG 400, PG, glycerol, and ethanol. In general, these solvents are considered to possess a low order of toxicity. This is essential, and obvious, since parenteral administration can result in fairly large amounts of these solvents being placed in the body over a short period of time.

Although the solvents used in cosolvent formulations are generally considered to be of low orders of toxicity, there have been numerous reports of adverse effects related to the vehicles themselves (Carpenter 1947;

Wang and Kowal 1980; Singh et al. 1982; Smith and Dodd 1982; American Academy of Pediatrics Committee on Drugs 1985; Demey et al. 1988; Golightly et al. 1988; Lolin et al. 1988; Andersen et al. 1989; Napke and Stevens 1990; Doenicke et al. 1992; Rhodes et al. 1993; Windebank et al. 1994; Farooqui et al. 1995). These adverse effects may result from administration of high doses of a single cosolvent formulation or concurrent administration of different formulations that contain similar cosolvent systems. It is important to note that any side effects associated with these usually well-tolerated solvent systems may be much more serious when administered to pediatric patients (Sweet 1958; Martin and Finberg 1970; Brown et al. 1982; Gershanik et al. 1982, Lorch et al. 1985; MacDonald et al. 1987; Huggon et al. 1990). Summaries of single dose LD_{50} values and reported human exposures for organic solvents commonly used in parenteral formulations are presented in Tables 11.3 and 11.4. It has been suggested that these solvents should be used at levels of no more than 25 percent of the LD_{50} value in order to avoid any unwanted pharmacological or toxicological effects, although they may be used at considerably higher concentrations depending on the purpose of the study (Bartsch et al. 1976). Others recommend that certain organic solvents should not be used in pharmacological or toxicological studies at concentrations above 10 percent (Singh et al. 1982). The following discussion addresses the reported safety/toxicity data reported in the literature for many of the solvents used in parenteral formulations.

Polyethylene Glycols

PEGs are polymers of ethylene oxide with the general formula

$$HO\text{-}CH_2\text{-}(CH_2\text{-}O\text{-}CH_2)_n\text{-}CH_2OH$$

where *n* represents the number of oxyethylene groups. The PEGs are designated by a numerical value, which is indicative of the average molecular weight for a given grade. Molecular weights below 600 are liquids, and molecular weights above 1,000 are solids at room temperature. These polymers are readily soluble in water, which make them quite useful for parenteral dosage forms. Only PEG 400 and PEG 300 are utilized in parenteral products, typically at concentrations up to 30 percent (v/v) (Wade and Weller 1994). These polymers are generally regarded as nontoxic and nonirritating. There are numerous reviews regarding the pharmaceutical and toxicological properties of these polyols (Smyth et al. 1950; Rowe and Wolf 1982).

PEGs have been shown to possess marked central nervous system (CNS) effects following IV administration (Lockard and Levy 1978; Lockard et al. 1979). Klugmann and coworkers (1984) found that pretreatment of mice with 15 percent PEG 400 at 20 mL/kg given three hours prior to the

Table 11.3. Single Dose LD_{50} Values in Rodents for Various Organic Solvents Commonly Encountered in Parenteral Formulations

	Parenteral LD_{50} Values (g/kg) for Various Species						
	Mouse			Rat			References
Solvent	ip	sc	iv	ip	sc	iv	
PEG 300				17		7.1	Rowe and Wolf (1982); Carpenter and Shaffer (1952)
PEG 400	13.2–14.5		8.6	12.3–14.7		4.7–7.3	Budden et al. (1978); Rowe and Wolf (1982); Bartsch et al. (1976)
PG	9.6–11.4	18.5	6.6–8.0	6.7–13.5		6.4–6.8	Davis and Jenner (1959); Bartsch et al. (1976); Latven and Molitor (1939)
EtOH	1.2–3.2	8.3–10.5	2.0–2.5	4.1–5.0		1.4–1.8	Latven and Molitor (1939); Bartsch et al. (1976); Trèmolières and Lowy (1964)
Glycerin	8.7–9.0	0.09–10.0	4.3–6.2	8.7	0.10	5.6	Budden et al. (1978); Latven et al. (1939); Anderson et al. (1950); Bartsch et al (1976); Tao et al. (1983)
DMA	2.3–3.5		2.5–3.0	2.8–4.4	5.3	2.6–4.8	Davis and Jenner (1959); Sherman et al. (1978), Bartsch et al. (1976); Auclair and Hameau (1964); Wiles and Narcisse (1971); Thiersch (1962)
DMF	1.2–5.9		2.8–3.5	4.4–6.1	6.1	2.8–5.7	Davis and Jenner (1959); Bartsch et al. (1976); Auclair and Hameau (1964); Wiles and Narcisse (1964); Theirsch (1962)
Cremophor® EL			2.6-4.2				BASF (1988)
DMSO	2.5–13.9		3.4–7.6	8.2–10.1		5.4–8.1	Bartsch et al (1976); Wiles and Narcisse (1971); Willson et al. (1965)
BA	1.0		< 0.52			0.05–0.08	McCloskey et al. (1986);
0.9%			> 52			> 41.6	Kimura et al (1971)

Table 11.4. Human Exposures to Selected Organic Solvents Commonly Encountered in Parenteral Formulations

Solvent	Dose	Route	Administered As	Clinical Observations	References
DMSO	1 gm/kg	IV	10 to 40% solutions	Hemoglobinuria observed following administration of 20–40% solutions, which cleared within 2–3 h post-	

Table 11.4. Human Exposures to Selected Organic Solvents Commonly Encountered in Parenteral Formulations

Solvent	Dose	Route	Administered As	Clinical Observations	References
DMSO	1 gm/kg	IV	10 to 40% solutions	Hemoglobinuria observed following administration of 20–40% solutions, which cleared within 2–3 h post-infusion; No indication of short-term nephrotoxicity following evaluation of beta-2-microglobulin.	Bennett and Muther (1981)
DMA	100–610 mg/kg/day for 2–5 days	IV	10% solution administered over 5 to 10 min	Dose-related side effects included nausea and vomiting within 14 h of administration, anorexia; liver toxicity as indicated by increased SGOT levels (5–7 days after start of therapy), returning to normal within 2–5 days after achieving peak levels; altered CNS function—depression, lethargy, confusion, hallucinations—returning to normal within several days after therapy; hypotension and high fever observed at high doses.	Weiss et al. (1962)
Cremophor® EL	2–20 mL	IV	Incremental doses administered every 4 min, each over a 30 sec period	Small transient fall in blood pressure and rise in pulse rate following each dose. No marked changes in respiratory rate and no consistent alterations in central venous pressure observed. Statistically significant effects only observed after the 20 mL dose.	Savege et al. (1973)
PG	5–21 g/day	IV	Administered as an infusion over a 4 h period	No alterations in plasma osmolality, free hemoglobin, or haptoglobin.	Speth et al. (1987)
BA	130–405 mg/kg/day	IV	0.9% BA (bacteriostatic concentration)	*Neonates:* Progressive metabolic acidosis, bradycardia, gasping respirations, seizures, and subsequent death in low birth weight neonates. *Adults:* No clinically significant changes observed in healthy males (hematology, vital signs, electrocardiograms, EEG, laboratory parameters), shown to be as well tolerated as same formulation preserved with parabens.	Brown et al. (1982); Santiero (1989); Evens (1975); Gershanik (1982); Novak et al. (1972)

administration of adriamycin (a potent antineoplastic agent) resulted in alleviation of some of the toxicity associated with the compound. They also showed that PEG 400 decreased both the acute high-dose and chronic low-dose adriamycin-associated lethality, as well as afforded protection against cardiomyopathy—one of the dose-limiting side effects observed in patients. Additionally, PEG 400 did not interfere with the antitumor activity of the compound. Laine et al. (1995) reported nephrotoxicity due to PEG 400 secondary to chronic high-dose intravenous administration of lorazepam.

PEG 300, PEG 400, and PEG 4000 administered intraperitoneally have been shown to have adverse effects on rat gastrointestinal physiology (Cho et al. 1992). The PEGs caused a decrease in gastric mucosal blood flow (GMBF) as well as gastric secretory function. They also exacerbated ethanol-induced gastric damage in a dose-dependent manner. The gastric damage appeared to be inversely related to molecular weight (PEG 300 > PEG 400 > PEG 4000). Other investigators have shown that the PEGs affect cardiovascular and autonomic systems. PEG 300, PEG 400, and PEG 600 administered intravenously and intra-arterially to dogs produced a dose-dependent enhancement of the blood pressure response to epinephrine and acetylcholine (Heilman et al. 1972). PEG 300 has also been implicated as the causative agent responsible for fatalities and near fatalities due to severe metabolic acidosis in patients (Sweet 1958).

Smith and Cadwallader (1967) evaluated the behavior of erythrocytes in PEG–water solutions. They observed that solutions of PEG 300 in water were hemolytic. They also observed that solutions of water–PEG 400 or water–PEG 600 could afford some protection from hemolysis. They concluded that polyethylene glycols could protect both rabbit and human erythrocytes in the order (MW): 200 < 300 < 400 < 600. The ability of the PEGs to contribute to the tonicity of the resulting solutions was also observed to be inversely related to molecular weight—low molecular weight PEGs contributed to tonicity, and the higher molecular weight species did not. They suggested that this lack of contribution to tonicity was related to decreased membrane permeability of the higher molecular weight species.

Nishio and coworkers (1982) investigated the effects of PEG 300 and PEG 400 on erythrocytes. They showed that incubation of erythrocyte suspensions in the presence of PEG–saline solutions resulted in the release of potassium ions and hemoglobin. They found that hemolysis and potassium ion loss decreased with increasing concentrations of PEGs, and that no loss was observed in iso-osmotic and hyperosmotic concentrations following a 2 min incubation time. However, longer incubation times (through 2 h) resulted in potassium loss and hemolysis in iso-osmotic and hyperosmotic solutions (PEG 300 > PEG 400).

Fort and coworkers (1984) evaluated the hemolytic potentials of mixtures of ethanol and water or saline with PEG 400 by both in vitro and in vivo methods. They showed that a PEG 400:ethanol:water mixture of 3:2:5 resulted in no hematuria in vivo in rats, while partial hemolysis was

observed in vitro using dog blood. All other mixtures resulted in hematuria and hemolysis. Reed and Yalkowsky (1985) reported that the in vitro hemolytic LD_{50} value (total volume percent cosolvent required to produce 50 percent hemolysis of healthy erythrocytes) for PEG 400 was 30.0 (total volume percent). This indicated that red blood cells were relatively tolerant of PEG 400.

Propylene Glycol

PG, a dihydroxy alcohol, is one of the more common solvents encountered in pharmaceutical cosolvent formulations, for both parenteral and nonparenteral dosage forms. PG is generally regarded as nontoxic. It is more hygroscopic than glycerin and has excellent solubilizing power for a wide variety of compounds. In addition, it has excellent bacteriocidal and preservative properties (Heine et al. 1950).

PG is metabolized to carbon dioxide and water via lactic and pyruvic acid intermediates; therefore, it is not prone to the severe toxicities associated with the use of other glycols, such as ethylene glycol (Huff 1961; Lehman and Newman 1937a, b). It is approximately one-third as intoxicating as ethanol (Seidenfeld and Hanzlik 1932). It is a generally recognized as safe (GRAS) listed material (*Federal Register* 1982). The World Health Organization (WHO) has established an acceptable daily intake (ADI) at 25 mg/kg body weight (FAO/WHO 1974).

When used in large concentrations, PG has been associated with marked hyperosmolality (Bekeris et al. 1979; Glasgow et al. 1983; Flinger et al. 1985); metabolic acidosis due to the formation of lactic acid (Kelner and Bailey 1985; Pesola et al. 1990); CNS depression (Arulanatham and Genel 1978; Lolin et al. 1988); intoxication (Cate and Hendrick 1980; Demey et al. 1984); augmentation of muscle twitch induced by benzodiazepines (Driessen et al. 1985); contact dermatitis in sensitive individuals (Fisher 1995); cerebral ischemia (Drummond et al. 1995); renal compromise (Levy et al. 1995); and cardiovascular side effects, including hypotension, bradycardia, atrial and ventricular conduction abnormalities (Gross et al. 1979), as well as allergic reactions leading to hypersensitivity myocardltis. These complications can be particularly serious in infants. Other investigators have suggested that the main toxic effect of PG is depression of the CNS (Martin and Finberg 1970; Zarolinski et al. 1971). Additionally, there have been numerous reported side effects following nitroglycerin (Hill et al. 1981; Col et al. 1985; Demey et al. 1988) and etomidate therapies (Morgan et al. 1977; Doenicke et al. 1982; Fellows et al. 1983; Bedichek and Kirschbaum 1991; Doenicke et al 1994; Moon 1994; Levy et al. 1995; Van de Wiele et al. 1995).

There are numerous reports regarding the use of PG based on safety/toxicity data (Seidenfeld and Hanzlik 1932; Braun and Cartland 1936;

Weatherby and Haag 1938; Morris et al. 1942; Dominguez-Gil and Cadorniga 1971a, b; Zarolinski et al. 1971; Ruddick 1972). Seidenfeld and Hanzlik (1932) reported single fatal doses of PG administered intramuscularly and intravenously to rats and rabbits. No symptoms were reported in rats and rabbits until IM doses exceeded 6.3 to 7.4 g/kg. Increased respiratory rate, loss of equilibrium, depression, and subsequent coma and death were observed. IM fatal doses were 14 g/kg and 7 g/kg in rats and rabbits, respectively. IV fatal doses were 16 g/kg and 5 g/kg in rats and rabbits, respectively. Braun and Cartland (1936) indicated that the minimum fatal IV dose to rats was 18.9 g/kg. They also noted that administration of undiluted PG destroyed the veins, making subsequent administration very difficult, and that PG was better tolerated than glycerol by IM and subcutaneous (SC) routes. There are numerous reports of convulsions following intraperitoneal (IP) administration in mice (Lampe and Easterday 1953; Braun and Cartland 1936).

The hemolytic potential of PG has been well documented by numerous investigators (Weatherby and Haag 1938; Randolph and Mallery 1944; Potter 1958; Brittain and D'Arcy 1962). Weatherby and Haag (1938) evaluated hemolysis of various PG–saline mixtures using an in vitro method. They observed hemolysis in cases where the PG concentration was greater than or equal to 0.14 M. They believed that PG permeated the erythrocytes so rapidly that it did not exert an appreciable osmotic effect on the cell. Brittain and D'Arcy (1962) later evaluated hematologic effects following IV administration of PG to rabbits. The rabbits were given a single dose of 4 mL/kg of either 12.5, 25, or 50 percent PG in normal saline via the marginal vein. They observed no effect on red blood cell count, total white cell count, or hemoglobin concentration. However, they observed a marked decrease in clotting times with an associated increase in platelet count. They also reported no effect of the PG concentrations on fragility of the red blood cell membranes. Fort and coworkers (1984) evaluated hemolysis due to PG–containing formulations by both in vitro (using dog blood) and in vivo (rats) methods. The compositions evaluated ranged from 10 to 60 percent PG, 0 to 40 percent ethanol diluted with either water or 0.9 percent NaCl. All of these formulations caused hemolysis in vitro. However, only the 1:3:6 PG:ethanol:saline mixture resulted in no hematuria when administered to rats, while all other compositions caused hematuria. Reed and Yalkowsky (1985) determined the in vitro red blood cell hemolytic LD_{50} for PG to be 5.7, which indicated that it was fairly hemolytic relative to the other solvents tested. Only glycerin and DMSO were found to be more hemolytic than PG by this method.

There has been some work conducted in humans evaluating hemolysis following administration of PG–containing solutions. In the work by Speth and coworkers (1987) evaluating the pharmacokinetics of PG in humans, they reported no alterations in plasma osmolality, free hemoglobin or haptoglobin following IV infusion (4 hour) of total PG levels ranging

from 5.1 to 21.0 g/day, with C_{max} values up to 425 μg/mL. They found that PG exhibited nonlinear pharmacokinetics and that clearance was dose and concentration dependent (saturable) in the dose range of 3 to 15 g/m^2, with a mean elimination half-life of 2.3 hours. There were no signs of metabolic acidosis or changes in osmolality in these patients, even though the plasma levels were in the range where these effects had been previously reported. The absence of effects could have been due to the slow rate of administration, or to the presence of additional excipients in the formulation (soybean lecithin, 0.5 mg/mL; PEG 300, 75 mg/mL; and PG, 25 mg/mL).

Ethanol

Ethanol (EtOH) is typically used as a solvent in pharmaceutical applications; however, it also possesses some antimicrobial properties. Parenteral products typically use 95 percent or 96 percent rather than absolute alcohol at use levels up to 50 percent. However, these levels typically are associated with pain on injection. EtOH is a component of commercial parenteral formulations for such compounds as diazepam, phenytoin, and digoxin. However, parenteral administration of EtOH-containing formulations has been associated with various complications. Such cases have been reported with IV administration of nitroglycerin (Shook et al. 1984). Intoxication was observed in several elderly patients receiving high doses of IV nitroglycerin. These patients received up to 20.7 mL EtOH/h during their course of therapy, which exceeded the average adult rate of EtOH metabolism of 10 mL/h (Hill et al. 1981). These effects would likely be more pronounced in patients with compromised hepatic function and myocardial ischemia or low cardiac output. Others reported that rapid infusion of EtOH may be cardiotoxic, in that it possesses both atrial and ventricular arrhythmogenic properties, as well as negative inotropic effects (Ahmed et al. 1973; Delgado et al. 1975; Child et al. 1979).

The toxicity of EtOH has been well documented (Lehman 1937b; MacGregor et al. 1964; Maling 1970; Wiberg et al. 1970). It is fairly toxic when administered intraperitoneally. Heistand (1952) reported that mortality increased with increasing concentrations of ethanol injected intraperitoneally when the amount of alcohol was held constant. Wiberg et al. (1970) showed that high concentrations of EtOH (20 percent w/v) produced a fatal chemical peritonitis. Maling (1970) determined the IV LD_{50} to be 2.0 g/kg and 4.2 g/kg in mice and rats, respectively. The LD_{50} following subcutaneous administration to mice was determined to be 8.3 g/kg. Lethal doses in dogs following subcutaneous and IV administration were found to be 6.0 to 8.0 g/kg and 5.4 g/kg, respectively. A comprehensive list of effects of EtOH as a function of blood level in humans is also listed.

EtOH is a well-known CNS depressant. The result of ingestion is intoxication, with associated loss of muscle coordination, slurred speech, or

more severe effects including lethargy, stupor, coma, respiratory depression, and possibly death. These same effects have been observed following IV administration. There are also reports of fatalities in neonates and children following IV administration of ethanol (Gettler and St. George 1935; Jung et al. 1980).

Fort et al. (1984) evaluated hemolysis due to various EtOH–containing concentrations ranging from 30 to 40 percent diluted in either water or 0.9 percent NaCl. They found that all mixtures caused hemolysis in vitro; however, the 3:7 EtOH:0.9 percent NaCl caused no hematuria in vivo. Reed and Yalkowsky (1985) determined the in vitro hemolytic LD_{50} to be 21.2 (total volume percent) for EtOH, indicating that it was fairly well tolerated by erythrocytes.

Glycerin

Glycerin (glycerol) is one of the oldest and most widely used excipients in pharmaceutical products. It is a clear, colorless liquid that is miscible with water and alcohol. Glycerol is hygroscopic, stable to mild acidic and basic environments, and can be sterilized at temperatures up to 150°C. It is well known as both a taste masking and cryoprotective agent, and as an antimicrobial agent. It has good solubilizing power and is a commonly used solvent in parenteral formulations. It is considered to be one of the safest excipients used since it is metabolized to glucose or to substances that are involved with triglyceride synthesis or glycolysis (Frank et al. 1981). It is a GRAS–listed excipient and is typically used at levels of up to 50 percent in parenteral formulations (Wade and Weller 1994).

Glycerol is a naturally existing sugar alcohol that is endogenous to humans. It is broken down to triglycerides, glucose by the gluconeogenesis pathways or to pyruvate by the glycolytic pathway. It has also been used in parenteral formulations as an energy source (Fairfull-Smith et al. 1982; Jones 1982; Tao et al. 1983). Glycerol has been used clinically to treat Reye's syndrome (Mickell et al. 1977), traumatic intracranial hypertension (Wald and McLaurin 1982), brain edema in stroke patients (Tourellotte et al. 1972; Macdonald and Uden 1982), reduce intraocular pressure in cataract surgery (Guindon et al. 1981), and improve hearing loss associated with Meniere's disease (Angleborg et al. 1982; Lunsford 1982).

Somewhat surprisingly, there are numerous reports of adverse effects following administration of this endogenous substance, including hemolysis, hemoglobinuria, renal damage, hyperglycemia, hyperosmolality, and convulsions. A fairly extensive review of adverse reactions resulting from IV administration of glycerol is given by Frank et al. (1981). There are reports that glycerol is approximately 20 times more toxic when administered intraperitoneally or subcutaneously, as compared to the IV route (Tao et al. 1983). However, some of this sensitivity to IP administration may be related to strain differences (Uche et al. 1987).

Patients with acute cerebral infarction received 10 percent glycerol solutions administered daily for 7 to 10 days over a 6 h period (Welch et al. 1974). In these reports, there were no reported side effects even with prolonged administration, with the exception of "transient hemoglobinuria" in cases where the glycerol content of the solutions was 30 percent or greater. However, side effects, including hematuria, hemoglobinuria, and hemolysis have been reported by other physicians (Cameron and Finchk 1956; Potter 1958; MacCannel 1969; Hagnevik et al. 1974). Hagnevik and coworkers (1974) reported that administration of 20 percent glycerol in normal saline to three patients during intracranial surgery resulted in either (1) no effect; (2) massive hemolysis and hemoglobinuria that dissipated quickly; or (3) severe hemolysis and hemoglobinuria, as well as serious renal damage. However, the rates of administration that resulted in these side effects were more rapid—60 g/15 min, 70 g/30 min, and 80 g/60 min—than those used previously (wherein the dose was infused over 6 h). The resulting hemolytic side effects were most likely due to the rapid rate of administration.

Early studies by Smith (1950) reported that glycerol did not have a direct toxic effect on erythrocytes, which seems reasonable since it is used as a cryoprotectant to prevent hemolysis during freeze-thaw studies. These studies showed that no hemolysis resulted from diluting blood with 30 percent glycerol in Ringer's solution (1:1 ratio), followed by freezing at -70°C. No hemolysis was reported for up to 8 weeks. The same results were obtained when the glycerol solution was prepared in normal saline. It should be noted that the absence of hemolysis could have been in part due to the presence of the various salt solutions.

However, glycerol is known to permeate red blood cells rapidly, causing fluid influx and subsequent hemolysis (Tourtellotte et al. 1972). Early work by Husa and Adams (1944) showed that glycerol was hemolytic even at iso-osmotic concentrations, and that the addition of NaCl reduced its hemolytic potential. Similar findings were observed by other investigators (Hammarlund and Pedersen-Bjergaard 1961; Zanowiak and Husa 1959). Cadwallader and coworkers (1963, 1964) calculated the isotonic coefficients for glycerin solutions and showed that the addition of increasing amounts of NaCl afforded some protection from hemolysis, again indicating that the degree of hemolysis resulting from IV administration was dependent on the tonicity of the glycerol-saline solutions. Reed and Yalkowsky (1985) reported that glycerol was the most hemolytic of the 15 organic solvents evaluated, with a hemolytic LD_{50} value of 3.7 (total volume percent).

Cremophors

The cremophors are water soluble polyoxyethylene derivatives of castor oil that are nonionic surface-active agents. Several grades are used in pharmaceutical formulations, particularly Cremophor® EL (Polyoxyl 35 castor oil) and Cremophor® RH40 (Polyoxyl 40 hydrogenated castor oil).

However, Cremophor® EL is the grade used for parenteral applications in humans. These substances are mixtures of hydrophilic and hydrophobic components, composed primarily of ricinoleic acid esters and fatty acid esters of glycerol/polyglycol and polyglycols. The main component of Cremophor® EL is glycerol–polyethylene glycol ricinoleate. Cremophor® EL is a pale yellow, oily liquid that forms clear solutions when mixed with water. It is also readily soluble in water-alcohol mixtures. It can be heat sterilized at a temperature of 120°C for 30 min, but it may be prone to hydrolysis if heated in the presence of strong acid or basic substances (BASF 1988).

The most common adverse effect reported following administration of cremophor-containing formulations are severe reactions related to histamine release. The cremophors have been implicated in anaphylactoid reactions, typically following rapid IV injections (Dye and Watkins 1980; Hopkins 1988; Reynolds and Aronson 1992; Dorr 1994). Hopkins (1988) and Reynolds and Aronson (1992) reported anaphylactoid responses following IV administration of vitamin K in a cremophor solution. However, Havel et al. (1987) reported that this formulation was well tolerated in patients. Patients treated with miconazole preparations containing cremophors have also presented unusual serum lipoprotein patterns, hypercholesterolemia, and hypertriglyceridemia (Golightly et al. 1988). There are numerous reports in the literature relating to anaphylactic reactions following administration of althesin and propanidid (Watkins 1979; Watkins et al. 1976, 1978; Forrest et al. 1977; Dye and Watkins 1980). Windebank and coworkers (1994) reported that cremophor was a potential neurotoxic agent since a total dose 0.1 percent (v/v) produced axonal swelling and degeneration of dorsal root ganglion neurons, and 0.001% (v/v) produced demyelination in vitro.

Earlier studies in dogs showed that Cremophor® EL caused histamine-like responses accompanied by marked hypotension in dogs. Studies were subsequently conducted to evaluate whether these cardiorespiratory effects occurred in normal human volunteers following IV administration of Cremophor® EL (Savege et al. 1973). Subjects were given incremental dose volumes ranging from 2 to 20 mL (administered every 4 min, each over a 30 sec period). Following administration of each dose of Cremophor® EL, there was a small, transient reduction in blood pressure and a rise in pulse rate. However, none of these changes were statistically significant, with the exception of the high dose (20 mL). These studies showed no marked change in respiratory rate or pattern and no consistent alterations in central venous pressure.

Benzyl Alcohol

Benzyl alcohol (BA) is a bacteriostatic agent used against gram-positive bacteria, yeasts, molds and fungi, and it is commonly used as a preservative in parenteral products. It also has anesthetic properties at levels of

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approximately 1 percent. The bacteriostatic activity is reduced in the presence of nonionic surface-active agents. It also has good solubilizing power, and is typically used in concentrations up to 2 percent as a preservative and up to 5 percent as a solvent. BA is commonly found as a preservative in intravascular flush solutions at a level of 0.9 percent. The WHO has established an ADI of 5 mg/kg (FAO/WHO 1980).

BA is metabolized in the body to benzaldehyde via alcohol dehydrogenase and subsequently to benzoic acid via aldehyde dehydrogenase. However, the reported toxicities, particularly acute toxicity, appeared to be associated with the parent compound and not the metabolite. Studies using the enzyme inhibitors pyrazole (alcohol dehydrogenase inhibitor) and disulfiram (aldehyde dehydrogenase inhibitor) showed that marked lethality was observed with increased plasma levels of BA, and not with benzaldehyde levels (McCloskey et al. 1986). These elimination pathways are saturable, indicating that additional amounts of BA would likely result in significantly higher plasma levels once the metabolic capacity has been exceeded.

Toxicity studies in adult and neonatal mice were conducted following IP administration of single doses of BA ranging from 500 to 1500 mg/kg administered in maximum dose volumes of 0.28 mL and 0.07 mL for adult and neonates, respectively (McCloskey et al. 1986). The data showed that the acute LD_{50} for BA was 1,000 mg/kg for both adult and neonatal groups after 4 h. However, deaths were observed in the adult group at day seven, resulting in a revised LD_{50} value of 650 mg/kg.

Macht (1920) reported on the toxicity of intravenously administered alcohols to cats. He reported that BA was approximately 8 times more toxic than ethanol, with lethal doses of 5.0 mL/kg and 0.6 mL/kg, respectively. Kimura et al. (1971) investigated the parenteral toxicity data for BA, finding that a 0.9 percent solution was quite safe following administration of 1 mL/kg to dogs and monkeys. They found no changes in complete blood counts or blood chemistry values. They also reported that rapid IV injections of 0.9 percent BA could be safely given to mice to a maximum volume of 50 mL/kg. Kimura et al. (1971) reported that BA was significantly more toxic than ethanol when administered at the same doses to mice, rats, and dogs.

Most of the early studies evaluating the toxicity of BA indicated that it was a relatively harmless substance with regard to humans. However, numerous incidences of BA toxicity following parenteral administration of solutions containing levels of only 0.9 percent have subsequently been reported in the literature. Reported toxicities of BA include hypersensitivity reactions, hemolysis, sedation, dyspnea, loss of motor function, and possible death. Toxicity has been reported following exposure to catheter flush solutions containing very low levels of BA (0.9 percent). However, the most severe toxic effects, including death, have occurred in neonates (Gershanik et al. 1982; Jarvis et al. 1983; Benda et al. 1986; Wilson et al. 1986; Hiller et

al. 1986; González de la Riva Lamana 1987; and Santeiro 1989). Its use has been implicated as the causative agent in "gasping syndrome" in neonates (Gershanik et al. 1982). This syndrome is characterized by a progression of symptoms from gradual neurological deterioration, severe metabolic acidosis, gasping respiration, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, to cardiovascular collapse.

Several investigators have reported that BA caused hemolysis of erythrocytes (Kimura et al. 1971; Ohmiya and Nakai 1978; McOrmond et al. 1980). Ohmiya and Nakai (1978) later reported that the hemolytic potential of BA was time, dose, and temperature dependent. They also showed that the concentration of erythrocytes had a profound effect on the amount of hemolysis observed. They determined that the hemolytic in vitro LD_{50} using their method was 100 mM following incubation for 60 min at 37°C. Kimura and coworkers (1971) evaluated blood chemistry profiles following administration of 0.9 percent solutions of BA to rats, mice, and dogs, and determined that these concentrations were completely nonhemolytic in dogs and monkeys at a dose level of 1 ml/kg. They determined that the lethal IV dose of 0.9 percent BA in dogs was 0.83 to 1.06 g/kg. Additionally, they showed that slow IV administration of up to 40 mL/kg 0.9 percent BA to rats resulted in no fatalities.

Amide Solvents

N,N-Dimethylacetamide

N,N-dimethylacetamide (DMA) is a clear liquid that is used as a solvent for poorly water-soluble compounds in the pharmaceutical industry. It is miscible with water and alcohols and very soluble in organic solvents and mineral oil. It is mildly hygroscopic, stable to heat and hydrolysis, and has a low vapor pressure. DMA is sequentially metabolized to monomethylacetamide, and subsequently to acetamide (Kim 1988).

Caujolle et al. (1970) reported "maximum doses never fatal" (MDNF) and "minimum doses always fatal" (MDAF), for DMA as 2.5 g/kg and 6.0 g/kg for mice, and 2.5 g/kg and 3.7 g/kg for rats, respectively. They also reported 24 h LD_{50} values for DMA as 4.19 g/kg and 3.84 g/kg for mice and rats, respectively. Testicular injury was reported following a single IP dose of up to 3 g/kg DMA. However, subchronic administration of 36 IP injections at low doses did not show any toxicity or histopathology.

Wiles and Narcisse (1971) evaluated the parenteral toxicity of DMA by IV and IP administration to mice and rabbits. They observed the same signs of toxicity by both routes of administration, which included decreased activity, weakness, anesthesia, analgesia, labored breathing, cyanosis, collapse, and convulsions accompanied by hemorrhage prior to death. They found that toxicity was dose related, with faster onset of toxic signs

following administration of higher doses. IV administration of 708 to 1,480 mg/kg DMA to rats resulted in a rapid period of hypotension, followed by a long-lasting hypertensive period. IV administration of DMA to dogs and cats at a dose of 95 mg/kg caused no changes in blood pressure. At 236 mg/kg, mild hypotension was observed over a 5 min period. A dose of 472 mg/kg was lethal to cats (Auclair and Hameau 1964).

DMA has been used as a solvent for numerous pharmaceutical preparations, including oxytetracycline, chloramphenicol, and reserpine (Spiegel and Noseworthy 1963). DMA has also been used as a solvent for certain anticancer compounds, including amsacrine. In vehicle studies conducted in mice, the single IV dose LD_{50} was found to be 2,341 mg/kg.

DMA was believed to possess some inherent antitumor activity and was subsequently taken into Phase I clinical trials in 17 patients as a potential antitumor agent (Weiss et al. 1962). DMA was administered at doses ranging from 100 mg/kg/day to 610 mg/kg/day from a 10 percent solution over 5 to 10 min for 3 to 5 days. Toxicity—specifically gastrointestinal, hepatic, and CNS—was observed at the high doses. However, all signs of toxicity appeared to be reversible, returning to normal following completion of the therapy. Gastrointestinal signs of toxicity included nausea, vomiting, and anorexia. Hepatic toxicity was manifested by elevated serum glutamic-oxaloacetic acid transaminase (SGOT) levels up to several days after the completion of therapy, which returned to normal 2 to 5 days after reaching peak levels. No evidence of hepatic toxicity was observed on biopsy 3 weeks after therapy was completed. CNS effects (including depression, lethargy, occasional confusion and disorientation) were observed after the second or third day of therapy. The degree of lethargy and confusion ranged from mild to severe. Some patients developed hallucinations, perceptual distortions, and, at times, became delusional at high doses of DMA (above 400 mg/kg). CNS symptoms preceded more severe side effects, including hypotension and high fever, in 3 patients. However, typical use levels for parenteral applications are approximately 30 mg/kg, and would not be expected to cause these side effects (Spiegel and Noseworthy 1963).

Reed and Yalkowsky (1985) determined that DMA was very nonhemolytic with an in vitro hemolytic LD_{50} value of 37.0 (total volume percent). Only dimethylisosorbide was found to be less hemolytic (39.5).

N,N-Dimethylformamide

N,N-dimethylformamide (DMF) is a widely used organic solvent with excellent solubilizing capacity. It has been referred to as the "universal organic solvent" due to its small size, electron-donating properties, and high dielectric constant (Budavari 1989). It is a colorless liquid that is miscible with water and other organic solvents.

Following parenteral administration, DMF is metabolized in vivo to either monomethylformamide or N-(hydroxymethyl)-N-methylformamide. It

is primarily excreted in the urine as either of the metabolites, with relatively small amounts excreted as intact parent compound (Kennedy and Short 1986).

Generally, the formamides possess a relatively low order of toxicity following single-dose administration. Kutzsche (1965) determined the acute toxicity (LD_{50} values) of DMF following IV administration in dogs, guinea pigs, and rabbits to be 0.47 g/kg, 1.0 g/kg, and 1.8 g/kg, respectively. However, liver damage has been reported in rats following single IP doses of 0.6, 0.9, or 1.2 g/kg DMF. Davis and Jenner (1959) reported the LD_{50} values following IP administration to mice to be 1.1 g/kg. Reported IP LD_{50} values in rats are 1.3 g/kg (Massmann 1956) and 2.5 g/kg (Thiersch 1962).

Montaguti et al. (1994) evaluated the relative hemolytic potentials of several organic solvents, including DMF, dimethylsulfoxide (DMSO), EtOH, PEG 400, and BA, in several different mouse strains. They found that DMF was well tolerated in terms of hemolytic and precipitation potentials (in vitro tests). Hemolytic potential was evaluated following incubation of the solvent with blood at 37°C for 45 min. In general, DMF was the best tolerated of the solvents evaluated in both of these studies. DMF has been reported to be hemolytic when incubated with human erythrocytes for 45 min at 37°C (Cadwallader and Phillips 1969). These amides have been shown to readily penetrate the red blood cell membrane and afford little to no protection from hemolysis.

Dimethylsulfoxide

DMSO is a colorless, aprotic solvent that has a relatively high dielectric constant. It is miscible with water and many common organic solvents, including glycerol, acetone, and EtOH, in all proportions. DMSO is also very hygroscopic, capable of absorbing over 70 percent of its own weight at 20°C/65 percent relative humidity (RH) (Willson et al. 1965). Additionally, it has excellent solubilizing properties. Pharmacological evaluations showed that drugs administered systemically in DMSO did not significantly alter their lethality or cellular penetration (Dixon et al. 1965).

Toxicity studies have shown that DMSO possesses a relatively low order of toxicity. Willson et al. (1965) evaluated both acute and multiple dose toxicity from IV and IP injections in mice, rats, and dogs. Anemia and peritoneal inflammation were observed following 24 daily injections of DMSO to rats. No fatalities were observed in dogs receiving 1.2 g/kg or less daily by IV injection for 24 days. They observed perivascular inflammation and intravascular thrombosis, which was attributed to repeated administration of undiluted DMSO. However, dilution of DMSO prior to administration eliminated these unwanted effects. Additionally, hemolytic anemia, which was found to be reversible, was observed in rats and dogs following repeated IV injections of DMSO.

Studies conducted in humans at doses of 1 gm/kg administered intravenously from 10 to 40 percent solutions resulted in transient hemoglobinuria, which resolved within 2 to 3 hours (Bennet and Muther 1981). These studies also showed no short-term nephrotoxicity.

DMSO has been shown to exert cryoprotective effects in the preservation of red blood cells, platelets, bone marrow, and tissue culture cells (Lovelock and Bishop 1959; Pyle and Boyer 1962; Porterfield and Ashwood-Smith 1962). Additionally, DMSO in concentrations up to approximately 20 percent has been shown to reduce the hemolytic activity of various antimicrobial preservatives, including phenols, BA, thimerosal, and benzalkonium chloride (Ansel and Leake 1966; Ansel and Cabre 1970).

However, there are numerous in vitro and in vivo reports of the hemolytic nature of DMSO. Cadwallader and Drinkard (1967) evaluated the behavior of human erythrocytes in the presence of water–DMSO cosolvent systems ranging from 5 to 40 percent DMSO. They found that hemolysis occurred in all DMSO-containing solutions, and those with compositions greater than 35 percent DMSO resulted in discoloration and precipitation. Norred et al. (1970) speculated that DMSO was capable of removing fatty acids from the erythrocyte membrane in a concentration-dependent manner. The leaching of fatty acids led to the formation of lesions, which subsequently disrupted the integrity of the membrane. Reed and Yalkowsky (1985) determined the in vitro hemolytic LD_{50} value for DMSO to be 5.1 (total volume percent). Only glycerin was found to be more hemolytic than DMSO of the 15 solvents tested in the study. Montaguti and coworkers (1994) reported marked hemolytic activity of DMSO, tested in dose ranges from 1.0 to 5.66 mL/kg in 3 inbred mouse strains. These reports were consistent with previous reports indicating high hemolytic potential in mice, rats, cats, and dogs (Rosenkrantz et al. 1963; DiStefano and Klahn 1965; Willson et al. 1965). These effects have been reported to be markedly reduced when the DMSO solutions were diluted with saline.

Hemolytic Potential of Solvents/Cosolvents

It is preferable to utilize injectables that are totally biocompatible with body fluids. However, the incorporation of cosolvents into parenteral formulations has long been recognized as having the potential to destroy red blood cells, as does the addition of water alone. These solvents have the ability to hemolyze cells via either membrane disruption/interaction or by osmotic action. Early investigators have shown that the composition of parenteral dosage forms directly influenced the hemolysis of erythrocytes (Husa and Rossi 1942; Easterly and Husa 1954; Grosicki and Husa 1954; Hartman and Husa 1957; Cadwallader and Husa 1958; Thomasson and Husa 1958; Ansel and Husa 1959; Marcus and Husa 1959; Winters and Husa 1960; Schnell

and Husa 1962; Cadwallader 1963; Ansel 1964, 1965; Ku and Cadwallader 1975). These authors have also shown that the effect on the erythrocytes depends not only on the concentration of the organic in the cosolvent but also its ability to penetrate or disrupt the cell membrane. Therefore, there have been numerous investigations as to which vehicles are more tolerated for parenteral applications. Tables 11.5a and 11.5b summarize the in vitro hemolytic LD_{50} values for several common organic solvents encountered in parenteral formulations and the effects of increasing concentrations of NaCl on the observed hemolytic potentials (Reed and Yalkowsky 1985, 1986).

Table 11.5a. LD_{50} Values Expressed as Total Volume Percents of Various Cosolvents for Lysis of Erythrocytes (Reed and Yalkowsky 1985)

Cosolvent	LD_{50}
Glycerin	3.7
DMSO	5.1
PG	5.7
10% EtOH, 40% PG	10.3
EtOH	21.2
PEG 400	30.0
DMA	37.0
DMI	39.5

Table 11.5b. Effect of Increasing Sodium Chloride Concentrations on LD_{50} Values Expressed as Total Volume Percents of Various Cosolvents for Lysis of Erythrocytes (Reed and Yalkowsky 1986)

	Aqueous NaCl Concentration			
Cosolvent	**0.9%**	**1.8%**	**2.7%**	**3.6%**
Glycerin	3.3	8.3	12.7	11.9
PG	6.2	14.7	20.0	19.3
PEG 200	10.2	22.4	26.6	27.9
DMA	36.6	40.4	39.3	36.9
PEG 400	29.6	33.5	27.6	23.9
DMI	17.9	16.6	15.9	9.6
EtOH	20.5	20.0	20.5	19.7

There is a great deal of information available in the literature regarding the hemolytic potential of various solvents/cosolvents. However, much of this information is contradictory as to whether a particular cosolvent system is hemolytic or nonhemolytic. The discrepancies regarding hemolytic potential of a particular solvent system apparently result from the differences in the test methods used to evaluate the degree of hemolysis, particularly relating to volume ratios of blood to cosolvent, incubation/contact times, and whether the systems are static or dynamic (Banziger 1967; Wickliffe et al. 1968; Fort et al. 1984; Obeng and Cadwallader 1989; Krzyzaniak et al. 1997a, b, c). The temperature at which samples are maintained has also been shown to have a direct effect on the observed degree of hemolysis, with lower temperatures resulting in lesser extents of hemolysis (Cadwallader et al. 1964; Kimura et al. 1971). Additionally, it is also important to note that there may also be some species and/or strain differences relating to how susceptible blood cells might be to hemolysis (Montaguti et al. 1994).

Reed and Yalkowsky (1985, 1986) performed numerous studies addressing the effect of various cosolvents on hemolysis using an improved hemolytic method that would be suitable for use in the presence of cosolvent systems. They used terminology that expressed the ratio of blood to cosolvent volume as a concentration (i.e., total volume percent of cosolvent). A blood to cosolvent ratio of 9:1 would be expressed as a 10 percent cosolvent. They determined the LD_{50} values for various cosolvent systems. They found that EtOH, PEG 400, DMA, and dimethyl isosorbide (DMI) were considerably less hemolytic than DMSO and PG (Table 11.5a). The 10 percent EtOH–40 percent PG vehicle commonly used in marketed products (and well accepted as a parenteral vehicle) had an LD_{50} value approximately twofold greater than the very hemolytic solvents DMSO and PG.

Reed and Yalkowsky (1985, 1986) investigated the hemolysis resulting from increasing amounts of various cosolvents in water, as well as the importance of the ratios of blood to test solution. They showed that hemolysis was clearly a function of the concentration of the organic component present in the cosolvent mixture. DMSO and PG cosolvent mixtures were found to be quite hemolytic, even at relatively low cosolvent fractions. Surprisingly, some solvents were well tolerated even when tested undiluted (DMA, DMI, PEG 400) at blood:test solution ratios of 9:1. Reed and Yalkowsky (1987) continued to investigate cosolvent-induced hemolysis in an attempt to determine the relationship between structure and hemolytic potential for the above cosolvents. They concluded that the simple alcohols became more hemolytic with increasing chain length, consistent with other reports for simple alcohols (Ku and Cadwallader 1984) and both anionic and cationic detergents (Ross and Silverstein 1954). They also observed that decreasing steric bulk attached to the hydroxyl groups, and decreasing the number of hydroxyl groups resulted in a decreased hemolytic potential.

Although they were unable to determine a relationship between LD_{50} values and physicochemical properties for all of the solvents tested, they did observe a good correlation between LD_{50} values and log partition coefficient (PC) values when only the simple alcohols were included in the regression analysis. Similar attempts to correlate physical parameters with hemolytic potential have been made for drug molecules using dielectric constants, pH values, hydrogen bonding numbers, van der Waals volume, pK_a, octanol-water partition coefficients, and lipid spin labeling. However, no clear association has been made between any single parameter and resulting damage to the erythrocytes.

Ward and Yalkowsky (1992) later proposed that the hemolytic potential of a cosolvent was most accurately described by a single parameter, the effective concentration (EC), which could be used to generate dose-response hemolysis curves. They used the data obtained by Obeng and Cadwallader (1989) for PG cosolvent systems as the basis for their work. They defined the EC as the concentration in the final mixture of aqueous PG cosolvent solution and blood:

$$EC = \frac{\text{PG concentration} \times \left(\dfrac{\text{solution volume}}{\text{injection time}}\right)}{\text{blood flow rate}}$$

They proposed that use of this term essentially condensed several parameters (including vessel diameter, blood flow rate, injection volume, concentration and rate of administration) into a single parameter. They demonstrated with the PG system that there was a relationship between hemolytic potential and effective concentration, and that these kinetic factors must be considered in order to evaluate hemolysis in an in vitro system accurately.

Krzyzaniak et al. (1997a, b) showed that the degree of solvent-induced hemolysis was not only dependent on the ratio of formulation to blood but also to the amount of time in which the formulation was in contact with blood. Their in vitro method of determining hemolysis incorporated factors relating to the dynamics of an IV injection. The fundamental basis for this was that once a cosolvent formulation is injected into a vein, it is immediately mixed (and subsequently diluted) with blood, resulting in a decreased concentration of cosolvent formulation to which the erythrocytes will be exposed. Initially, the effect of contact time and volume of water and various concentrations of salt solutions were evaluated (Krzyzaniak et al. 1997a). Research showed that longer contact times resulted in greater degrees of hemolysis, with more hemolysis observed for systems where the ratio of test solvent to blood was increased. Subsequent evaluations were focused on various cosolvent systems, using EtOH, glycerol, PG, and PEGs (Krzyzaniak et al. 1997b). They determined a hemolytic potential rank order

for these tested solvents to be: glycerin > PG > PEG 300 > EtOH, although there was no difference between PEG 300 and EtOH at short contact times. For all cosolvent systems tested the observed extent of hemolysis increased as a function of cosolvent composition as well as contact time.

Krzyzaniak and coworkers (1997c) pointed out the range of conditions utilized in the most common in vitro methods, and the differences as to whether hemolysis occurred in the presence of a given cosolvent. The conditions used in the various models were so different, it is not surprising that there were inconsistencies with regard to hemolysis caused by cosolvents. The amount of hemolysis resulting from an IV injection of any given cosolvent depends on the initial concentration of the cosolvent, the concentration of the formulation after initial mixing with blood, and the amount of time to be completely diluted by the total blood volume.

In Vitro/In Vivo Hemolysis Comparisons

Fort and coworkers (1984) investigated the hemolysis of aqueous PEG 400, PG, and EtOH combinations in vivo and in vitro. Hemolysis was evaluated following a 2-week period of IV administration of a PG:EtOH:water solution (5:1:4) to rats and dogs. After 2 weeks, observations included decreases in hematocrit, hemoglobin, and number of erythrocytes, as well as marked hematuria. Further evaluation of urine samples showed that they were positive for occult blood, bilirubin, ketones, and protein. Several cosolvents (PG, PEG 400, and EtOH) of varying compositions were also evaluated in vivo in rats and in vitro in dog blood. It was found that any combination of EtOH and water with PG (10–30 percent) resulted in hematuria and complete in vitro hemolysis in all tested ratios. The same results were obtained when 0.9 percent NaCl was substituted for water with the exception of 10:30:60 (PG:EtOH:saline), which did not cause hematuria in vivo, but caused complete hemolysis in vitro. They also found that 40 percent EtOH in the presence or absence of normal saline caused hemolysis. Lower concentrations of EtOH (30 percent or less) in solutions containing normal saline did not cause hematuria even though some hemolysis in vitro was observed. The solution containing PEG:EtOH:water (3:2:5) was found to be nonhemolytic. Fort et al. (1984) concluded that intravenously administered PEG solutions were less hemolytic than similar solutions containing PG.

Krzyzaniak and coworkers (1997c) compared hemolysis using nine different in vitro methods, including a dynamic method which represented a more realistic picture of what happens to the formulation in vivo following an injection. They found that the hemolysis data generated by their dynamic model was much more representative of what was observed in vivo as compared to data generated by the other in vitro methods (Table 11.6). Excellent agreement was observed when comparing hemolysis data obtained from their dynamic in vitro method to that observed in vivo. Several

Table 11.6. Detection of Hemolysis by In Vivo and In Vitro Methods (Krzyzaniak 1997a)

Number	Formulation Composition	Hemolysis Observed in vivo	In Vitro Method (% Hemolysis Detected)			
			Husa and Adams (1944)	Fort et al. (1984)	Reed and Yalkowsky (1985)	Krzyzaniak et al. (1997c)
1	Normal saline (NS)	no[a,b,c]	0.0	0.0	0.0	0.0
2	10% EtOH in NS	no[c]	1.7	1.7	0.0	0.7
3	30% EtOH in NS	no[a]	92.4	89.2	0.0	0.5
4	40% PG in NS	yes[c]	50.7	23.3	61.0	5.6
5	60% PG in water	yes[a]	87.3	100.0	100.0	9.5
6	10% PG + 30% EtOH in NS	no[a]	82.3	85.3	0.0	1.2
7	10% EtOH + 20% PG in water	no[b]	89.5	81.3	8.8	2.0
8	10% EtOH + 40% PG in water	yes[a,b]	63.0	78.9	69.2	10.3
9	20% EtOH + 30% PEG 400 in water	no[a]	44.1	37.4	0.0	0.3

a: Fort et al. (1984)

b: Gerald (1988)

c: Turitto (1996)

of the vehicles tested by the static in vitro methods gave false-positive results when compared to results obtained from in vivo hemolysis studies (due to the high ratio of formulation to blood and the long incubation times). Although these static in vitro methods were not accurate in assessing the degree of hemolysis in vivo, they can be useful in assessing potential cellular damage resulting from IM injections, where there is a prolonged contact time between the vehicles and the tissues.

Methods to Reduce Hemolysis

Use of Additives. Numerous investigators have reported that the addition of various salts, including NaCl and sodium sulfate (Na_2SO_4), affords partial to full protection from hemolysis. It is well known that solutions of various therapeutic compounds (such as ammonium chloride, urea, boric acid, EtOH, and glycerin) fail to prevent hemolysis even when used at isotonic levels, indicating marked differences between iso-osmotic and isotonic values for compounds that can affect the red blood cell membrane (Husa and Rossi 1942; Husa and Adams 1944; Easterly and Husa 1954; Grosicki and Husa 1954; Hartman and Husa 1957; Cadwallader and Husa 1958; Thomasson and Husa 1958; Ansel and Husa 1959; Marcus and Husa 1959; Zanowiak and Husa 1959; Winters and Husa 1960; Hammarlund and Pedersen-Bjergaard 1961; Schnell and Husa 1962; Cadwallader 1963; Ansel 1964; Cadwallader et al. 1964). This is due to the fact that some of these additives may permeate the red blood cell membrane, causing an influx of water, resulting in hemolysis. Therefore, whether an additive has protective effects on erythrocytes will depend on its ability to penetrate the cell membrane. Such cosolvent compositions that are iso-osmotic with blood (0.9 percent or 0.15 M NaCl isotonic comparators) include 2.6 percent glycerin in water, 2.0 percent PG in water, 8.7 percent PEG 300, and 11.6 percent PEG 400.

Over the years, Husa and coworkers found that hemolysis occurred in solutions containing less than 0.45 percent NaCl, and that it was prevented with the use of concentrations from 0.45 to 0.9 percent. Hemolysis also resulted from solutions containing 1 to 2 percent dextrose, partial hemolysis at 3 percent dextrose, and solutions containing 4 to 5 percent dextrose resulted in no hemolysis. They showed that the 9 substances tested fell into 3 categories: prevents hemolysis (NaCl, dextrose), induces hemolysis (ammonium chloride, boric acid, carbitol) and those of moderate hemolytic potential (EtOH, PG, glycerin, diethylene glycol). Ammonium chloride, boric acid, and carbitol appear to cause hemolysis by a mechanism other than osmotic effects, probably by changing the permeability of the erythrocyte membrane.

Hammarlund and Pedersen-Bjergaard (1958, 1961) evaluated the effect of iso-osmotic solutions on erythrocyte hemolysis. They evaluated various salts for their potential for protecting erythrocytes from hemolysis.

They showed that monovalent amine salts typically resulted in hemolysis, whereas divalent and trivalent amine salts usually protected from hemolysis. They also showed that the addition of either NaCl or Na_2SO_4 was able to prevent hemolysis of erythrocytes exposed to various iso-osmotic solutions of ephedrine. They found that an iso-osmotic solution of EtOH (1.39 percent) required 0.5 percent NaCl to prevent hemolysis. Cadwallader and Drinkard (1967) also showed that the addition of isotonic amounts of various compounds (NaCl, calcium chloride, dextrose, lactose, potassium bromide, sodium citrate, sodium bromide, sodium iodide, and sodium salicylate) prevented hemolysis in aqueous solutions containing 5 to 40 percent DMSO. These studies again illustrate the difference between iso-osmotic concentrations and isotonic concentrations.

Cadwallader (1963) calculated "hemolytic" isotonic coefficients for several polyhydric alcohol-water solutions (PG, glycerol). These data showed that water-glycerin and water–PG mixtures should not be assumed to be hypertonic with respect to blood. In fact, all mixtures studied were found to be hypotonic with respect to rabbit and human erythrocyte membranes. Therefore, isotonicity calculations were not valid for these applications. They also showed that PG was more hemolytic than glycerin, consistent with Jacobs and coworkers' (1935) observation that each additional hydroxyl group added to the propane molecule decreased the rate of penetration into erythrocytes.

Reed and Yalkowsky (1986) showed the effect of increasing amounts of NaCl on the hemolytic LD_{50} values of the common organic solvents found in parenteral formulations (Table 11.5b). They showed differences in the degrees of protection afforded by NaCl between the various solvents. For example, the presence of NaCl had essentially no effect on the LD_{50} value for EtOH, whereas it decreased the LD_{50} value for glycerol by almost fourfold.

Fu et al. (1987) investigated several parenteral vehicles for hemolytic potential both in vitro and in vivo following IV administration to rats. The animals were dosed daily with a single bolus dose of 2.5 mL/kg through the tail vein for 2 weeks. They reported a high degree of hemolysis for a 15 percent PG solution, which was significantly reduced by the addition of either 1.8 percent NaCl or 20 percent sorbitol (concentrations higher than those yielding isotonic solutions). They also showed that PEG 400 had the ability to reduce the hemolytic potential of a 15 percent PG solution from approximately 80 percent hemolysis (with no added PEG 400) to approximately 20 percent hemolysis with addition of 20–45 percent PEG 400. This is useful to formulators in that it makes the vehicle more biocompatible, as well as provides increased solubilization power for the cosolvent system.

Use of Slow Infusion Rates. One of the easiest ways to minimize hemolytic consequences of administration of parenteral products containing cosolvents is to administer these doses as slow infusions, as opposed to bolus

injections. This results in lower effective concentrations of cosolvent in the plasma. Slow administration of the dose also reduces the chance of precipitation of the drug in the vascular compartment by allowing for gradual dilution with the plasma components.

Welch et al. (1974) reported that glycerol has been used successfully in the treatment of more than 500 patients with acute cerebral infarctions when administered daily for 7 to 10 days infusing 500 mL of 10 percent glycerol in normal saline over 6 h with none of these adverse effects. This study did report that hemolysis was seen when the solution was administered as a rapid infusion. However, Hagnevik et al. (1974) reported hemolytic changes ranging from hemolysis and mild to marked hemoglobinuria following administration of 20 percent glycerol at rates of 60 g/15 min, 70 g/30 min and 80 g/60 min to 3 patients undergoing intracranial surgery. As one can see, there were enormous differences in the rates of administration of the glycerol solutions between these reports. The side effects were associated with much faster infusions than those used by others to treat stroke patients (Meyer et al. 1971). Therefore, one can observe that the rate of administration has a tremendous effect on the glycerol-related hemolysis observed following IV administration. These data from Welch and coworkers suggest that it would be entirely possible to greatly reduce or eliminate the hemolysis when administering such solutions slowly.

Obeng and Cadwallader (1989) evaluated the effect of various parameters on the observed degree of hemolysis. These included flow rate of red blood cells at the site of injection, internal diameter, distance downstream from the site of injection, injection volume, rate of administration, and cosolvent composition. This method was a more realistic model for hemolysis, since it allowed for mixing of the cosolvent with blood at the site of injection and a relatively short contact time between the test solution and the blood. These studies clearly showed that the kinetic factors (rate of administration, blood flow rate) affected the degree of hemolysis associated with various cosolvents and recommended that solutions having known hemolytic potentials be administered slowly via large veins.

The *Physicians Desk Reference* (PDR 1994) recommends slow administration for many cosolvent-containing compounds that have been associated with various complications following IV administration. Such compounds include phenytoin, digoxin, diazepam, pentobarbital, lorazepam, and etoposide. Typically, the recommendations are to administer these doses slowly as infusions, with rates not to exceed 2 to 50 mg/min, depending on the compound. When administering doses to neonates or children, the rates of administration may need to be even slower, as is the case with phenytoin (not to exceed 1 to 3 mg/kg/min for neonates, compared to 50 mg/kg for adults). Slow administration allows for adequate mixing with blood and minimizes the risk of precipitation of the dose.

Muscle Damage

Administration of formulations by the IM and SC routes is somewhat more flexible than formulations administered by the IV route because solutions or suspensions, either aqueous or oily, can be given. Use of these formulations tends to result in a more controlled release of drug. Cosolvents are frequently used to reduce the aqueous solubility of a given compound, such that it precipitates upon administration into tissues. The precipitation is followed by a resolubilization of the compound over time as the compound is slowly absorbed. The rate of solubilization is dependent on the properties of the tissues, such as pH and blood flow (Evans et al. 1973), and the vehicles used to administer the compound. Local muscle damage may result from direct damage to the sarcolemma membrane of the muscle fibers, or by some toxic effect of either the drug or the vehicle on myofibril intracellular organelles and membranes. Muscle damage may also contribute to the pain at the site of injection.

Hem and coworkers (1974–1975) evaluated the tissue irritation (muscle damage) and injectability of 23 potential nonaqueous parenteral vehicles. They found that several vehicles caused very little irritation (benzyl benzoate, 1,3-butylene glycol, ethyl oleate, glyceryl triacetate, sesame oil: benzyl benzoate [1:1], sesame oil) and were well absorbed; several caused moderate irritation (butyl lactate, castor oil, glyceryl monoricinoleate) and were not absorbed; and a number that caused necrosis (ethyl formate, isoamyl formate, octyl alcohol, polyoxyethylene oleyl ether, n-propyl alcohol, propylene carbonate, sorbitan trioleate). They included DMA in the study, finding that it was very well absorbed from the site of injection but caused moderate irritation that was found to dissipate within 7 days postinjection. Oshida and coworkers (1979) evaluated the physicochemical properties and local toxic effects of 335 parenteral formulations. They evaluated pH, osmotic ratio, hemolytic potential, cytotoxic effects on cultured cells, and muscle lesions following IM administration of 0.5 mL to the vastus lateralis or sarcospinalis muscle of rats. They showed there was a close correlation between the hemolytic potential of the formulation and the severity of muscle damage observed.

Svendson (1983) and Svendson and coworkers (1985) evaluated the muscle damage resulting from IM injections of several neuroleptic drugs in aqueous and oil vehicles, including Viscoleo®, sesame oil, methyl oleate, and squalane. They observed the injection site three days after IM administration of 2 mL of the various formulations. The most damage was observed with cis-(Z)-clopenthixol, regardless of formulation. Postmortem findings showed well-defined, relatively large areas of muscle necrosis in all of the animals administered aqueous formulations. These areas were considerably larger than those observed in the oil-treated animals. Generally, Viscoleo® (a triglyceride vegetable oil composed of short chain and saturated fatty acids, caprylic acid, capric acid, and lauric acid) resulted in

much less damage than the aqueous solutions. Formulation of haloperidol, cis-(Z)-clopenthixol, or chlorpromazine in any of the oil vehicles essentially eliminated the observed muscle damage that resulted from administration of the aqueous solutions—necrotic areas were reduced from 5- to 34-fold when the oily vehicles were used instead of the aqueous formulations.

It has been observed that one of the consequences of IM injections is release of the enzyme creatine kinase (CK) into plasma, which is found in large amounts in skeletal muscle. This enzyme has been used as a marker of muscle damage (Attar and Matta 1971; Anderson and Damsgaard 1976; Greenblatt et al. 1976; Steiness et al. 1974, 1978; Svendson et al. 1979; Diness 1985). Steiness et al. (1974) reported that the size of the resulting necrotic area following IM administration of digoxin or the vehicle control to pigs was related to the injection volume (ranging from 1.5 to 4.0 mL). The necrotic areas resulting were, however, much smaller for the vehicle groups than those receiving the digoxin formulation, indicating that the drug itself contributed greatly to the necrosis.

Several investigators evaluated the effects of PG and glycerol formal vehicles on muscle necrosis (Rasmussen and Svendson 1976; Svendson et al. 1979). Svendsen et al. (1979) evaluated the effects of different dilutions of PG or glycerol formal in distilled water or 0.9 percent saline on the measured CK activity in muscle taken from the injection area and the contralateral uninjected site for up to 72 h postinjection. They showed that CK depletion from the muscle, which subsequently appeared in the plasma, was dependent on the PG or glycerol formal content of the vehicle—higher cosolvent compositions led to higher plasma CK levels, with PG causing greater CK release than glycerol formal. They also showed that local muscle damage (as indicated by weight of the isolated damaged muscle tissue) correlated with relative CK activity depletion in the muscle.

Brazeau and Fung (1989a, c) also evaluated PEG 400, PG, and EtOH cosolvent mixtures for their myotoxic potential using an in vitro model that they developed. This model measures cumulative release of CK as a marker of muscle damage, and the values can be compared to positive and negative control values. The specific details of this model are discussed in other chapters in this volume. They showed that at moderate cosolvent concentrations (20–40 percent, v/v), PG was considerably more myotoxic than PEG 400 or EtOH (PG > EtOH > PEG 400). This seemed to correlate with hemolytic potentials of the cosolvent mixtures as reported by Reed and Yalkowsky (1985). These results were compared to those obtained in vivo in rabbits, evaluating serum CK levels following IM administration of 40 percent PG, 40 percent PEG 400, or normal saline. They showed that in all cases serum CK levels increased following the injection. However, the levels were much higher for the cosolvent formulations (PG >> PEG 400 > saline). They observed that it took 3 days to return to normal serum CK levels.

In more recent studies, we have investigated the in vitro myotoxicity of DMA, Cremophor® EL, polysorbate 80, safflower oil, and Labrafil® using the isolated muscle model as above. The results from these studies are shown in Table 11.7 and are compared to our historical positive and negative control values (Dilantin® injection and normal saline, respectively). The toxicity of all these solvents, with the exception of safflower oil and 30% Cremophor® EL (very close to the negative saline control value), was intermediate between the positive and negative control values. This would be consistent with an oily vehicle being less toxic to tissues versus an aqueous vehicle. It is unclear as to why there was no concentration-myotoxicity response between the concentrations of Cremophor® EL. Of all these solvents, DMA and polysorbate 80 were found to be the most toxic. This could be attributed to their ability to solubilize the muscle membrane leading to release of CK.

In an attempt to elucidate the factors responsible for muscle damage, Brazeau and Fung (1989c) evaluated how physicochemical properties of the vehicle composition affected muscle damage following IM administration of various cosolvents, including PG–water, EtOH–water and PEG 400–water mixtures. The properties that were evaluated were dielectric constant, apparent pH, surface tension, and viscosity. They made several notable observations, including (1) as the hydrophilicity of the cosolvent mixtures increased, myotoxicity decreased; (2) there was no defined pH range where muscle damage could be minimized; and (3) that, unlike hemolysis, the addition of NaCl had no protective effect on muscle damage produced. They concluded that myotoxicity was not exclusively related to a single parameter or a combination of the four parameters evaluated.

Table 11.7. Myotoxicity of Selected Solvent Vehicles

Vehicle	Myotoxicity – Cumulative CK Release over 2 h Mean CK (× 100) and (SEM); $n = 4–6$
20% DMA	9.50 (2.60)
30% DMA	13.4 (2.10)
20% Cremophor® EL	6.87 (1.69)
30% Cremophor® EL	4.94 (0.83)
5% Tween 80®	20.1 (3.21)
Safflower oil	2.89 (1.47)
20% Labrafil®	7.90 (1.65)
30% Labrafil®	8.94 (1.69)
Positive control Dilantin® injection	70.1 (4.71)
Negative control normal saline injection	5.06 (0.50)

Chu and Brazeau (1994) also showed that PG and PEG 400 had different effects on skeletal muscle sarcoplasmic reticulum calcium uptake and release. They showed that 10.5 percent PEG 400 stimulated calcium uptake without significantly altering the adenosine triphosphatase (ATPase) activity of the calcium pump. However, at 10.5 percent PG, there was no significant effect on either calcium uptake or ATPase activity of the pump. These findings further supported the role of calcium in mediating cosolvent-induced muscle damage, as suggested earlier (Brazeau and Fung 1990b). They also provided a possible explanation for the differences in the two cosolvents in their potentials to cause muscle damage, based on increased myoplasmic calcium removal and reduced calcium release.

Cosolvent-Related Pain on Injection

The use of parenteral routes of administration may result in pain and irritation at the site of injection. This may be related to the injection itself or the properties of the drug substance. However, the pain and irritation many times appears to be associated with the formulation vehicle, particularly those that contain high fractions of cosolvents or those that have high osmolalities. In general, comparisons between solutions containing lower or different cosolvent compositions or lower osmolalities have shown fewer incidences of pain on injection, as well as reduced local toxicity (Bjork et al. 1969; Almèn and Tragardh 1973; Almèn et al. 1977; Tillman et al. 1979).

There have been numerous methods and guidelines published relating to the assessment of pain (Beecher 1957; Woodforde and Merskey 1972; Ohnhaus and Adler 1975; Celozzi et al. 1980; Vierck and Cooper 1984; Comerski et al. 1986; Marcek et al. 1992; Gupta et al. 1994). These methods can be characterized as reflexive (tail-flick, paw-lick, hot plate, or pinch test), conscious escape (flinch-jump test), prolonged protective activity (fleeing/fighting), and retreat/withdrawal responses. These models vary in the degree of subjectivity of the pain assessment and are discussed elsewhere in this book.

Cosolvents Known to Cause Pain

Glycerin has been recognized as an irritating agent that caused pain and inflammation at the site of injection. Van Metre et al. (1996) reported pain and dermal reactions caused by the administration of glycerin in immunotherapy solutions. Such solutions come prepared in 50 percent glycerin to preserve potency for 2 to 3 years. The solutions are supposed to be diluted prior to administration to levels between 10 to 30 percent glycerin and administered in volumes ranging from 0.1 to 1.0 mL. Their results showed that

pain scores of subjects given glycerin increased significantly as both glycerin concentration and dose volume increased.

When used undiluted, PG can cause considerable pain and irritation at the site of injection. These effects have been reported for parenteral administration of nitroglycerin (Demey et al. 1984; Shook et al. 1984; Col et al. 1985; Demey et al. 1984,1988); etomidate (Bedichek and Kirschbaum 1991; Levy et al 1995), multivitamins (Glasgow et al. 1983), and phenytoin (Hitotsumatsu et al. 1995). Other investigators have shown that altered formulations of various cosolvent-containing preparations, containing either reduced organic fractions or using a mixture of different organic solvents to minimize the load of a particular solvent, were less painful than when administered in the traditional formulation (Burton et al. 1974). Many of these studies have shown that pain on injection was associated with the formulation vehicle, particularly when containing relatively high amounts of PG.

Diazepam, which contains 40 percent PG, has been associated with many incidences of pain on injection, which has been related to the composition of the formulation vehicle. Pain on injection has been reported in up to 22 percent of patients, with subsequent development of venous sequelae (phlebitis, thrombosis, or thrombophlebitis) appearing in up to 30 percent of patients (McClish 1966; Brown and Dundee 1968). It is suspected that precipitation of the poorly water-soluble drug on administration is at least partially responsible for these side effects. Langdon et al. (1973), however, did not observe any correlation between pain on injection and development of venous sequelae.

While evaluating pain and irritation following injection of various parenteral formulations using the rat paw-lick model, Gupta and coworkers (1994) suggested that there was a pain "threshold limit" in terms of observed number of paw licks related to the concentration of a pain-inducing component, at least in the case of PG–containing formulations. In these studies, concentrations above this "threshold limit" did not result in increases in the pain responses, making predictions using this model somewhat problematic. These data showed that administration of formulations containing 50 percent PG caused less pain than formulations containing 40 percent PG, in both the presence and absence of 5 percent EtOH. The same observation was made for PG solutions containing 15 percent EtOH, whereby more pain was observed at 35 percent PG, as compared to preparations containing 40 or 50 percent PG. Analysis of CK levels following these injections showed that they increased (indicative of muscle damage) as a function of the cosolvent composition. Therefore, one must be cautious when interpreting data from these pain models, since pain may not correlate with damage resulting from the injection of the formulation.

Methods to Minimize Pain

There have been numerous investigations as to how to reduce the pain following parenteral administration of various formulations. In many cases, these methods are similar to those used to minimize hemolysis. The most common methods used to minimize pain on injection are (1) administration of the dose via a large vessel; (2) dilution of the formulation in some manner that does not result in precipitation, or similarly, administration of the dose as a slow infusion to reduce the effective concentration of cosolvent in the system at a given period of time; (3) formulation of the compound using solvents that are less irritating; or (4) prior or coadministration of an anesthetic or analgesic agent, such as lidocaine or morphine, to reduce the pain.

Administration Via Large Vessels

Kawar and Dundee (1982) investigated the effect of choice of injection site, including the variables of vein size and location. They observed that the greatest incidence of pain occurred when administering various formulations via small to medium sized veins, and that using the hand and wrist veins caused more pain than those in the antecubital space (Table 11.8). The use of large veins rather than small veins, and selecting the antecubital space rather than the back of the hand or wrist consistently showed better tolerability, regardless of whether the formulation contained 0.9 percent saline or various cosolvents.

Similarly, Langdon et al. (1973) reported that venous sequelae occurred less frequently when administering IV doses of diazepam through larger veins. They noticed that phlebitis almost always resulted when administering the doses through small veins. The incidence of pain resulting from administration of propofol, an anesthetic agent, has been reported to range from 25 to 100 percent if given via a vein on the dorsal side of the hand (Hynynen et al. 1985; Stark et al. 1986; Sebel 1989; Stokes et al. 1989; Johnson et al. 1990), and only 3 to 36 percent if injected into larger, proximal veins in the antecubital fossa (McCulloch and Lees 1985; Scott et al. 1988; Gehan et al. 1991).

Dilution of the Formulation

Dilution of cosolvent formulations has been shown to reduce the incidences of both pain and venous sequelae. However, precipitation of a poorly water-soluble drug is likely to result if diluted into an aqueous medium (water, saline, or even plasma). Precipitation may be immediate or may develop over time. Van Metre and coworkers (1996) showed that pain resulting from subcutaneous injections of glycerol solutions (0, 10, 20, and 30 percent glycerol with dose volumes ranging from 0.1 to 1.0 mL) to

Table 11.8. Frequency of Pain on Injection and Venous Sequelae Following Administration of Various Test Formulations (Total Number of Patients Evaluated in Parenthesis) (Kawar and Dundee 1982)

Drug/Formulation	Primary Solvent	% Frequency of Pain on Injection	% Frequency of Venous Sequelae	% Sequelae Related to Vein Size		% Sequelae Related to Vein Site	
				Large	Small + Medium	Antecubital Fossa	Back of Hand + Wrist
0.9% Saline	Water	0 (50)	2 (50)	0 (18)	3 (32)	0 (23)	4 (27)
2.5% Thiopentone	Water	9 (100)	4 (50)	5 (20)	3 (30)	17 (12)	0 (38)
1.0% Methohexitone	Water	12 (100)	10 (50)	12 (24)	8 (26)	12 (33)	6 (17)
1.0% ICI 35868 (Disoprofol)	Cremophor® EL	4 (50)	10 (50)	12 (24)	8 (26)	8 (48)	50 (2)
0.5% Diazepam Valium®	Propylene glycol	37 (100)	40 (50)	18 (28)	32 (22)	17 (30)	50 (20)
Diazemuls®	Soya bean oil	0 (50)	2 (50)	0 (31)	5 (19)	0 (32)	6 (18)
0.5% Midazolam	Water	1 (400)	8 (100)	11 (65)	3 (35)	11 (70)	0 (30)

15 subjects increased significantly as a function of both injection volume and glycerol concentration.

Alteration of the Vehicle Composition

In efforts to minimize both pain and venous sequelae, alternative formulation vehicles have been used for administering diazepam to patients. Burton and coworkers (1974) used a solution of 1 percent Cremophor® EL in saline to dilute diazepam to a final concentration of 1 mg/mL. Following administration of this formulation to over 400 patients, it was reported that incidences of pain on injection were essentially eliminated, even when injected into small veins, and incidences of venous sequelae in these patients were reduced to less than 1 percent. This eliminated precipitation of the solution, which was observed in the traditional formulation (Jusko et al. 1973). They also observed that if pain was observed following IV administration, flushing the vein with 5 mL saline or 10 mg of heparin sodium through the same needle diminished the incidence of venous sequelae.

Kortilla et al. (1976) evaluated the effects of PG following IM injection in humans, comparing pain, muscle damage and precipitation for the following diazepam formulations: Valium® (Roche), Diapam® (Orion) and an experimental formulation 301-K 2/74 (Orion). The 301-K 2/74 formulation contained a lower concentration of PG (20 percent) with 60 percent PEG 300. The Valium® and Diapam® formulations contained the same cosolvent composition (41 percent PG, 8.5 percent EtOH). These formulations provided no statistical differences in plasma levels following IM administration, although the levels for Valium® tended to be lower than for the other formulations. At doses of 0.15 mg/kg, they found that pain was significantly greater in the Valium® and Diapam® formulations than in the 301-K 2/74 or placebo (301-K 2/74 with no drug) in double blind crossover studies. This is consistent with earlier rat studies showing a lack of irritation after IM injections of the PG/PEG vehicle. They also showed that the PG/PEG formulation was less likely to precipitate as compared to the Diapam® formulation. Addition of 10 mg (2 mL) of Diapam® to 100 mL of 5 percent glucose caused precipitation, whereas up to 25 mg (5 mL) of the PG/PEG formulation could be added before precipitation was observed.

Kawar and Dundee (1982) evaluated the pain on injection of several preparations that were formulated in different solvent systems in a patient population. They evaluated factors such as composition, size of the vessel through which the dose was administered, and the frequency of venous sequelae. They found that the formulation causing the most irritation was the Valium® formulation containing 40 percent PG and 10 percent EtOH. The same compound formulated in an oil-based system caused no pain on administration. The other formulations composed of either water or Cremophor® EL caused less pain. Additionally, the PG formulation caused the

highest percentage of venous sequelae as compared to the other vehicles. Diazepam formulated in the oil-based vehicle was essentially the same as the saline controls, suggesting that these sequelae were the result of the cosolvent.

Administration of Anesthetic/Analgesic Agents

The use of anesthetic/analgesic agents to minimize pain following injection of various parenteral formulations has been studied using agents ranging from aspirin to morphine (Comerski et al. 1986; King et al. 1992; Marcek et al. 1992; Doenicke et al. 1996). Comereski et al. (1986) observed that coadministration of lidocaine (0.5 to 1 percent) offered protection from pain but not from the associated muscle damage resulting from the injection. Marcek and coworkers (1992) reported the effect of morphine administered 15 min prior to being given an infusion of an irritating solution (0.05 M potassium chloride). They found that administration of morphine (ranging from 2 to 4 mg/kg) virtually eliminated the pain associated with the test solution alone. Celozzi and coworkers (1982) also showed that coadministration of a local anesthetic (lidocaine) reduced the pain associated with subplantar administration of antibiotic solutions. They showed that the administration of the anesthetic reduced the pain to approximately the same level as the control water injections. It is typically thought that pain on injection is related to muscle damage caused by the administration of the dose.

Propofol (Diprivan®) has a very high incidence of pain on IV injection. Several investigators showed that the use of various anesthetic/analgesic agents resulted in abatement of pain caused by the administration of propofol (Bahar et al. 1982; Brooker et al. 1985; Helbro-Hansen et al. 1988; Gehan et al. 1991; King et al. 1992). King and coworkers (1992) showed that coadministration of lidocaine (ranging from 5 to 20 mg doses) resulted in the reduction of both the incidence of pain and its severity. In this study of 368 patients, the incidence of pain following administration of lidocaine was 32 percent, relative to 73 percent following saline injection. The degree to which the pain was alleviated was found to be dose responsive. However, 6 percent of patients treated with 20 mg lidocaine still reported unpleasant pain.

CONCLUSIONS

The use of cosolvents as solubilization enhancers in parenteral formulations has been, and continues to be, a valuable tool for the formulation scientist. However, it becomes crucial for the formulator to understand prior to the selection or use of these cosolvent systems that they differ widely in

their physicochemical properties, which in turn can result in varying degrees of adverse effects such as hemolysis, muscle damage, and pain at the injection site. The most commonly used cosolvents in parenteral formulations—including the polyethylene glycols, propylene glycol, ethanol, glycerin, cremophors, benzyl alcohol, dimethylacetamide, and dimethylsulfoxide—have been highlighted in this chapter. Furthermore, cosolvent-related factors, mechanisms, and approaches to offset the hemolysis, muscle damage, or pain following injection have been generally presented so that the formulator can rationally select and incorporate these agents into the design of injectables.

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17

Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products

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Parenteral products significantly contribute to global health by providing effective and immediate therapy through direct delivery of therapeutic compounds to the patient. However, as with most routes of delivery, parenteral drug administration has both real and perceived disadvantages. The two potential disadvantages that are typically associated with parenteral therapy are tissue damage and injection pain. Whether this pain is real or imagined makes little difference to the patient, and there exists a significant literature that both highlights the pain caused by injectable drug products and offers methods to reduce these effects.

The first section of this chapter provides a strategy that can be used to develop a parenteral product. Emphasis is placed on the two formulation parameters, pH and tonicity, that are usually associated with tissue damage and injection pain. It is through the adjustment of these parameters that the product formulator can minimize adverse effects. The second section of this chapter describes administration techniques used by

healthcare professionals to reduce tissue damage or pain caused by commercial parenteral products. By recognizing the potential risks these alterations may confer to commercial formulations (such as decreased product stability or modified efficacy), the formulator will be better prepared to support the "real-world" use of the product.

FORMULATION DEVELOPMENT

The development strategy for parenteral products is similar for all products. The challenge is in the details of solving the physical/chemical difficulties encountered with a specific molecule within the timeline allowed for development. This section provides a parenteral product development outline with an emphasis on two formulation parameters, pH and tonicity, which may be modified to minimize tissue damage and pain caused by a parenteral product.

The activities necessary to develop a parenteral product can be placed into the following three broad areas: preformulation, formulation, and scale-up. While there are alternative development perspectives, all development ultimately needs to accomplish the same activities. Preformulation includes the characterization of the bulk drug plus initial screening for excipient compatibility with the drug. Formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous, or cosolvent system), necessary excipients with appropriate concentrations (buffers, antioxidants, antimicrobials, chelating agents, and tonicity contributors), and the container/closure system. Scale-up activities aid in moving the product to a manufacturing site (although not discussed here, references are available to provide guidance).

Preformulation

Preformulation studies provide fundamental data and the experience necessary to develop formulations for a specific compound. Activities are initiated and experiments performed for the purpose of characterizing specific and pharmaceutically significant physicochemical properties of the drug substance. These properties include interactions of the drug with excipients, solvents, packaging materials, and, specifically relating to the subject of this book, biological systems. These investigations also evaluate the drug under standard stress conditions of temperature, light, humidity, and oxygen. Many of these factors should be considered critically prior to animal testing, since these data will influence activities such as samples prepared for toxicology and animal testing, solubilization techniques, and design of subsequent studies.

Areas of specific interest during preformulation are provided in outline form below, along with an outline of additional characterization information needed to formulate a protein drug substance. Since analytical methods are usually developed concurrently with the preformulation data and then refined during formulation activities, the team must effectively communicate and collaborate to ensure appropriate assays are used to obtain data having sufficient accuracy and precision.

Preformulation Physicochemical Properties

1. Molecular weight
2. Color
3. Odor
4. Particle size, shape, and crystallinity
5. Thermal characteristics
   - 5.1. Melting profile
   - 5.2. Thermal profile
6. Hygroscopicity
7. Absorbance spectra
8. Solubility
   - 8.1. Selected solvents (water, ethanol, propylene glycol, polyethylene glycol 400, plus others as necessary)
   - 8.2. pH profile
   - 8.3. Temperature effects
   - 8.4. Partition coefficient
9. Stability
   - 9.1. Selected solvents
   - 9.2. pH profile
10. Ionization constant (pK or pI)
11. Optical activity

Additional Characterization for Protein Drugs

1. Physical stability
   - 1.1. Aggregation
2. Solubility
3. Chemical stability
   - 3.1. Beta-elimination
   - 3.2. Deamidation
   - 3.3. Isomerization/cyclization
   - 3.4. Oxidation
   - 3.5. Thiol disulfide exchange
4. Analytical methods
   - 4.1. Fluorescence spectroscopy
   - 4.2. Electrophoresis
   - 4.3. Calorimetry
   - 4.4. Size exclusion chromatography
   - 4.5. Reverse phase high performance liquid chromatography (HPLC)
   - 4.6. Circular dichroism
   - 4.7. Mass spectrometry
   - 4.8. Light scattering

Formulation

Formulation activities include the identification and selection of a suitable vehicle (aqueous, nonaqueous, or cosolvent system), necessary excipients with appropriate concentrations (buffers, antioxidants, antimicrobials, chelating agents, and tonicity contributors), and the container/closure system. The formulator is interested in the same list of activities given for preformulation; however, the activities are focused on specific excipients and characterization of the formulation. The principles of formulating a parenteral product have been outlined by several authors, although most do not specifically include the evaluation of tissue damage or pain caused by injection of the final product. This is likely due to the assumption that

deviation of pH or tonicity from physiological conditions causes these effects. It is, however, important to consider that a product may cause tissue damage with little associated pain, pain with little tissue damage, or both pain and tissue damage. Therefore, the models utilized to assess either the pain or tissue damage associated with a product need to be selected carefully. Several complementary methods may be needed, and these models are provided throughout this book.

Significant formulation activities begin with initial preformulation data and knowledge of the specific route of administration. These data provide the formulator with the requirements and limitations for the final formulation. Due to the location of human pain receptors, formulation approaches to reduce pain are more critical for subcutaneous (SC) and intradermal injections and less critical for intramuscular (IM) and intravenous (IV) administration.

Injection volume is one of the most important considerations in the formulation development of a commercial product. This volume is selected based on the proposed injection route. Since veins have a relatively large volume and blood flow rate, a product administered by the IV route can have a volume greater than 10 mL; as the volume increases, the delivery rate may need to be controlled. This is in contrast to IM injections, which are normally limited to 3 mL, SC injections to 1 mL, and intradermal injections to 0.2 mL. Recommended maximum injection volumes are author dependent but not radically different.

Thus, the factors that need to be considered in evaluating the hemolysis caused by a product include both the quantity and proportions of the substances and how rapidly the blood dilutes the product. The data in Table 17.1 provide some perspective on the vascular system's capability of diluting an injected IV product, in terms of both volume and rate. The choice of solvent is dependent both on the route of administration, which

Table 17.1. Physical Characteristics of the Arteriovenous System

Anatomical Section	Volume (cm^3)	Velocity (cm/sec)
Aorta	100	40
Arteries	325	40–100
Arterioles	50	10–0.1
Capillaries	250	0.1
Venules	300	0.3
Veins	2,200	0.3–5
Vena cava	300	5–30

as noted above imparts volume limitations, and on drug solubility in the selected solvent. IV injections are typically restricted to dilute aqueous solutions to ensure compatibility with the blood; however, IM or SC injections allow for oily solutions, cosolvent systems, suspensions, or emulsions. Pain, soreness, and inflammation of tissues are frequently observed in the administration of parenteral suspensions, particularly with products having a high solid content.

A third important consideration in the development of a parenteral product is compatibility of the formulation with the tissue. An isotonic solution is less irritating, causes less toxicity and pain, and minimizes hemolysis. An isotonic product, however, is not always the goal since for SC or IM injections a hypertonic solution may facilitate drug absorption. Having an isotonic product is, however, very important for intraspinal injections, where the fluid circulation is slow and abrupt changes in osmotic pressure can contribute to unwanted and potentially severe side effects.

The choice of acceptable excipients in parenteral product development remains limited compared to other dosage forms, due to concerns of injection safety and feasibility of sterilization. In order to avoid uncertainty and reduce development time, most formulators select excipients successfully used in marketed products. A short list of commonly used additives, their functions, and typical concentrations is given in Tables 17.2 and 17.3. As the number of biotechnology products increases, excipients such as human serum albumin (HSA), amino acids, and sucrose are finding increasing utility. In Europe, the use of animal-derived excipients such as HSA and some polysorbate surfactants has become problematic due to the increasing concern with bovine spongiform encephalitis (BSE). This concern is expanding to the rest of the world and has impact on the selection of excipients.

An excipient selected for a parenteral product may serve one or more purposes. For example, benzyl alcohol is primarily a preservative; however, it has a transient local anesthetic property. Dual roles may help in the goal to minimize both the number of product ingredients and their quantity. The justification for each selection will become a part of the formulation development report.

Antimicrobials

Preservatives are always included in a product when multiple doses will be drawn from a single vial unless the drug itself is bacteriostatic. The addition of an antimicrobial is not a substitute for good manufacturing practices; however, many times they are added to single-use containers. They are specifically excluded from large-volume products intended for infusion. In some cases, as with benzyl alcohol, the excipient may have multiple functions. Therefore, the decision whether or not to include a preservative in a single-use product may be product specific. The rationale

Table 17.2. Additives Commonly Used in Parenteral Products

Substance	Concentration (percent)
Antimicrobial	
Benzalkonium chloride	0.01
Benzethonium chloride	0.01
Benzyl alcohol	1–2
Chlorobutanol	0.25–0.5
Chlorocresol	0.1–0.3
Metacresol	0.1–0.3
Phenol	0.5
Methyl p-hydroxybenzoate	0.18
Propyl p-hydroxybenzoate	0.02
Butyl p-hydroxybenzoate	0.015
Antioxidants	
Acetone sodium bisulfite	0.2
Ascorbic acid	0.1
Ascorbic acid esters	0.015
Butylhydroxyanisole (BHA)	0.02
Butylhydroxytoluene (BHT)	0.02
Cysteine	0.5
Monothioglycerol	0.5
Sodium bisulfite	0.15
Sodium metabisulfite	0.2
Tocopherols	0.5
Glutathione	0.1
Surfactants	
Polyoxethylene sorbitan monooleate	0.1–0.5
Sorbitan monooleate	0.05–0.5

for any preservative addition should be a part of the product development report.

Common antimicrobial agents are given in Table 17.2. These agents are grouped into five chemical classes: quaternary ammonium compounds, alcohols, esters, mercurials, and acids. The alcohols and esters are commonly used in parenteral products. The quaternary compounds, which are commonly used in ophthalmic products, are not compatible with negatively charged ions or molecules.

Table 17.3. Common Buffers Used in Parenteral Formulations

Buffer	pK_a	Usual Buffering Range
Acetic acid	4.8	3.5–5.7
Citric acid	3.14, 4.8, 5.2	2.1–6.2
Glutamic acid	2.2, 4.3, 9.7	8.2–10.2
Phosphoric acid	2.1, 7.2, 12.7	2–3.1, 6.2–8.2
Benzoic acid	4.2	3.2–5.2
Lactic acid	3.1	2.1–4.1
Ascorbic acid	4.2, 11.6	3.2–5.2
Tartaric acid	3.0, 4.3	2.0–5.3
Succinic acid	4.2, 5.6	3.2–6.6
Adipic acid	4.4, 5.28	3.4–6.3
Glycine	2.34, 9.6	1.5–3.5, 8.8–10.8
Malic acid	3.4, 5.1	2.4–6.1
Triethanolamine	8.0	7–9
Diethanolamine	9.0	8.0–10.0
Tromethamine	8.1	7.1–9.1

The literature reports interactions of the parabens with surfactants and formation of molecular complexes with gelatin, methylcellulose, polyvinyl pyrrolidone, and polyethylene glycol. These interactions may decrease preservative efficacy. Some antimicrobial compounds, such as benzyl alcohol, may be adsorbed by the container closure. Thus, microbial preservation must be demonstrated for the final formulated product.

Buffers

The buffer system establishes and maintains the product pH. A specific buffer system is selected such that the pK_a of the system is within one pH unit of the pH desired for the product. A list of common buffers is provided in Table 17.3. The selection of the product pH is based on the stability of the active drug. When alternative buffers are available, a comparison of their respective effects on stability will usually aid in the final choice. The acetate buffer system is not a good choice for a lyophilized product due to the volatility of acetic acid. Loss of acetic acid results in a pH shift when the product is reconstituted. The pH of solutions containing a phosphate buffer system have been shown to shift during cooling due to precipitation of sodium phosphate species. These pH shifts during freezing may cause

damage to a protein. Since the specific buffer and the buffer capacity can contribute to injection pain, these effects should be evaluated in the selection of the buffer. Each species of the buffer system affects the tonicity of the final product; this influence must be considered during product development. For example, as the pH of a formulation containing monosodium phosphate is adjusted, the disodium salt is formed and contributes to product tonicity.

Antioxidants

Preformulation data will identify compounds sensitive to oxidation. Free radicals or molecular oxygen mediates oxidation, and several alternative stabilization approaches are available. In many cases, several approaches are utilized concurrently. One approach is lowering the product pH, which, according to the Nernst equation, increases the oxidation potential of the drug and thus increases stability. When oxygen contributes to degradation, it can be displaced during the filling operation by "bubbling" an inert gas such a nitrogen or argon gas through the solution prior to filling the vials. Additionally, the container headspace can be overlaid with the inert gas. An antioxidant may be useful if further protection is necessary. The specific antioxidant selected should have a lower oxidation potential than the drug. Several antioxidants and concentrations should be evaluated because, in many cases, a single agent is not sufficient. Sulfites are associated with allergic reactions in some patients. This reaction has a rapid onset and is not always confirmed by an oral challenge. Despite this reaction potential, sulfites may be used in a formulation if necessary to stabilize a life-saving product.

Examples of antioxidants include sodium bisulfite, ascorbic acid, glutathione, and propyl gallate. Sodium bisulfite tends to react irreversibly with the double bonds found in aldehydes and some ketones, and frequently results in a significant loss of biological activity. Epinephrine forms a bisulfite addition product, as do other sympathomimetic drugs having ortho- or para-hydroxybenzyl alcohol derivatives. The meta-hydroxy alcohol does not react with sodium bisulfite. Sulfites are converted to sulfates in the oxidation reaction, and if small amounts of barium are present, a precipitate will form.

Chelating Agents

Chelating agents are used to increase the solubility of a drug or to impart some product stability. Compounds such as ascorbic acid, citric acid, and ethylenendiaminetetraacetic acid chelate metals, which would otherwise catalyze oxidation reactions, and provide measurable benefits for some products.

Surfactants

Surfactants are used to solubilize a drug and, for protein products, to minimize adsorption of the protein on surfaces. Most polysorbates are derived from animal sources, and their use in Europe is becoming problematic due to the increasing concerns with BSE. This concern is expanding to the rest of the world and will impact in the selection of excipients. Several suppliers are beginning to offer polysorbates from vegetable sources. Polysorbates can contain peroxides that may adversely affect product stability and, as for all excipients, specifications will need to be established.

Tonicity Agents

The active drug and each excipient contribute to the tonicity of the formulation. When the tonic contribution of these combined ingredients is not sufficient to provide an isotonic solution, then tonicity agents, such as dextrose, sodium chloride (NaCl), sodium sulfate, or mannitol can be added. Additional details are provided in the osmolality section below.

In summary, formulation activities focus on the selection of the solvent, the necessary excipients (buffers, antimicrobials, antioxidants, chelating agents, surfactants, and tonicity agents) with corresponding concentrations, the container/closure system, and on demonstrating adequate stability.

Focus on Osmolality, Cosolvents, Oils, and pH

The contribution of isotonicity in reducing injection pain is not always clear but, at a minimum, it may reduce tissue irritation. Injection pain may occur during and immediately following product administration but may be delayed or prolonged, with an increase in severity with subsequent injections. Pain can be difficult to assess because significant patient variation exists, and there are few preclinical methods for evaluation.

Literature describing pain associated with parenteral products has focused on three areas: osmolality, cosolvents, and pH. This is a pragmatic focus since osmolality and pH are easy to measure. Unfortunately, the adjustment of pH and osmolality may not be possible for some formulations due to physical or chemical stability of the product. In other products, the drug molecule may be inherently painful when injected. In both of these cases, formulations must be delivered at a low drug concentration or in complex formulations (such as emulsions or liposomes), in an attempt to "hide" the drug from pain receptors. Due to volume constraints, these are not always a viable alternative for IM or SC injections, leaving the formulator to design the best possible product and otherwise relying on the health professional to further minimize the injection pain at the time of administration. Since these formulations pose significant development

issues, most formulators optimize the pH and isotonicity and provide information on appropriate dilution for administration.

Osmolality

The primary purpose for adjusting product osmolality is to minimize red blood cell lysis, tissue damage, and pain when the product is administered. An isotonic solution provides an electrolyte environment that allows human erythrocytes to maintain "tone." If cells are placed into a hypertonic solution, the cells may lose water and shrink (crenation). If placed in a hypotonic solution, the water moves into the cells, which can then swell to the point of breaking. Thus, the formulator's goal is to develop a product that, when administered, will be as close to isotonic as possible. In fact, the British Pharmacopoeia states that aqueous solutions for SC, intradermal, or IM injections should be made isotonic if possible. Unfortunately, there is no formulation solution for a product that is hypertonic. The necessity for administration in a diluted form or by slow infusion is appropriately noted in the product package insert.

Common agents used to adjust tonicity of a product include dextrose, NaCl, mannitol, and sodium sulfate. Care must be taken if sodium sulfate is selected for a product packaged in barium-containing glass, because even extremely small amounts of leached barium can lead to the precipitation of barium. Since all ingredients contribute to the tonicity of the product, it is necessary to measure or calculate the contribution of each and then, if necessary, adjust the product tonicity with additional agents.

Measuring Osmolality. Determination of osmolality is performed by measuring one of the four colligative properties, which depend only on the number of "particles" in the solution: (1) osmotic pressure elevation, (2) boiling point elevation, (3) freezing point depression, and (4) vapor pressure elevation. Of these methods, freezing point depression and vapor pressure elevation are most commonly utilized. These methods are relatively easy to perform and reasonably accurate. Commercial instruments are readily available.

Iso-osmolality, as determined by physical methods such as freezing point depression or vapor pressure reduction, is different from isotonicity determined by biological methods such as erythrocyte hemolysis. This difference is important since cells do not always behave as semipermeable membranes, and measuring biological compatibility by direct methods will identify problematic molecules that can cause lysis or tissue damage. Urea is the most frequently cited example of such a molecule; a 1.8 percent solution of urea has the same osmotic pressure as NaCl at 0.9 percent, but causes cell lysis. Other compounds that have specific cellular effects include glycerin, propylene glycol, and boric acid.

Although physical methods such as freezing point depression and vapor pressure are valuable tools in formulation development and quality control of the product, it is imperative to have direct methods to measure the effect of the product on red blood cells and tissue. Methods to evaluate cellular effects are given below, and methods to evaluate tissue effects are provided in other chapters of this book. The references provide additional information, and formulators are encouraged to include them in their library.

Determining Tonicity (Hemolysis). A common in vitro method to evaluate a product is by measuring erythocyte hemolysis. Typically the release of hemoglobin from the damaged cells is measured spectrophotometrically; however, a more sensitive method is to directly observe the changes in cell volume. An aqueous isotonic NaCl solution is used as the standard. Several protocols are available that describe incubating the product with erythrocytes suspended in defibrinated blood for a specified time, centrifuging to separate the erythrocytes and ghost cells, and then using a spectrophotometer to determine the absorbance of the supernatant versus a standard at 520 nm. Solution to blood ratios of 100:1 have been used. Concerns that this ratio is not realistic and can often give misleading results has lead investigators to use dilutions of 1:10—a complete reversal of proportions—with no hemolysis found.

Others have evaluated product effects by directly observing variations of red blood cell volume when suspended in solution. This method is more sensitive to small tonicity differences than the hemolysis method.

An alternative method to determine the compatibility of a product with blood is proposed by Ito et al. (1966). The coil planet centrifuge (CPC) method was originally developed to examine dynamic membrane properties of erythrocytes. The system comprises three instruments: the CPC itself, gradients for preparing the solution having an osmotic gradient in a coil, and a scanning spectrophotometer for recording a hemolytic pattern of the sample coil. The CPC is a specific centrifuge that rotates at 1,600 rpm around the main axis at a constant temperature of 37°C, while the coil holder fitted with coils rotates at 16 rpm. The design of this equipment ensures that the centrifugal force is constant irrespective of the distance from the main axis. It has been found that measuring the hemolysis of oil injections and those of high concentration or viscosity by this method is difficult, if not impossible.

The "osmogram" output shows red blood cell hemolysis as a function of the osmotic gradient. The hemolytic pattern of injections are divided into the following four patterns:

1. Hemolysis is remarkable, or erythrocyte is coagulated and does not move.

2. Hemolysis takes place gradually and then continues or is shifted to the side of high osmotic pressure.
3. No change is observed.
4. Pattern is shifted to low osmotic pressure, indicating stabilization of the erythrocyte membrane.

This method may provide valuable information for the evaluation of parenteral products; however, the full potential of the method is unknown since there is little information available.

Calculating Tonicity. Several methods used to calculate tonicity are summarized below.

(1) The method of NaCl equivalents expresses tonicity in terms of the amount of drug equivalent to NaCl since, in most cases, when an aqueous solution is iso-osmotic with 0.9 percent NaCl, it will be isotonic with physiologic systems. The NaCl equivalent value, E, is defined as the weight of NaCl having the same osmotic effect as 1 g of the drug. A 1 percent NaCl solution has an equilibrium freezing temperature of -0.58°C and is given a NaCl E value of 1.00. The freezing temperature of serum is -0.52°C, equivalent to the freezing temperature of a 0.9 percent NaCl solution. Therefore, if a 1 percent solution of a specific compound has a freezing temperature of -0.058°C, then it has an E value of 0.1. Thus, 1.0 g of this compound will have the same tonic value as 0.1 g of NaCl; to prepare 100 mL of an isotonic solution containing 1 g of this substance, 0.8 g of NaCl must be added. *Remington's* (Gennaro 1995) has an extensive list of NaCl equivalents for specific excipients and drugs.

Different compounds can be used to adjust solution tonicity. For example, in the above calculation, 0.8 g of NaCl was needed to render the solution isotonic. If, however, dextrose is desired to adjust tonicity, then the amount of dextrose would be

$$(1 \text{ g dextrose}/0.16 \text{ g NaCl}) \times 0.8 \text{ g NaCl} = 5 \text{ g dextrose}$$

A comparison of measured osmolality to calculated values using the NaCl equivalent method shows agreement within 10 percent; for most systems this is sufficiently accurate.

(2) The freezing point depression method uses "D" values having units of °C per x percent of drug. The D values for some drug compounds can be obtained in the literature.

(3) The V value of a drug is the volume of water used to dissolve a specific weight of drug to prepare an isotonic solution. The purpose of this method is to prepare an isotonic solution of the drug and then to dilute this to the desired final concentration with a suitable isotonic vehicle. This method is most commonly used for ophthalmic preparations. Values for commonly used drugs are available in the literature.

(4) Other calculations such as the L_{iso} method can be used for estimations when values for a specific compound are not available. The mathematical relationship of L_{iso} to the NaCl equivalent, E, is:

$$E = 17 (L_{iso}/M)$$

where M is the molecular weight of the compound. Average L_{iso} values for different types of compounds are given in Table 17.4.

Cosolvents and Oils

Cosolvents are commonly used to enhance drug solubility and stability. Cosolvents may include ethanol, propylene glycol, polyethylene glycols, and glycerin. These components have intrinsic effects on biologic tissue and can alter the properties of other excipients, thus influencing the tissue damage or pain caused by the product. There is a dearth of literature on the pain caused by cosolvents, but there is also a growing body of knowledge on the tissue damage that they can cause. It is not certain that tissue damage is always directly correlated with injection pain, but minimization of both pain on injection and potential for tissue damage should be included in the product development plan.

In studies by Brazeau and Fung (1989a, b), moderate concentrations of organic cosolvents (20 to 40 percent v/v) show the following relative myotoxicity ranking: propylene glycol > ethanol > polyethylene glycol 400. These investigators also discovered that total myotoxicity equaled the sum of the individual myotoxicity of each component, with the exception of preparations containing polyethylene glycol 400, which apparently has a protective effect.

Table 17.4. Average L_{iso} Values for Different Types of Compounds

Compound Type	L_{iso}	Example
Nonelectrolyte	1.9	Sucrose
Weak electrolyte	2.0	Phenobarbital, boric acid
Di-divalent electrolyte	2.0	Zinc sulfate
Uni-univalent electrolyte	3.4	Sodium chloride
Uni-divalent electrolyte	4.3	Sodium sulfate, atropine sulfate
Di-univalent electrolyte	4.8	Calcium chloride
Uni-trivalent electrolyte	5.2	Sodium phosphate
Tri-univalent electrolyte	6.0	Aluminum chloride
Tetraborates	7.6	Sodium borate

Consideration must also be given to cosolvent effects on other product excipients. Since most buffers are conjugates of a weak acid or base, the polarity shift caused by cosolvents may shift the pK_a of the buffer species. It is best to evaluate biological compatibility using direct biological methods, because cosolvents may have both specific cellular effects and indirect excipient effects.

Another class of nonaqueous vehicles used in parenteral formulations are the fixed oils, including corn, cottonseed, olive, peanut, sesame, and soybean. Oils of vegetable origin are selected because they can be metabolized, are liquid at room temperature, and will not rapidly become rancid. To remain liquid at room temperature, a fixed oil must contain unsaturated fatty acids, which, when present in excessive amounts, can cause tissue irritation. The U.S. Pharmacopeia (USP) includes specifications for rancidity, solidification range of fatty acids, and free-fatty acids. The formulator may include antioxidants, such as tocopherol (a natural component of many fixed oils) to prevent the product from becoming rancid.

pH

A product buffer system is selected to help maintain an environment in which the drug is stable throughout the commercial shelf life of the product. These systems are composed of a weak acid or base and a corresponding salt. The ratio of these species determines the pH, and the concentration provides a buffer capacity to resist pH changes due to product degradation or container-closure interactions. A buffer system is most efficient at its pK_a, thus, buffers are generally chosen within one pH unit of the desired product pH.

The buffer concentrations typically chosen for a product range from 1 to 2 percent, although higher concentrations of up to 5 percent have been used with citrate buffers. The more a pH deviates from physiological conditions and the higher the buffer capacity, the more likely the product will contribute to tissue damage or injection pain. Table 17.3 provides a list of acceptable buffers with pK_a values and usual pH buffer ranges.

Buffer systems are in an equilibrium that is sensitive to temperature and the concentration of each species. Each species in this equilibrium may contribute differently to product osmolality. There may be an error in estimating the contribution to osmolality of each species at room temperature, since the most common method to measure osmolality is by freezing point depression. Cutie and Sciarrone (1969) demonstrated for boric acid, Sorensen, and Palitzsch buffers that if formulated to be isotonic as measured by freezing point depression, the solutions may be slightly hypertonic at 37°C. Sodium tetraborate has, in fact, been demonstrated to have a NaCl equivalent (E value) of 0.45 at 37°C but 0.35 at 0°C, a 23 percent change. For most formulations, this is not of physiological significance;

however, it should not be discounted for those formulations where close tolerance to isotonicity is necessary.

A vapor pressure osmometer provides an alternative to the freezing point method and may be particularly useful when the data for temperature and concentration effects on ionization constants are not available. A limitation of the vapor pressure method includes interference by volatile substances such as ethanol.

Post-Formulation Procedures

Despite efforts to minimize or eliminate pain through formulation optimization, some products remain painful when injected. The literature is replete with suggestions on how to reduce pain during the administration of a product. Unfortunately, much of these data are incomplete or seemingly contradictory. Deficiencies in the research conducted on children's pain have been noted, and the point is frequently made that children are shortchanged with respect to pain management. Post-formulation efforts to alleviate pain which are discussed in this chapter are included in the following categories: pH, additives or solvent adjustments; devices or physical manipulations, and psychological.

pH, Additives, and Solvents

Drugs stable only in acidic conditions are purposefully formulated to ensure an adequate commercial shelf life. Because these acidic products are associated with injection pain, sodium bicarbonate is extemporaneously added prior to administration to more closely match physiological pH (pH 7.3). This approach appears to successfully reduce the pain caused by local anesthetics; however, studies with other products have been equivocal. For anesthetics, this increased pH will alter the stability of the product and may result in the precipitation of the less soluble, nonionized species. The amount of sodium bicarbonate that can be safely added is variable given the range of anesthetic products (pH of 3.5 to 5.5), the concentration of sodium bicarbonate, and other variables.

The reduction in pain for anesthetic products does not appear to be entirely due to the increased pH of the solution. The indirect effect of increasing product pH is to shift the equilibrium of anesthetics to the uncharged species that may diffuse more rapidly and consequently inhibit pain perceptions. Individual drugs or drug species (charged or uncharged) may have different intrinsic pain induction potential, independent of pH. The study design and product ingredients must be considered when evaluating data, because some excipients such as benzyl alcohol have local anesthetic properties.

Another extemporaneous technique is to add lipids to the commercial formulation. This method shifts more of the drug from the aqueous phase and has been successful in reducing injection pain for methohexital and propofol. Such additions need to be supported by studies to verify product stability, similar pharmacokinetics, and efficacy.

Clinicians also minimize or eliminate injection pain by topical administration of local anesthetics, which decrease pain sensation, or nitroglycerin ointment, which dilates local blood vessels and promotes absorption of the irritating substance. Although of interest to the formulator, these topical approaches do not pose formulation issues.

Devices and Physical Manipulations

Parenteral administration techniques will affect the magnitude of the pain. These include the practical training received by healthcare professionals; proper selection of administration equipment; and manipulation of the injection rate, injection site, and temperature. The formulator should note how health professionals may use the product and consider the need for pertinent data during product development.

Parenteral administration techniques are part of a nurse's education. This practical training is aimed at increasing the comfort of the patient and efficiency of the nurse. The references given at the end of this chapter provide additional detail and information on less common parenteral routes of administration.

Subcutaneous Injection

Drugs recommended for SC injection include nonirritating aqueous solutions and suspensions contained in 0.5 to 2.0 mL (target 1 mL or less) of fluid. The needle sizes are 25 gauge 5/8 in. length for an average adult and 25 gauge 1/2 in. length for an infant, child, elderly, or thin patient. After cleaning the area with an alcohol sponge, allow the skin to dry before skin penetration to avoid the stinging sensation caused by the alcohol entering the subcutaneous tissue.

With the nondominant hand, grasp the skin around the injection site firmly to elevate the subcutaneous tissue, forming a 1 in. fat fold. This provides rigidity for needle entry. Tell the patient "you will feel a prick as the needle is inserted." Holding the syringe in the dominant hand with the needle bevel up, insert the needle quickly in one motion. Release the patient's skin to avoid injecting the drug into compressed tissue to minimize irritation of nerve fibers, confirm the needle is in the tissue, and inject slowly. After the injection, remove the needle quickly. Cover the skin and massage the site gently (unless contraindicated as with heparin or insulin) to help distribute the drug and reduce pain.

Intradermal Injection

Intradermal injections are typically used only for local effects or diagnostic purposes in volumes of 0.5 mL or less. Needles of 26 or 27 gauge and 1/2 to 5/8 in. in length are used. The injection is given at a 15° angle about 1/8 in. below the epidermis at sites 2 in. apart. Stop when the needle bevel tip is under the skin and inject slowly; some resistance should be felt. A wheal should form; if it does not, the injection is too deep. Withdraw the needle at the same angle as the entry. Do not massage the site, as this may cause irritation.

Intramuscular Injection

IM injections deliver medication into highly vascularized deep muscle tissue. Because there are few sensory nerves in these tissues, pain is minimized when injecting irritating drugs. The volume for IM injection can be up to 5 mL, although it is typically less than 3 mL. A 20 to 25 gauge needle of 1 to 3 in. in length is used. Once the appropriate injection site has been selected and properly prepared, gently tap it to stimulate nerve endings and minimize pain when the needle is inserted. The gluteal muscles should not be used for a child under the age of 3, nor for someone who has not been walking for the prior year. Never inject into sensitive muscles, especially those that twitch or tremble when you assess site landmarks. Injections in these trigger areas may cause sharp or referred pain, such as pain caused by nerve trauma.

Intravenous Bolus Injection

Bolus drug administration is used when immediate drug effects are necessary, when the drugs cannot be diluted (diazepam, digoxin, phenytoin), or for drugs that are too toxic or irritating for other routes of administration. A 20 gauge needle is typically used. Bolus injections are given through the largest vein suitable, since the larger the vein, the more dilute the drug becomes, thus minimizing vascular irritation. An in-depth discussion of specific routes of administration, techniques, equipment, and cautions is readily available in the literature referenced at the end of this chapter.

Devices

Devices offer significant opportunities to reduce the fear and increase the consistency of parenteral injections. Some of these devices are needle free, with the product propelled through the skin under pressure. Some studies have demonstrated reduced pain during administration. These devices may affect the quality of a shear-sensitive macromolecule or alter drug

pharmacokinetics (PK) due to the pattern of drug deposition. For a given product, additional product or PK characterization may be necessary. These devices deliver subcutaneous injections; however, controversy remains on whether they can deliver an IM injection.

Other devices use "hidden" needles with guides that facilitate insertion of the needle and subsequent injection of the medication. These allow for reproducible injections. Their utility is dependent on the perception of the patient, the cost of the device, and the ease of use. These devices have been shown to be less painful and improve compliance for chronic administration of SC injections.

Temperature

Healthcare providers continually explore methods to increase the comfort of the patient by altering the temperature of the product or skin. Numbing the skin surface with ice or other means has successfully been used to reduce injection pain; in one case, injecting a cool solution before infusing the drug appeared to be successful in reducing pain. Changing the product temperature is more significant to the product formulator. Warming propofol to 37°C has been demonstrated to decrease the incidence of pain by 37 percent. Since both cooling and warming have been shown to reduce injection discomfort, it may be that some relief is provided by the quick, but transient temperature effects on the nociceptor receptors or pain mediators. The formulator should be aware that products might be either cooled or warmed by healthcare professionals and, therefore, consider the impact of temperature changes on the formulation during product development.

Psychological

The contribution of psychological factors to injection pain is substantial and has been considered in the design of the new devices mentioned previously. Psychology is used in the clinic to minimize injection pain, particularly in children. These are interesting and provided here for completeness.

The pain experience is influenced by age, physical, emotional, cultural, and, social factors as are the preferred control methods. A Gallup Poll stated that 58 percent of children rely on their own coping skills, such as thinking about something else to make shots bearable, and 47 percent said they specifically disliked needles. Perhaps we as healthcare providers can provide more assistance.

Several articles provide lists and examples of proactive psychological techniques shown to minimize injection pain, including distraction, honesty, and a demonstration of caring. Distraction asks the patient to focus on an image and and to use breathing techniques. The person giving the injection should be honest yet supportive while making general sympathetic statements that indicate the child can control pain. The child should

be involved in discussions, and all actions should be described before or as they are being performed.

The psychology and perception of pain are important factors in pain management and both the healthcare provider and formulator can effectively utilize the techniques mentioned above in the development, support, and administration of therapeutic products.

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ATTACHMENT F - COMPILATION

TAB 5

United States Patent Office

3,164,520

Patented Jan. 5, 1965

3,164,520

INJECTABLE STEROID COMPOSITIONS CONTAINING AT LEAST 75% BENZYL BENZOATE

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No Drawing. Filed Oct. 29, 1962, Ser. No. 233,931

4 Claims. (Cl. 167—58)

This invention relates to compositions of matter and more particularly to new parenterally administrable pharmaceutical compositions comprising one or more active medicaments and a physiologically acceptable non-toxic pharmaceutical vehicle, comprised essentially of benzyl benzoate.

The active medicament which may be incorporated in the novel compositions of this invention may be any one which is administered for use in comparatively large unit dosages, for example, 10 mg./ml. to 500 mg./ml. and which is soluble in benzyl benzoate. Examples of the medicaments which may be employed in this invention include inter alia, steroid hormones, especially those steroid hormones which exhibit anabolic, estrogenic, androgenic and progestational activity, for example, 17-hydroxyprogesterone and the esters thereof, testosterone, estradiol and the acid esters thereof, progesterone and its derivatives and Δ^1-testololactone and its derivatives. In the most preferable embodiment of this invention the active medicament is a steroid hormone although other pharmaceutically active compounds may also be employed, with satisfactory results.

Heretofore it has been well recognized in the preparation of parenterally administrable pharmaceutical compositions that a suitable solvent must be employed to render the composition injectable. However, as the science of medicine has progressed it has been found that increasingly higher dosages of certain medicaments must be employed in the treatment of certain ailments in order to achieve several advantages. Among these advantages can be numbered the prolongation of activity of the medicaments involved and the lessening of the total number of individual injections which are needed to obtain the same results.

Additionally, it has been found that new chemical modifications of medicaments are continually being discovered and the solubility of these modified medicaments in the solvents commonly employed, appears to be more and more limited and it has therefore become increasingly difficult to dissolve these new modified medicaments in parenterally acceptable vehicles. It is well-known that certain pharmaceutical vehicles yield satisfactory results at low level medicament concentrations when employed in compositions for parenteral administration. Such vehicles are the vegetable oils such as cotton seed oil, peanut oil, sesame oil, or corn oil, in combination with small amounts of benzyl benzoate. However, when an increased dosage level of the medicaments is employed, along with a correspondingly necessary increased amount of pharmaceutical vehicle it has been found that certain undesirable disadvantages exist.

The undesirable disadvantages which are present when the prior art vehicles are employed with a high dosage level of medicaments, are many. In addition to the prior art vehicles being incapable of solubilizing any great quantities of the medicaments, it has been found that the compositions heretofore employed produce an undue amount of irritation at the site of injection, when parenterally administered into the animal being treated.

It has now been found that the disadvantages encountered in the parenteral administration of high dosage levels of the medicaments of this invention can be avoided by employing the novel pharmaceutical compositions of

this invention. It has been found that these disadvantages can be overcome by employing benzyl benzoate as the essential component of the pharmaceutical vehicle of parenterally administrable compositions. The benzyl benzoate has been found to be capable of dissolving great quantities of the medicaments of this invention and the resulting parenterally administrable composition employing this vehicle does not produce undue irritation when injected into the animals being treated.

The amount of benzyl benzoate which may be employed in the compositions of this invention while still yielding satisfactory results has been found to range from about 75% to 100% by volume of the pharmaceutical vehicle employed. Thus the ratio of benzyl benzoate present in the pharmaceutical vehicle as compared to any other ingredients therein must be at least 3 to 1. In the most preferable embodiment of this invention it has been found that a pharmaceutical vehicle consisting essentially of pure benzyl benzoate yields the best results although at lower levels satisfactory results are also obtained.

As is common in the art of preparing parenterally administrable pharmaceutical compositions other additives such as preservatives, antioxidants or anesthetics, such as benzyl alcohol and the other like well known additives may also be included in the pharmaceutical compositions of this invention. However, their use herein is permissive and not mandatory as their incorporation or omission in the final product of this invention does not substantially affect the results herein obtained.

The compositions of this invention are easily prepared by merely taking the desired amount of medicament and dissolving it in the pharmaceutical vehicle of this invention by any means known in the art, for example, by mere stirring.

The final compositions of this invention are parenterally administrable to the animal being treated. The administration of the composition may be accomplished intramuscularly, subcutaneously or in any other manner known to the art as may be determined in the individual cases wherein this invention is employed. It has been generally found that the most preferable results are obtained when an intramuscular route of administration is employed, although other methods of administration will also give satisfactory results.

The invention is more particularly illustrated by the following examples:

Example 1

Two g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 10 ml. of benzyl benzoate with stirring and warming. The resultant solution is then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for two hours.

0.25 ml. of the resulting solution is then injected into the vastus lateralis muscle of a rabbit producing a lesion at the site of the injection having the size of about 640 cubic millimeters after two days.

When 2 g. of the acetophenone derivative of 16,17-dihydroxyprogesterone are dissolved in 4.5 ml. of benzyl benzoate and 5.5 ml. of castor oil in accordance with the procedure of Example 1 and 0.25 ml. of the resultant solution is injected intramuscularly into the rabbit a lesion at the site of injection having a size of 967 cubic millimeters after two days.

Example 2

The procedure of Example 1 is followed except that 2 g. of testosterone palmitate are substituted for the acetophenone derivative of 16,17-dihydroxyprogesterone of Example 1.

0.25 ml. of the resultant solution is injected intramus-

cularly into a rabbit producing a lesion at the site of injection having the size of about 420 cubic millimeters after two days. When 2 g. of testosterone palmitate are dissolved in a vehicle consisting of 40% castor oil and 60% benzyl benzoate and the resultant solution is injected intramuscularly into the rabbit, a lesion at the site of injection having a size of 610 cubic millimeters is produced after two days.

Example 3

A 25% solution of progesterone is prepared by dissolving 2.5 g. of progesterone in benzyl benzoate to make 10 ml. Sterilization is obtained by autoclaving the solution at 121° C. for 2 hours. When 0.25 mg. of this solution is injected into the vastus lateralis muscle of the rabbit, a lesion is produced which, after 2 days, measures 672 cubic millimeters.

When 2.5 g. of progesterone are dissolved to make 10 ml. in a mixture of 50% benzyl benzoate and 50% castor oil as the vehicle, and 0.25 ml. of this solution is injected into the rabbit muscle, a lesion size of 898 cubic millimeters is produced after two days.

Example 4

A 50% solution of hormones is prepared by dissolving 2.5 g. of progesterone and 2.5 g. of 17-hydroxyprogesterone caproate in benzyl benzoate to make 10 ml. of final product. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle and the lesion size is measured after 2 days. A lesion consisting of 572 cubic millimeters was produced. When this same hormone combination in the same proportions was dissolved in a vehicle consisting of 46% benzyl benzoate and 54% castor oil, a rabbit muscle lesion size of 1047 cubic millimeters is produced 2 days after injection of 0.25 ml. of test material.

Example 5

A 40% solution of testosterone enanthate is prepared by dissolving 4.0 g. in benzyl benzoate to make 10 ml. of final volume. After autoclaving at 121° C. for 2 hours to sterilize, 0.25 ml. of the solution is injected into the vastus lateralis muscle of the rabbit and the lesion size is measured after 2 days. A lesion consisting of 847 cubic millimeters is produced.

When this same quantity of hormone is dissolved in a vehicle consisting of 20% benzyl benzoate and 80% sesame oil and 0.25 ml. is injected a lesion size of 1441 cubic millimeters is produced.

Example 6

A 5% solution of Δ^1-testololactone is prepared by dissolving 50 mg./ml. in benzyl benzoate and after autoclaving to sterilize, 0.25 ml. of the solution is injected into a rabbit muscle. After 2 days a lesion size of only 483 cubic millimeters is produced.

Example 7

15 mg. of Δ^1-testololactone is dissolved in a solution comprised of 7.5 ml. of benzyl benzoate and 2.5 ml. of castor oil. The resultant solution is sterilized, then filled in vials of 5 ml. each and sterilized by autoclaving at 121° C. for 2 hours. The injectable solution may then be administered to the patient being treated.

This invention may be variously otherwise embodied within the scope of the appended claims.

What is claimed is:

1. A parenterally administrable pharmaceutical composition comprising the acetophenonide of 16,17-dihydroxyprogesterone and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

2. A parenterally administrable pharmaceutical composition comprising testosterone palmitate and a physiologically acceptable non-toxis pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

3. A parenterally administrable pharmaceutical composition comprising testosterone enanthate and a physiologically acceptable non-toxic pharmaceutical vehicle wherein at least 75% by volume of said vehicle is benzyl benzoate.

4. A method of administering a large single dosage of a steroid which comprises parenterally administering to the patient being treated a composition comprising a steroid selected from the group consisting of 17-hydroxyprogesterone, the caproate ester of 17-hydroxyprogesterone, testosterone, the enanthate ester of testosterone, the palmitate ester of testosterone, estradiol, progesterone, and Δ^1-testololactone, and a pharmaceutical carrier, said carrier being at least 75% by volume of benzyl benzoate.

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ATTACHMENT F - COMPILATION

TAB 6

USE OF NONAQUEOUS SOLVENTS TO PREPARE INJECTION SOLUTIONS

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T. P. Litvinova, and L. M. Yakimenko

UDC. 615.456.2.014.24

Until now a rather considerable number of solvents which are used to prepare injection solutions has been described in the literature. These can be divided into three basic classes: aqueous, nonaqueous, and mixed solvents.

To the class of aqueous solvents we can assign those in which water is the main component. This can be water for injections, solutions of various inorganic salts in water, cosolvents used to accelerate the solution of the active materials, and the like.

To the class of nonaqueous solvents we may assign those in which the main component is some organic compound which permits one to obtain solutions of medicinal agents that are suitable for injections – vegetable oils, polyethylene oxides, or the like.

And finally, to the class of mixed solvents we may assign solvent mixtures which enable one to prepare injection solutions when it is not possible to prepare stable solutions by using the individual solvents, or when one wishes to make sure of obtaining a number of fixed solution characteristics, for example, a given dwelling time of the active substance in the blood system, or the like.

The present review is devoted to the use of nonaqueous solvents to prepare injection solutions.

Solvents which belong to the nonaqueous class present special interest, since using them permits one to prepare injection solutions of substances which are unstable in water or do not dissolve in it, to obtain solutions with an increased suitability time, and also to solve a number of other technological and pharmacological problems.

The following requirements are imposed on these solvents:

1. Pharmacological harmlessness: a) limited acute toxicity; b) limited chronic toxicity (on repeated introduction); c) absence of local (irritating) action in the doses employed.

2. Absence of an effect of increasing toxicity at an adequate therapeutic action of the solution and medicinal agent.

3. Chemical compatibility.

4. Technological suitability: a) high dissolving power; b) possibility of sterilization; c) low viscosity; d) absence of reaction with apparatus; e) absence of fire hazard.

5. Availability.

From the point of view of therapeutic effect, an important property of a solvent is its solubility in water or miscibility with it. On this may depend the rate of action of the medicine, the rate of solvent reabsorption, and local transferability.

In a number of cases, when the active substance is insoluble or poorly soluble in water, contact with tissues causes precipitation of the active substance at once after subcutaneous or intramuscular introduction;

Institute of Experimental and Clinical Oncology, Academy of Medicinal Sciences of the USSR, Moscow.
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TABLE 1. Most Important Characteristics of Vegetable Oils Used to Prepare Injection Solutions

Oil	Saponification No.	Iodine number	Acid No.	Refractive Index	Density
Almond oil	190—195	93—102	<2,5	1,470—1,472	0,913—0,918
Peanut oil	185—197	85—105	<2,0	1,468—1,47250 (40°)	0,910—0,920
Cottonseed oil	190—198	109—116	<0,4	1,4645—1,4655 (40°)	0,915—0,921
Sunflower oil	188—194	125—136	<0,5	—	0,917—0,924
Corn oil	187—193	102—128	<0,4	—	0,914—0,921
Olive oil	190—195	79—88	<0,2	—	0,910—0,915
Peach oil	187—195	96—103	<2,5	1,470—1,473	0,914—0,920
Sesame oil	188—195	103—116	<2	1,472—1,476	0,916—0,921

this is regulated by the rate of diffusion and resorption of the solvent by the organism. Thus, in this case the solvent has the function of a carrier, which permits one to make the injection.

In other words, a substance which is insoluble in water has a different "fate," depending on where it was introduced – under the skin or into a muscle, and whether it was dissolved in a nonaqueous solvent which mixes or does not mix with water. In the first case the medicine is precipitated more or less rapidly, and naturally is resorbed more or less rapidly by the organism. In the second case it remains in a solution which diffuses slowly around the site of injection. When the solution is resorbed, the medicine manifests its activity. Therefore, in each separate case of preparing an injection solution in an nonaqueous solvent it is necessary to take into account the properties of the solvent and the therapeutic effect which one wishes to attain.

Of all the nonaqueous solvents, the following have the greatest practical value: vegetable oils, ethyl oleate, propylene glycol, and polyethylene glycols with molecular weights of 300 and 400.

Together with water, vegetable oils are most frequently used as solvents. This is explained not only the appropriate properties of the oils, which determine their use for injections, but also by the fact that they came first into pharmaceutical practice as solvents. The long time of use of vegetable oils as solvents for injection has made it possible to find rather effective and reliable methods for purifying them, for storing and sterilizing them, and for studying their pharmacological properties.

It should be noted that oils are used mainly for intramuscular injections; only rarely for subcutaneous ones. In recent years a number of authors have proposed ultra-emulsions of vegetable oils (cottonseed, soya, sesame, or sunflower) for parenteral feeding.

In Table 1 we give the most important characteristics of the oils which are used as solvents, according to data from various pharmacopoeias. And, still, fatty oils have limited use; first, they have a high viscosity, in connection with which oil injections are painful; second, only a small number of medicines dissolve in oils. Finally, oil injections can cause granuloma formation. Attempts are being made to reduce the significance of these defects of oil solutions. For example, in individual cases ethyl ether or an ethylene glycol ether is added to reduce viscosity. The solubility of some materials is increased by adding "cosolvents" (benzyl benzoate, benzyl alcohol, or the like). In those cases where the substance dissolves only in an oil or the oil is a stabilizing agent for the medicine, the use of oil is quite justified.

In recent years, synthetic and semisynthetic preparations have been acquiring ever-increasing importance as solvents for injection; these make up a very numerous group of the nonaqueous solvents and belong to various classes of chemical compounds. Here belong the alcohols (ethyl, benzyl, phenylethyl, propylene glycol, butylene glycol, trichloro-t-butyl, etc.), ethers and esters (polyoxyethylene glycol, ethyl ether, phenoxyethanol, ethyl acetate, ethyl oleate, benzyl benzoate, etc.), amides (N-methylacetamide and N,N-dimethylacetamide), sulfoxides, and the like.

In Table 2 we give the basic characteristics of solvents of the ester or ether group. The solvents of this group belong to the esters and ethers formed by various alcohols and acids. Some of them are used as replacements for oils. The esters used as solvents are less viscous media. To these belong the esters of organic acid with 8 to 23 carbon atoms: those of oleic and butyric acids, octyl levulinate, etc. Ethyl oleate has received very wide circulation at present; its characteristics are given in more detail below.

TABLE 2. Basic Characteristics of Solvents of the Ether–Ester Type

Name, formula	Mol. wt.	d	Bp (in deg)	Solubility	Toxicity
Diethyl ether $C_2H_5OC_2H_5$	74,12	0,713	35,6	Solubility in water – 6.5%; dissolves in alcohol, readily soluble in chloroform or benzene	Toxic
Ethyl acetate $CH_3COOC_2H_5$	88,10	0,901	77,15	Soluble in water, alcohol, or ether	Toxic
Phenoxyethanol $C_6H_5OCH_2CH_2OH$	138,17	1,1094	237, 245	Solubility in water, 2.6 g per 100 ml; readily soluble in alcohol or ether	—
Ethyl lactate $CH_3CH(OH)COOC_2H_5$	118,14	1,031	134—135 [18] 150—152, 154	Readily miscible with water. Used as a cosolvent in preparing oil solutions of steroid hormones	LD_{50} subcutaneously, 2.5 ml/kg; intravenously, 0.6 ml/kg (mice)
Isopropyl myristate $CH_3(CH_2)_{12}CH_2COOCH(CH_3)_2$	978,0	0,852	—	Immiscible with water; miscible with oils	LD_{50} intraperitoneally, 100 ml/kg (mice)
Diethyl carbonate $C_2H_5OCOOC_2H_5$	118,14	0,9751(20) 4	125,8	Immiscible with water; miscible with alcohol or ether.	LD_{50} (60% in olive oil) 28 ml or 15 mg per kg of weight (rats)

ETHYL OLEATE

$C_6H_5COOCH_2C_6H_5$

This is a light yellow, oily liquid with a strong disagreeable odor. It is insoluble in water, but mixes with fatty oils, alcohol, or ether. Its specific gravity is 0.869–0.870 (at 20°). Its acid number is 0.3–0.5 mg KOH/g; peroxide number, 0.07% iodine (not more); iodine number, 73–82.

According to the recommendation of the International Pharmacopoeia, it should be used as the solvent for desoxycorticosterone acetate, menadiol, estradiol monobenzoate, progesterone, and testosterone propionate. Ethyl oleate is described also in the pharmaceutical codes of England (1963) and the U. S. A. (volume XXV), as well as in the pharmacopeias of France (1958) and England (1958, 1963).

In distinction from vegetable oils, ethyl oleate has a greater dissolving power and a constant chemical composition. Like the fatty oils, it is well tolerated by the ill, with this sole difference – it is less viscous and is absorbed more rapidly into the tissue. A greater intensity and duration of action of testosterone phenylpropionate or testosterone propionate in ethyl oleate has been noted, as compared with preparations in corn oil [4]. A greater activity of hormones in ethyl oleate solution has also been reported more recently [5].

Ethyl oleate is sterilized by heating at 150° for 1 h. The coefficient of thermal expansion is rather large (over 10% on heating to 150°). It is recommended to sterilize solutions in closed vessels, which are filled with an inert gas (nitrogen). If the substances to be dissolved in it do not withstand sterilization, then the ethyl oleate is sterilized separately. It is recommended to add 2 or 3% of benzyl alcohol [6]. Ethyl oleate reacts with rubber to a greater extent than fatty oils.

BENZYL BENZOATE

$CH_3(CH_2)_7CH = CH(CH_2)_7COOC_2H_5$

This is the ester of benzyl alcohol with benzoic acid. It is a transparent, colorless, oily liquid with an agreeable aromatic odor; its taste is sharp and stinging. It hardly dissolves at all in water or glycerine, but it mixes with alcohol, chloroform, ether, or fatty oils. Its specific gravity is 1.118; bp, 323°.

According to the literature [5], the toxicity of this ester is slight; however, it exerts its own pharmacological action (a depressive action on the operation of the heart and respiratory organs), which should apparently limit its use. In the USSR it was authorized for medicinal use by order No. 182 of the Ministry of Public Health of the USSR, March 30, 1970. As a medicinal preparation it is used in dermatological practice for treating all forms of rashes. By the state pharmacopoeia of the USSR, edition 10, it is authorized for use in injections of a 2.5% solution of progesterone in peach oil: progesterone, 10 or 25 g; benzyl benzoate, 200 ml; peach oil, to 1 liter.

A "pure" benzyl benzoate manufactured in the USSR is offered by the S. Ordzhonikidze Scientific-Research Institute of Ord-

TABLE 3. Basic Properties of Solvents of the Monohydric Alcohol Group

Name, formula	Mol. wt.	d	Bp (in deg)	Solubility	Toxicity, LD_{50}
Ethyl alcohol C_2H_5OH	4607	0.789	78.32	Readily soluble in water, ether, chloroform, or methanol	Intravenous, 1973 mg/kg (mice); subcutaneously, 8285 mg/kg.
Benzyl alcohol $C_6H_5CH_2OH$	108.14	1.050 (15/15) 1.0427 (19)	205.2	Solubility in 100 ml of water, 4 g of preparation; in 100 ml of alcohol 66.7 g. Very readily soluble in ether, acetone, methanol, or chloroform.	Toxic. Used in concentrations of not over 3%. Has irritant action in concentration of 5%.
1-Phenylethanol $C_6H_5CH(OH)CH_3$	122.17	1.013	205	Insoluble in water. Readily soluble in alcohol or ether.	
2-Phenylethanol $C_6H_5CH_2CH_2OH$	122.17	1.0235 (25/4)	219-227	Solubility in 100 ml of water, 1.6 g of preparation. Soluble in alcohol or ether.	

zhonikidze, and it complies with the requirements of foreign pharmacopoeias (U.S. Pharmacopoeia, 17th edition, and British pharmacopoeia, 1968). Benzyl benzoate is used extensively abroad. It is included in the Polish Pharmacopoeia, 4th edition, 1965, the British pharmacopoeia for 1968, the Yugoslavian pharmacopoeia for 1951, the Czechoslovakian for 1970, and several others.

According to the British pharmacopoeia for 1968, benzyl benzoate is used in oil injection solutions of dimercaprol. The composition of the prescription is: dimercaprol, 5.0 g; benzyl benzoate, 9.6 ml; peanut oil, to 100 ml. It is also used in hydroxyprogesterone preparations which have been admitted to sale, where the benzyl benzoate enters in a 30% concentration in sesame oil or 46% in castor oil. Benzyl benzoate has been investigated in the USSR [7] with the objective of using it for injections of hormone preparation solutions. The experience of many years in use of oil solutions of some preparations, mainly of the steroid class, has shown that they are either very difficultly soluble in oil, or gradually crystallize out of the solutions during the storage process, forming rather coarse crystals which do not dissolve again even on heating.

Benzyl benzoate has been used as a cosolvent to obtain stable oil solutions of hormone preparations. Solutions of 5% androstenediol dipropionate containing 30% benzyl benzoate, 12.5% hydroxyprogesterone carbonate containing 30% benzyl benzoate, or 5% testosterone propionate containing 20% benzyl benzoate have withstood a year of storage at 26°. During the storage period, crystals of the preparations did not separate from the solutions. It was also established that mixtures of benzyl benzoate with peach oil in concentrations from 10 to 50% are completely nontoxic. The amount of benzyl benzoate was established experimentally in each individual case.

In Tables 3 and 4 we give the basic characteristics of solvents of the alcohol group. Polyhydric alcohols are good solvents for many substances widely used in pharmaceutical practice (alkaloids, sulfanilamides, antibiotics, barbiturates, and anesthetics), and the solutions obtained are more stable than the corresponding aqueous solutions. Of these, propylene glycol (1,2-propanediol) presents the greatest interest. It is a transparent, colorless, and viscous liquid with a specific gravity of 1.036, which absorbs moisture from the air; it has a freezing point of −59° and a bp of 188°. It is miscible with water, acetone, and chloroform, but does not mix with fatty oils. Under normal conditions it is stable, but at high temperatures it is oxidized to propionaldehyde and lactic, pyruvic, and acetic acids. The toxicity of this solvent is very low. According to the literature [8], the minimum lethal dose on intravenous injection to rats is 1.68 g/kg,

TABLE 4. Basic Characteristics of Solvents of the Polyhydric Alcohol Group

Name, formula	Mol. wt.	d	Bp (in deg)	Solubility	Toxicity, LD_{50}
Ethylene glycol CH_2OHCH_2OH	62.07	1.1155 (20/4)	198-200	Soluble in water, ethanol, or ether (7.89 g/100 ml).	Toxic
Propylene glycol $CH_3CH(OH)CH_2OH$	76.10	1.0364	188	Miscible with water, acetone, or chloroform; immiscible with fatty oils.	Intraperitoneally, 9.7 g/kg; intravenously, 8.0 g/kg; subcutaneously, 18.5 g/kg (mice).
1,3-Butanediol $CH_3-CH(OH)-CH_2CH_2OH$ / $CH_3CH(OH)CH_2CH_2OH$	90.12	1.0053	204	Soluble in water, or alcohol; insoluble in ether.	Subcutaneously, 16.5 ml/kg (mice); subcutaneously, 20.06 ml/kg (rats).
Diethylene glycol $CH_2OHCH_2OCH_2CH_2OH$	106.0	1.118	244.33	Miscible with water, alcohol, or glycols; insoluble in hydrocarbons.	By mouth, 23-25 ml/kg (mice).
Polyethylene glycols (polyethylene oxides) with various molecular weights	200 300 400*	1.11 1.14		Soluble in water, alcohol, or ketones; not hydrolyzed.	Intraperitoneally, 7.75, 9.25, 11.75 ml/kg (mice); 32.5, 35.6, 49.0 g/kg (rats).
Glycerin† $CH_2OHCHOHCH_2OH$	92.10	1.261	290	Miscible with water or alcohol.	Subcutaneously, 10 ml/kg; intravenously, 6 ml/kg; subcutaneously, 12 ml/kg; intravenously, 7 ml/kg.

*Freezing point, 2-6°.
†17.9, 20°.

and to rabbits is 5.25 g/kg. The minimum lethal dose on intramuscular injection is 14.7 g/kg for rats, and for rabbits is 7.5 g/kg. The LD_{50} for mice on intraperitoneal injection is 9.7 g/kg; subcutaneously, 18.5 g/kg; and intraveneously, 8.0 g/kg. Some investigators [9] do not confirm the toxicity of propylene glycol after it has been sterilized with a bactericidal lamp at a dose of 2.5 Mrad. The action of propylene glycol on the nervous system is like that of ethyl alcohol, but is three times as weak. When propylene glycol injections were made in physiological solution in concentrations up to 50%, it did not cause changes in the amount of erythrocytes, hemoglobin, or leucocytes in rabbits [10]. An increase in the number of polymorphic corpuscles was noted, plus a decrease in the number of lymphocytes, as well as a considerable shortening of the blood coagulation time. Propylene glycol is a good solvent for sulfanilamides, barbiturates, vitamins A and D, antibiotics (tetracycline, chlorotetracycline, oxytetracycline, or chloramphenicol), anesthesine, procaine, alkaloid bases, and many other medicinal substances [5].

Undilute propylene glycol causes a burning sensation at the site of injection; diluted solutions do not cause this effect. Solutions of propylene glycol should be injected deeply into the muscular tissue. The solutions used most often are 60%. The solution prepared for barbiturates may serve as an example: benzyl alcohol, 2 ml; propylene glycol, 60 ml; water to 100 ml [6]. The Hungarian pharmacopoeia (1967) recommends using propylene glycol to inject quinidine sulfate. Here it is emphasized that alkaloid bases in propylene glycol solutions do not separate out as precipitates on considerable dilution with water. According to the literature [11], a solution of quinidine hydrochloride consisting of 10.0 g of the preparation and 75.0 g of propylene glycol did not give any color changes or crystallize over a six-month period. The quinidine action is displayed in children already after 15 min, and is retained for 2 h on intramuscular injec-

TABLE 5. Basic Characteristics of Polyethylene Glycols

Type of PEG	Av. mol. wt.	Viscosity at 25° (cP)	Hydroxyls (in mg KOH/g)	Toxicity, LD_{50}: mice, intraperitoneally (in ml/kg)	Toxicity, LD_{50}: rats (in g/kg)	Time required for filtration: through filter No. 3, 20°	Time required for filtration: through filter No. 4, 20°	Time required for filtration: through filter No. 4, 40°	Time required for filtration: through filter No. 4, 60°
200	190—210	45—55	533—589	7,75	32,5	1 min 30 sec	30 min	12 min	7 min
300	285—315	60—85	356—392	9,25	35,6	2 min 50 sec	32 »	12 min 30 sec	7 min 30 sec
400*	380—420	85—115	271—299	11,75	49,0	2 min	35 »	10 min 30 sec.	9 min

*Congealing point, 2-6°.

tion. In the literature [12], the use of propylene glycol is described as a solvent for the intravenous injection of desoxycorticosterone in a concentration of 10 mg/ml. The authors recommend injecting this solution slowly, at a rate of 2.5 ml/min, since the preparation crystallizes out at the moment of dilution with water. Good results were obtained on adding digoxin in a solution of 40% propylene glycol and 10% ethanol [13]. Intramuscular introduction of oxytetracycline in propylene glycol makes it possible to increase considerably the circulation time of the preparation in the blood. Such a solution is stable on storage for 2 years at room temperature; in the absence of propylene glycol, it is stable for only 2 days. Phenobarbital and amobarbital are made up in solutions which contain 60% propylene glycol and 2% benzyl alcohol. Pure propylene glycol dissolves phenobarbital better, and in larger amounts than pure alcohol; however, upon gradual addition of water the solubility of the preparation in propylene glycol is reduced more rapidly than that in alcohol [5].

Propylene glycol stabilizes ascorbic acid well. According to the literature, it is less toxic (LD_{50} on intraperitoneal injection, 9.7 g/kg; intravenously, 8 g/kg; subcutaneously, 18.5 g/kg) than ethylene glycol or glycerin (LD_{50} on subcutaneous injection, 10 ml/kg; intravenously, 6 ml/kg). Sterilization of propylene glycol is effected by heating to 140° for 3 h [14]. This solvent is included in many foreign pharmacopoeias. According to the British pharmacopoeia (1968), a digoxin solution for injection is official which contains 0.025 mg of the preparation in 1 ml, melarsoprol and sodium phenobarbital in a mixture of 90 parts propylene glycol and 10 parts water. According to the Czechoslovakian pharmacopoeia for 1970, the digoxin solution for injection which is official is made up in a mixture of glycerin, propylene glycol, and water. Propylene glycol also is found in the French (1965) and International pharmacopoeias, and in the pharmacopoeia of the U. S. A. (1970).

Polyethylene Glycols (PEG). These represent a promising group of nonaqueous solvents. They are products of the polymerization of ethylene oxide, and have the general formula:

$$H-[OCH_2CH_2]_n-OH,$$

where n is in the range from 4 to 455, which corresponds to a molecular weight range from 200 to 20,000. Some synonyms are polyethylene oxide (PEO) polyoxyethylene, polyglycol, carbowax, skurol, postonal, macrogolyum, and macrogol.

Depending on the degree of polymerization, PEG can have a consistency from a viscous liquid to a solid material (Tables 4 and 5). The PEG with molecular weights of 200, 300, 400, and 600 are practically colorless, hygroscopic, and viscous liquids. The viscosity increases with increase in molecular weight, and the hygroscopicity decreases. PEG dissolve in water, aliphatic alcohols (methyl, ethyl, propyl, isopropyl, butyl, etc.), esters (methyl acetate, ethyl acetate, butyl acetate, amyl acetate, etc.), acetone, cyclohexanol, chloroform, carbon tetrachloride, benzene, toluene, xylene, etc. They are insoluble in ether, vaseline oil, turpentine, or fatty oils. The PEG do not have acute or chronic toxicity; they are stable to the action of light, heat, and moisture; they are inert; they accept coloring well; they dissolve easily in the digestive tract; they have no flavor; and they mix well with one another [15].

PEG esters are also used, for example PEG stearate, Tweens, polyglycol 1000 VRS monocetyl ether, glycofurol, and some others; this offers the possibility of obtaining solutions of substances which are difficultly soluble in water, plus stable emulsions and suspensions.

TABLE 6. Basic Properties of Solvents of the Amide Group

Name, formula	Mol. wt.	Solubility	Toxicity, LD_{50}
N-Methylacetamide* $CH_3CONHCH_3$	73.0	Soluble in water	Intravenously, 4.2 g/kg (mice)
N,N-Dimethylacetamide $CH_3CON(CH_3)_2$	87.12	Miscible with water, soluble in organic solvents and mineral oils	Intraperitoneally, 3236 mg/kg (mice); intraperitoneally, 5012 mg/kg (mice)
N-β-Hydroxyethyllactamide† $CH_3CH(OH)CONHCH_2CH_2OH$	133	Readily miscible with water	Subcutaneously, 15.8 g/kg (mice); subcutaneously, 16.1 g/kg (rats)

*Mp 26-28°
†Density, 1.192

The PEG are colorless, transparent, involatile, viscous liquids of low hygroscopicity, with a faint characteristic odor. They are used most often in mixture with other solvents to prepare injection solutions of medicinal preparations which easily undergo hydrolytic decomposition.

In spite of their antibacterial properties, it is recommended that the PEG should be sterilized. PEG which have been diluted with water are similar to aqueous media; the pure substances are like oils. Instead of sterilization, one can make use of distillation, collecting the distillate in a sterile receiver [5]. PEG are good solvents for many medicinal preparations which readily undergo hydrolysis. Intramuscular injections are tolerated well. The PEG are isolated from the urine after 24 h; 77% is isolated after 12 h.

Intramuscular injection to rats in doses which exceed the dose for humans 5- or 10-fold causes necrosis of muscle if the dose undergoes infiltration into the muscle ligaments. The reaction of tissues is defined as a mild inflammatory process caused by chemicals. The toxicity of vancomycin has been studied in 50% PEG-200 and in the 100% glycol [16]. The authors stated that the glycol does not exert a toxic action on dogs if it is used in a dose of 1 ml/kg intramuscularly daily for 80 days or in doses of 0.5, 1.0, 2.5, or 5.0 ml/kg intravenously one time only. The content of carbon dioxide in the venous blood, nonprotein nitrogen in the blood, and alkali phosphatase remains within norms. No macro- or microchanges were confirmed in the kidneys, the circulation system, or other organs, although there are data according to which serious poisoning was noted, plus kidney disease, when a solution of nitrofurantoin in PEG-300 was injected intravenously to sick persons. Two fatal cases are known.

It should be emphasized that the toxicity and toxicity level of a biologically active substance can differ considerably after solution in glycol as compared with the toxicity of a solution or emulsion of this substance in water. Pathological changes were not noted in a study of the action of subcutaneous injections of solutions of barbiturates in PEG-200.

In intramuscular injection of aqueous solutions of the sodium salts of barbiturates, a stronger tissue inflammation was noted than when solutions in PEG were injected. The stability of the sodium salt of pentabarbital in an aqueous solution containing 0 to 60% PEG-400 has been studied [17]. A stable solution is obtained at a 30% PEG concentration and pH 10.0. Addition of 10% ethanol makes it possible to sterilize the solution in an autoclave without changing its color. Solutions containing 60% of the glycol and 10% ethanol and having a pH below 8.0 are also stable on heating in an autoclave. A 10% solution of PEG-300 is used to stabilize injection solutions of reserpine (2.5 mg/ml) [17]. The product issued for sale contains either 10% PEG-300 or 25% PEG-400.

It has been observed that phenobarbital forms strong stoichiometric molecular compounds with PEG [18]. Pentabarbital and barbital do not give such compounds. The phenobarbital molecule is bonded to two ethylene oxide residues in the polyether chain. It has been noted that phenolic compounds are bonded by polyethylene glycols in the same way. Compounds of high molecular weight have a definite tendency to form complex compounds. Such compounds as salicylic and p-hydroxybenzoic acids are bonded very weakly. Fifty percent solutions of PEG are used to prepare injection solutions of erythromycin ethyl succinate and secobarbital for intramuscular injection. The stability of the sodium salts of some barbiturates has been studied in PEG solutions (phenobarbital, barbital, pentabarbital, etc.) [19]. It was shown that PEG causes a strong stabilizing effect, the stability of the preparations increasing with rise in PEG concentrations. The least PEG concentration adequate for stabilization was 50%. The barbiturates dissolved in pure PEG were the most stable.

The solubility of some medicinal materials in PEG-400 and in aqueous solutions of PEG of various molecular weight has been studied [20, 21]. It was noted that substances which have a basic nitrogen in their make-up (glutamic and nicotinic acids) do not dissolve or are poorly dissolved in the presence of PEG. Solubilization is usually attained at a PEG concentration over 30%. In a study of the solubilization of medicines of low solubility it was established that the solubility of benzoic, salicylic, and acetylsalicylic acids; barbital; synthomycin; camphor; anesthesine; codeine base; sulfanilamide compounds; butadione; cortisone acetate; reserpine; phthivazide; erythromycin; phenacetin; and novocaine base in PEG (molecular weight, 400) many times exceeds the solubility of these compounds in water. The following have an exceptionally high solubility: Streptocid (87 g/100 ml), anesthesine (34 g/100 ml), and salicylic acid (31.8 g/100 ml). The solubility is increased (as compared with the solubility in water) in PEG of higher molecular weight (600, 1500, or 4000).

PEG solutions of various concentrations have obtained particularly wide use abroad. PEG enters into many foreign pharmacopoeias. At the present time PEG-400 has not found use as a solvent for preparations for injection in the USSR, since it is thought that the large moisture content of PEG-400 and its hygroscopicity does not permit using it to prepare parenteral solutions.

We have used polyethylene glycol of domestic manufacture to prepare solutions for injection of some sarcolysine derivatives, especially Asalei and Astiron, which have a definite antitumor activity on a number of experimental animal tumors. Asalei and Astiron are practically insoluble in water, ether, propylene glycol, ethylene glycol, diethylene glycol, glycerin, or ethyl oleate. In the presence of moisture they hydrolyze and lose their antitumor activity. As preliminary studies showed, the solubility of Asalei and Astiron in PEG-400 is very small. To increase the solubility, we developed a three-component solvent system, composed of 80 ml PEG-400 and 20 ml of a 0.5% alcoholic solution of Tween-80. In the mixed solvent the preparations dissolved on stirring for a few minutes at room temperature. This made it possible to prepare 2.5% solutions of Asalei or Astiron in PEG-400.

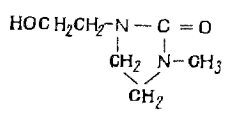
Studies of the stability of Asalei and Astiron to hydrolysis in the solutions obtained were performed by the mercurimetric titration method. The stabilizing properties of the solvents proved to be quite high. Thus, the degree of hydrolysis of the preparations was barely more than 1% on storage for two months in the dark in a cool place. However, after this time interval the solutions changed their outward appearance from colorless to yellow in the case of Asalei, and from yellow to brown in the case of Astiron. This is apparently connected, on one hand, with the ability of chloroethylamine antitumor preparations to enter into chemical reaction with many organic compounds which have in their make-up such functional groups as OH, NH_2, COOH, or the like, and, on the other, with the ability of polyethylene glycols to form complex compounds with some medicinal substances. Taking this fact into consideration, we suggest that solutions of Asalei and Astiron in PEG-400 be made up ex tempore.

The results of preliminary pharmacological studies which we have carried out on animals with experimental transplantable tumors have shown that the activity of preparations is considerably increased in PEG-400 solution. Thus, in a dose equal to one-half the maximum tolerable dose (MTD) for suspensions of these compounds on methyl cellulose, solutions of Asalei and Astiron caused the death of approximately 50-60% of the animals. Reducing the dose to one-fourth the maximum tolerable dose did not cause a reduction in the therapeutic effect, but the loss of animals did not exceed 10%.

The results which we obtained agree with data in the literature, which indicate a considerable change in the toxicity and activity of some medicines used in the form as solutions in PEG, as compared with the same qualities of their aqueous solutions or emulsions [16, 22, 23, 24].

In recent times, steadily increasing attention is being given to other solvents from the groups of ethers amides, heterocyclic compounds, or sulfoxides (Table 6), for example, dimethyl sulfoxide and oximazone.

Oximazone [1-Methyl-3-(2-hydroxyethyl)imidazolidone].



Oximazone mixes in all proportions with water; it is soluble in ethanol, acetone, chloroform, or methylene chloride. Its density is 1.16; bp, about 125-126°; n_D^{21} 1.496; viscosity at 20°, 25 cP. Its LD_{50} is 5600 mg/kg for rats on intravenous injection of a 50% solution in water. Clonic convulsions set in after introduction

of 4000 mg/kg into animals (secondary effect). The acute toxicity in experiments on rats in oral introduction of a 50% aqueous solution was 10-15 ml/kg, $LD_{50} > 8000$ mg/kg. A dose of 16,000 mg/kg causes the death of 8 animals out of 10. On use of oximazone internally in the form of a 4-20% aqueous solution daily for a period of 4 weeks, a good toleration of this preparation by animals was noted. Appetite, animal weight, state of blood-producing organs, liver function, and urine remained within norms. On subcutaneous injection of a 20% aqueous solution of oximazone over a 4-week period daily, the urine, blood-forming organs, and liver function also remained normal. On local injection of 500 or 1000 mg/kg, inflammatory phenomena were noted at the site of injection. The higher the dose, the greater the inflammation. In a dose of 250 mg/kg, local reaction by the preparation was not observed. When a 10 or 20% aqueous oximazone solution was used intraveneously in experiments on dogs (subacute toxicity) daily, intoxication phenomena were not observed. Injections in some animals were accompanied by a certain bulging of the vein.

On introduction of a 20% aqueous solution to cats in a dose of 1000 mg/kg of body weight, the animals did not experience change in heart-beat or respiratory rate; a 40% aqueous oximazone solution raises the blood pressure. Oximazone in a dose of 1000 mg/ml exerts a cytostatic action. Moreover, aqueous oximazone solutions have a bacteriostatic action. On 1:10 dilution of the oximazone, this action is not observed (bulletin of the Asta company).

Dimethyl sulfoxide (DMSO). CH_3SOCH_3. DMSO is a transparent, colorless liquid with a mild odor; its molecular weight is 78.13; specific gravity, 1.108 at 20°; bp, 189°; mp, 18.4°; n_D 1.4783; viscosity, 2.14 cP at 20°; dipole moment, 4.3; dielectric constant, 48.9. DMSO is very hygroscopic. It absorbs up to 70% water at 20°. It is infinitely miscible with water, methanol, octanol, glycerin, acetaldehyde, acetone, ethanol, diethyl ether, ethyl acetate, toluene, etc.

For laboratory animals, the LD_{50} of DMSO on intravenous introduction is 5.75-8.8 g/kg; on oral introduction, 21.4-28.3 g/kg; the LD_{50} for mice, chickens, or rats is 20 ml/kg. Subdural introduction of DMSO does not change the reflex activity of dogs or monkeys. In a dose of 1 g/kg the preparation does not change the electrocardiograms of monkeys. Intensification of the toxicity of medicines in the presence of DMSO is not observed [25].

As one may convince himself from the review given, a very large number of organic solvents are used in pharmaceutical practice; these have varied dissolving power, antihydrolytic and stabilizing properties, and anesthesizing and bactericidal properties, or the ability to prolong or intensify the action of the active component. But far from all of them are finding wide use. The fatty oils and ethyl oleate, propylene glycol, and polyethylene glycol are used the most often of the nonaqueous solvents. The remaining solvents are used as yet only in exceptional cases. It is quite obvious that the use of nonaqueous solvents makes it possible to expand possibilities of preparing medicinal forms. However, one should take into account the fact that any preparation in a nonaqueous solvent may be new in essence, and should be appropriately studied.

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ATTACHMENT F - COMPILATION

TAB 7

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Tolerability of intramuscular injections of testosterone ester in oil vehicle

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We undertook a prospective survey of the tolerability of deep i.m. injections of testosterone enanthate in a castor oil vehicle, the most widely used form of androgen replacement therapy. Over a period of 8 months, 26 men received 551 weekly injections into the gluteal, deltoid or thigh muscle and side-effects were recorded immediately and 1 week after each injection by the same nurse using a standardized questionnaire. Most injections caused no complaints [389/551, 70.6% (95% confidence interval 66.6–74.4%)] but minor local side-effects, mostly pain and bleeding, were common [162/551, 29.4% (25.6–33.4%)]; no serious side-effects were observed. Considering all side-effects, the gluteal site had fewer complaints and was less prone to bleeding but was painful more often than deltoid or thigh injection sites. The laterality of injection at any site had no significant effect on side-effects. The only systemic side-effect was episodes of sudden-onset, non-productive cough associated with faintness following eight injections [1.5% (0.6–2.9%)] which we speculate may have been due to pulmonary oil microembolism. We conclude that, when administered by an experienced nurse, deep i.m. injection of testosterone enanthate in a castor oil vehicle is generally safe and well tolerated but causes relatively frequent minor side-effects, including pain and bleeding. An improved depot form of testosterone would be highly desirable for androgen replacement therapy and hormonal male contraception.

Key words: androgen replacement therapy/intramuscular injection/laterality/side-effects/testosterone

Introduction

Testosterone has been used clinically in androgen replacement therapy for over 50 years (Nieschlag and Behre, 1990). Over the past few decades the most frequent mode of administering testosterone has been deep i.m. injections of testosterone esters in a vegetable oil vehicle. Despite this long usage, no systematic studies of side-effects from oil-based i.m. injections of testosterone esters could be located after extensive computer-based and manual library searching. The opportunity to study systematically the tolerability of these injections and the pattern of side-effects was provided by an ongoing male contraceptive study requiring healthy men to have weekly i.m. injections of testosterone enanthate in castor oil vehicle administered by the same research nurse for up to 18 months. The aims of this study were to estimate prospectively the pattern and incidence of side-effects of oil-based, deep i.m. injections in normal men and to determine whether anatomical site and/or laterality of injection influences the incidence of these side-effects.

Materials and methods

Study design

This was a prospective survey of adverse effects from i.m. injections of oil-based testosterone enanthate. The injections were given during a World Health Organization (WHO) contraceptive efficacy study of a prototype hormonal male contraceptive and the design and results of that study have been described in detail elsewhere (WHO Task Force on Methods for the Regulation of Male Fertility, 1990). Injections were given and side-effects recorded by the same right-handed research nurse (M.A.M.) both immediately following and 1 week after injection using a standard questionnaire. The questionnaire recorded date, site and side of injection as well as eliciting specific responses to potential side-effects, including pain or stinging, bleeding or bruising, swelling, numbness, muscle twitch, erythema, faintness, coughing. For reported symptoms, the duration, severity and degree of interference with daily living was recorded. For the analysis, the categories of pain and bleeding included both immediate and delayed reports. The criterion for recognition of pain was the subject's response to the question 'Was that injection painful?' and was applied and recorded consistently for each subject.

Subjects and injections

Men involved in this study were 26 healthy males aged between 21 and 45 years recruited from the general population to participate in a multicentre male contraceptive study (WHO Task Force on Methods for the Regulation of Male Fertility, 1990). Entry criteria were that men had to be healthy, in a stable relationship and requiring contraception. Volunteers were required to have their injection administered by the study nurse (M.A.M.) on the same day (± 1 day) each week for up to 18 months. The vials of testosterone enanthate (250 mg in

1 ml castor oil, Testoviron Depot; Schering AG, Berlin, Germany) were kept at air-conditioned room temperature and injections of 200 mg (0.8 ml) were administered with a 21 gauge (0.80×38 mm) needle into one of three muscular sites; the anatomical site of the injection (gluteal, deltoid, thigh) was chosen by the subjects and injections were routinely alternated from side to side. Deep i.m. injections were given according to standard methods, including aspirating the syringe to exclude vascular puncture before injection and injecting slowly.

Data analysis

Data were cross-tabulated and analysed by appropriate methods for categorical data using BMDP software (BMDP Statistical Software Inc., Los Angeles, CA, USA) implemented on a VAX computer network. Power was estimated using Poisson confidence intervals (Gardner and Altman, 1989) and PASS software (Hintze, 1991).

Results

During 8 months, 602 scheduled injections were given without any injections missed and complete information was available after 551 (92%) injections. The remainder were accounted for by injections administered when men were out of Sydney for work or holidays. During this period, only two out of 26 men changed their preferred site of injection.

Most injections caused no complaints [389/551, 70.6% (95% confidence interval, 66.6–74.4%)] and any adverse effects were recorded after only 162/551 [29.4% (25.6–33.4%)] injections. There were no significant differences in rate of complaints of side-effects according to laterality of injection for gluteal [left 19/68 (27.9%) versus right 27/151 (17.9%)], thigh [left 17/51 (33.3%) versus right 27/85 (31.8%)] and deltoid [left 49/114 (43.0%) versus right 29/82 (35.4%)]. The overall pooled (Mantel–Haenszel) relative risk was 1.40 [95% (confidence interval 0.95–2.06), test for homogeneity of risk across strata $P = 0.61$].

Considering all adverse effects (Table I), the total number of complaints was significantly higher for deltoid [2.0 (1.5–2.8)] and thigh [1.6 (1.1–2.3)] than for gluteal sites of injection. Considering specific adverse effects, gluteal injections caused more complaints of pain [relative risk 2.4 (1.3–4.3)] and fewer of bleeding [0.16 (0.08–0.32)] compared with the other two sites combined (Table I). Immediate bleeding was minor in all cases, requiring only light topical pressure for a few minutes or was recorded in retrospect as minor bloodspot staining of clothing or slight bruising. Pain was usually not sufficient to require analgesia; at worst, discomfort was present for several days on sitting or lying on the injection site. There were no reports of local erythema or acute inflammatory reactions following injections. Apart from coughing episodes, all reported reactions were considered by volunteers and investigators as minor; none ceased injections due to such side-effects during the study.

Table I. Side-effects of i.m. injections

Side-effect	Deltoid	Thigh	Gluteal	Total	*P*
Nil	119 (61%)	94 (69%)	176 (80%)	389 (70.6%)	<0.001
Bleeding	49 (25%)	27 (20%)	8 (4%)	84 (15.3%)	<0.001
Pain	13 (7%)	5 (4%)	23 (11%)	41 (7.4%)	0.050
Muscle twitch	10 (5%)	5 (4%)	7 (3%)	22 (4%)	0.598
Cough ± faint	4 (2%)	3 (2%)	2 (1%)	9 (1.6%)	0.552
Other	1 (1%)	2 (1%)	3 (1%)	6 (1.1%)	0.621
Total	196 (100%)	36 (100%)	219 (100%)	551 (100%)	

The only systemic side-effect was coughing fits observed immediately after eight injections [prevalence 1.5% (0.6–2.9%)], associated with faintness and sweating on one occasion. On another occasion, faintness and sweating occurred without coughing. Two characteristic cases are described. In the first, a 25 year old man without known asthma or allergies developed an intense, non-productive cough without wheeze immediately after having received 21 previous i.m. injections into the gluteal muscle uneventfully. He also developed an injection site reaction after withdrawal of the injection needle which required him to remain recumbent until the coughing subsided (5 min). After this episode he had six further weekly injections without recurrence or complaint before he discontinued from the study to initiate a planned pregnancy. In the second, a 35 year old man without known asthma or allergies and having received 24 injections into the deltoid muscle, including one previous similar episode, developed an intense non-productive cough with associated pallor, nausea and chest tightness but no wheeze or injection site reaction which gradually subsided after 10 min. He subsequently had another 35 injections into the gluteal muscle without experiencing further such episodes.

The power of this study was >50, >80 and >90% to detect (one-sided, $\alpha = 0.05$) events with underlying prevalence of 1.3, 1.7 and 2.0% respectively. Conversely in order to detect events with a prevalence of 1.0% with 80% power, a sample size of 4000 observations would have been required. For adverse effects not observed in this study, the upper 95% (Poisson) confidence limit was 0.67%.

Discussion

Depot formulations are widely used to enhance therapeutic compliance and convenience by prolonging the duration of drug action. Among the most widely used depot formulations are drug esters administered in an oil vehicle. Esterification of base drugs with appropriate lipophilic fatty acids forms a pro-drug ester whose hydrophobic side-chains partition preferentially into the oil vehicle. Prolongation of pro-drug release is provided by the rate-limiting retarded diffusion of the pro-drug ester into the extracellular fluid where ubiquitous non-specific esterases hydrolyse the ester bond to liberate active drug. In addition to forming a hydrophobic depot, the oil vehicle limits local chemical irritation and cytotoxicity caused by some drugs (Svendsen and Blom, 1984). This oil-based formulation has been widely and successfully used for sex steroids including androgens, oestrogens and progestins as well as psychotrophic drugs such as fluphenazine, haloperidol and related major tranquilizers (Gilman *et al.*, 1990). Oils derived from vegetable sources such as castor or sesame seeds

or peanuts (*Arachis*) have been widely used whereas mineral oils are too irritating (Symmers, 1955).

Testosterone esters in an oil vehicle have been for decades the most widely used modality of delivering androgen replacement therapy in male hypogonadism (Behre *et al.*, 1990). Despite this long usage, or perhaps because of it, there have been few systematic studies of tolerability of i.m. administration of testosterone esters in oil-based formulations. The general pharmacology of i.m. injections has been reviewed (Schou, 1971; Greenblatt and Koch-Weser, 1976; Zuidema *et al.*, 1988) but most studies concern aqueous formulations of drugs administered to hospitalized patients. For example, the only large survey of i.m. injections reported adverse local effects in only 0.4% of 12 134 hospitalized patients receiving i.m. injections of drugs in aqueous formulations (Greenblatt and Allen, 1978). No comparable surveys in ambulatory care settings or involving oil-based steroid ester formulations are available to our knowledge.

Overall, while nearly 30% of our subjects had some complaints, they were considered by patients and investigators as minor in nature and serious adverse effects were not observed. Satisfaction was greatest for the gluteal site, lowest for the deltoid, with the thigh being intermediate. Discrepancies in patterns of pain and bleeding accounted for these differences. The level of recorded complaints may be conservative as determined among highly motivated volunteers agreeing to participate in a prolonged study requiring weekly i.m. injection for up to 18 months. Administration by less expert staff or by self-injection may lead more frequently to dissatisfaction. Furthermore, the tolerance of discomfort among hypogonadal men requiring life-long androgen replacement therapy or fertile men considering hormonal male contraception among other family planning methods may be lower. Although the sites of injection were not randomized but were selected by the subjects, it is unlikely that this significantly biased the outcomes, unless men predisposed to complain of side-effects were systematically more likely to choose a particular injection site, which seems unlikely. Although this survey included nearly 550 injections, it could provide reliable estimates for only relatively common (>2%) side-effects. The frequency of rare side-effects, especially those not observed during the survey period, could not be reliably estimated. For example, the power of this survey was adequate (>80%) for events with a true underlying rate of occurrence of ≥1.7%, but would need to include more than seven times as many injections to detect events with a 1.0% prevalence.

The lower risk of minor bleeding at the gluteal injection site may be attributed to its lower blood flow (Evans *et al.*, 1975) as well as the fact that most gluteal i.m. injections are actually intralipomatous (Cockshott *et al.*, 1982) and adipose tissue blood flow is even lower than muscle. Conversely, the reason for the higher rate of discomfort following gluteal injections is unclear and conflicts with experimental observations that intralipomatous injection causes less local toxicity than i.m. injection of irritant psychoactive drugs in rabbits (Svendsen *et al.*, 1985). The precise cause of injection pain remains unclear (Travell, 1955), although presumably local cytotoxicity due to insertion of the injection needle as well as the chemical nature of the drug, its vehicle and their local metabolites are relevant factors. Possibly the functional significance of various anatomical sites may also influence injection pain. For example, extrinsic pressure on the injection site may be more common after gluteal injections (e.g. during sleeping or sitting) than for other sites.

More serious local injection site side-effects, including sciatic nerve damage, muscular fibrosis, gas gangrene, and distal ischaemia following intra-arterial injection were not observed in this survey, consistent with their rarity among adults. We also observed no evidence of either acute or chronic inflammatory reactions which have been reported rarely to cause lipogranulomas and/or pseudotumour foreign body reactions (Symmers, 1955; Balogh, 1986; Hamann *et al.*, 1990; Khankhanian and Hammers, 1992) causing diagnostic confusion and serious clinical consequences. As inflammatory reactions have been reported following subdermal injections of vegetable oils alone (Brown *et al.*, 1944) or containing non-steroidal drug esters (Hamann *et al.*, 1990) while aqueous suspensions of testosterone esters are non-irritating (Behre and Nieschlag, 1992), the side-effects observed in this study are most likely to be attributable to the oil vehicle rather than the testosterone ester. As the present survey had sufficient power to exclude non-observed events with an underlying frequency of at least 2%, this figure provides an upper limit for the likelihood of such reactions which were not observed during our study.

The only systemic side-effect observed was coughing reactions consisting of sudden-onset, non-productive coughing with or without faintness which was observed on eight occasions giving a prevalence of 1.5% [95% (confidence interval 0.6–2.9%)]. Although disturbing to subjects, the coughing was transient, lasting for 10 min at most and subsided spontaneously without known sequelae. Acute drug-related respiratory distress not due to bronchospasm or laryngopulmonary oedema is rare but has been described after i.m. administration of an oil-based solution of pitressin tannate (Hoigne *et al.*, 1990). The sudden onset of coughing without wheeze or injection site reaction together with a history of uneventful injections before and after the episodes suggests an idiosyncratic, mechanical phenomenon related to a particular injection. Neither allergy to testosterone enanthate or the castor oil vehicle have been reported and would seem clinically unlikely given the isolated occurrence of the events and speed of onset. We speculate that these respiratory reactions may be due to pulmonary oil microembolization following lymphogenic (Svendsen *et al.*, 1980) or venous absorption of oil (Svendsen and Aaes-Jorgensen, 1979), leading to transient acute pulmonary hypertension possibly related to mechanical vascular occlusion and/or intravascular liberation of free fatty acids from hydrolysis of the oil (Hofmann *et al.*, 1976; Szabo *et al.*, 1977). Clinically significant pulmonary manifestations of oil embolism have been reported following injection of 2.5 ml oil reaching the bloodstream (Bron *et al.*, 1963; Gough and Thomas, 1964). The relatively mild clinical manifestations observed with our smaller injection volume (0.8 ml) are consistent with this mechanism. An alternative, albeit unlikely, explanation that cannot be fully excluded is that intralipomatous injection

may rarely provoke embolism of cellular fragments such as adipocyte lipids. The low frequency and mild clinical features observed do not require any major change in current standard clinical practice but suggest caution when injecting larger volumes of oil i.m. Apart from the recent addition of warnings concerning the occurrence of 'coughing fits, urge to cough and respiratory distress' to the product information for testosterone enanthate, such side-effects do not appear to have been reported previously.

We conclude that deep i.m. injections of testosterone enanthate in castor oil vehicle are generally safe and reasonably tolerated when administered by a single experienced research nurse. Minor side-effects, mainly pain and bleeding, are relatively common but serious side-effects are rare. The anatomical site, but not laterality, of injections influences tolerance, as the gluteal site has fewer overall side-effects and is less prone to bleeding but more liable to pain than the deltoid or thigh sites. Coughing reactions, not previously reported but observed after 1.5% of injections, we speculate may be due to pulmonary oil microembolization. As our observations reflect the properties of an oil vehicle, similar findings would be expected with other similarly formulated drugs. These findings highlight the need for better depot testosterone formulations for patients requiring life-long androgen replacement therapy, as well as for future regimens for hormonal male contraception.

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ATTACHMENT F - COMPILATION

TAB 8

REVIEW ARTICLE

Excipients and Their Use in Injectable Products

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ABSTRACT: Formulation of a new drug product with excipients, that have been previously added to an approved injectable product, may save pharmaceutical companies developmental time and cost. The Physicians' Desk Reference (PDR) and Handbook on Injectable Drugs were reviewed, extracting all information on excipients. The information was consolidated into eight tables, categorizing excipients as 1) Solvents and Co-solvents, 2) Solubilizing, Wetting, Suspending, Emulsifying or Thickening agents, 3) Chelating Agents, 4) Antioxidants and Reducing Agents, 5) Antimicrobial Preservatives, 6) Buffers and pH Adjusting Agents, 7) Bulking Agents, Protectants, and Tonicity Adjustors, and 8) Special Additives. Where applicable, tables list frequency of use, concentration, and an example of a commercial product containing the excipient. Excipients which are included in the 1996 FDA 'Inactive Ingredient Guide,' but do not appear in the PDR or Handbook on Injectable Drugs, were included as a separate list.

Introduction

Injectable products require a unique formulation strategy. The formulated product has to be sterile, pyrogen free and, in the case of solutions, free of particulate matter. Preferably, the formulation will be isotonic, and depending on the route of administration (for instance, for intra-spinal or intra-cisternal routes), antioxidants and preservatives may not be allowed. For a given drug, the risk of adverse events is higher if it is administered as an injection versus a non-parenteral route. The requirement for sterility demands that the excipients be able to withstand autoclaving or other sterilization processes. These factors limit the choice of excipients available to the formulators.

Generally, a knowledge of which excipients have been deemed safe by the FDA or are already present in a marketed product provides increased assurance to the formulator that these excipients will probably be safe for their new drug product. However, there is no guarantee that the new drug product will be safe as excipients are combined with other additives and/or with a new drug, creating unforeseen potentiation or synergistic toxic effects. Regulatory bodies may view an excipient previously approved in an injectable dosage form favorably, and will frequently require less safety data. A new additive in a formulated product will always require additional studies adding to the cost and timeline of product development.

The purpose of this paper is to present the various excipients that have been included in the formulation of injectable products marketed in the USA. This information is not readily available. A literature search indicates that the last paper dealing with this was published in 1980 (1). Products approved outside the US are not covered in this review. Also, sterile dosage forms not administered parenterally, such as solutions for irrigation, ophthalmic or otic drops, and ointments were excluded.

Methodology

Physicians' Desk Reference published in 1994 & 1996 (2, 3), and Handbook on Injectable Drugs (4) were used as the primary source of information. Entries on all injectable drugs were summarized in an Excel worksheet. Each product was classified by Manufacturer, Trade name, Drug name, Route of Administration, SVP/LVP, pH of Product, Solvent Used, Solubilizing/Suspending Agent, Preservative, Antioxidant, Chelator and Other Formulation Additives.

The resulting Excel sheet had information on more than 700 products. This information was condensed into easy-to-read tables. Each table has been categorized based on the primary function of excipient in the formulation. For example, citrates are classified as buffers and not as chelating agents, and ascorbates are categorized as antioxidants, although they can serve as buffers. This classification system was based on our experience in formulation development and on the published literature. Such simplification avoids duplication of entries and provides the audience with easy-to-read tables.

Some duplication was unavoidable. Tables VII and VIII contain some excipients which may have also been listed in the first six tables. Whenever the reference specifically designated a specific function to an ingredient it was re-listed in Tables VII and VIII. For example, glycine can be used as a buffer or as a stabilizing (protecting) agent. Therefore, glycine is listed in Tables VI and VII. Methyl paraben is a preservative (Table V) but also has a special function in Adriamycin RDF® formulation (Table VIII).

The concentration of excipients is listed as percentages weight by volume (w/v) or volume by volume (v/v). If the product was listed as lyophilized or powder, these percent-

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TABLE I
Solvents and Co-solvents

Excipient	Frequency	Range	Example
Benzyl Benzoate	2	20% v/v	Depo-Testosterone® (Upjohn) 20% v/v
Cottonseed Oil	1	73.6% w/v	Depo-Testosterone® (Upjohn) 73.6% w/v
N,N Dimethylacetamide	1	6% w/v	Vumon® (Bristol Myers) 6% w/v
Ethanol	24	0.6–80%	Prograf® (Fujisawa) 80% v/v
Glycerin (Glycerol)	9	1.6–70% w/v	Multitest CMI® (Connaught) 70% w/v
Peanut oil	1	*	Bal in Oil® (Becton Dickinson)
Polyethylene glycol			
PEG	4	0.15–50%	Secobarbital sodium (Wyeth-Ayerst) 50%
PEG 300	2	50–65%	VePesid® (Bristol Myers) 65% w/v
PEG 400	2	*	Ativan® (Wyeth-Ayerst)
PEG 3350	5	0.3–3%	Depo-Medrol® (Upjohn) 2.95% w/v
Poppyseed oil	1	1%	Ethiodol® (Savage) 1%
Propylene Glycol	25	0.2–75.2%	Terramycin Solution (Roerig) 75.2%
Safflower oil	2	5–10%	Liposyn II® (Abbott) 10%
Seasme oil	6	*	Solganal Inj.® (Schering)
Soybean oil	4	5–20% w/v	Intralipid® (Clintec) 20%
Vegetable oil	2	*	Virilon IM Inj.® (Star Pharmaceuticals)

* No data available.

ages were derived based on the reconstitution volume commonly used. The tables list the range of concentration used, typical or most common concentration employed, and examples of products containing the excipient, specifically those which use extremely low or high concentrations.

Discussions

Table I list solvents and co-solvents used in parenteral products. Water for injection is the most common solvent but may be combined or substituted with a co-solvent to improve the solubility or stability of drugs. Oils like safflower and soybean are used in total parenteral nutrition products where they serve as a fat source and as carriers for fat-soluble vitamins. Ethanol and propylene glycol are used, either alone or in combination with other solvents, in more than 50% of parenteral co-solvent systems. It is surprising to see propylene glycol used more often than polyethylene glycols (PEGs) in spite of its higher myotoxicity and hemolyzing effects (5, 6). Probably, the presence or generation of peroxides in PEGs is a major limitation.

Table II includes a broad category of excipients whose function in formulation could be—(1) Viscosity imparting or suspending agents like carboxy methyl cellulose, sodium carboxy methyl cellulose, sorbitol, acacia, Povidone, hydrolyzed gelatin; (2) Solubilizing, wetting or emulsifying agents like Cremophore EL, sodium desoxycholate, Polysorbate 20 or 80, PEG 40 castor oil, PEG 60 castor oil, sodium dodecyl sulfate, lecithin or egg yolk phospholipid; (3) Aluminum monostearate which is added to fixed oil to form viscous or gel-like suspending medium. Polysorbate 80 is the most common and versatile solubilizing, wetting and emulsifying agent.

Only a limited number of chelating agents are used in parenteral products (Table III). They serve to complex heavy

TABLE II
Solubilizing, Wetting, Suspending, Emulsifying or Thickening Agents

Excipient	Frequency	Range	Example
Acacia	2	7%	Tuberculin Old Test® (Lederle) 7%
Aluminum monostearate	1	2%	Solganal Inj.® (Schering) 2%
Carboxy methyl cellulose	4	1%	Bicillin® (Wyeth-Ayerst) 0.55%
Carboxy methyl cellulose, sodium	9	0.1–0.75%	Lupron Depot® (TAP) 0.75% w/v
Cremophore EL*	3	50–65% w/v	Sandimmune® (Sandoz) 65% w/v
Desoxycholate sodium	1	0.4% w/v	Fungizone® (Bristol Myers) 0.41% w/v
Egg yolk phospholipid	3	1.2%	Intralipid® (Clintec) 1.2%
Gelatin, Hydrolzyed	1	16% w/v	Cortone® (Merck) 16% w/v
Lecithin	7	0.4–1.2% w/v	Diprivan® (Zeneca) 1.2% w/v
Polyoxyethylated fatty acid	1	7% w/v	AquaMephyton® (Merck) 7% w/v
Polysorbate 80 (Tween 80)	31	0.01–12%	Cordarone X I.v.®. (Wyeth-Ayerst) 10%
Polysorbate 20 (Tween 20)	5	0.01–0.4%	Calcijex® (Abbott) 0.4% w/v
PEG 40 castor oil**	1	11.5% v/v	Monistat® (Janssen) 11.5% v/v
PEG 60 castor oil***	1	20% w/v	Prograf® (Fujisawa) 20% w/v
Povidone (Polyvinyl pyrrolidone)	6	0.5–0.6% w/v	Bicillin® (Wyeth-Ayerst) 0.6% w/v
Sodium dodecyl sulfate (Na lauryl sulfate)	1	0.018% w/v	Proleukin® (Cetus) 0.018% w/v
Sorbitol	3	25–50%	Aristrospan® (Fujisawa) 50% v/v

* Cremophor EL: Etocas 35, polyethoxylated castor oil, polyoxyethylene 35 castor oil.
** PEG 40 castor oil; polyoxyl 40 castor oil, castor oil POE-40, Croduret 40, polyoxyethylene 40 castor oil, Protachem CA-40.
*** PEG 60 hydrogenated castor oil; Cremophor RH 60, hydrogenated castor oil POE-60, Protachem CAH-60.

TABLE III
Chelating Agents

Excipient	Frequency	Range	Example
Calcium disodium EDTA*	9	0.01–0.1%	Wydase® (Wyeth-Ayerst) 0.1% w/v
Disodium EDTA	34	0.01–0.1%	Calcijex® (Abbott) 0.11% w/v
Sodium EDTA	1	0.20%	Folvite® (Lederle) 0.2%
DTPA**	1	0.04%	Magnevist® (Berlex) 0.04%

* EDTA = Ethlenediaminetetraacetic acid.
** DTPA = Diethylenetriaminepentaacetic acid; Pentetic acid.

metals and therefore can improve the efficacy of antioxidants or preservatives. In our opinion, calcium EDTA has an advantage over tetrasodium salt by not contributing sodium and not chelating calcium from the blood.

An antioxidant as a class is defined as those compounds that can act as reducing agents or may serve as free radical scavengers. Table IV summarizes the antioxidants, their frequency of use, concentration range and examples of products containing them. Sulfite, bisulfite, and metabisulfite constitute the majority of antioxidants used in parenteral products despite several reports of incompatibilities and toxicity (7, 8). Butylated hydroxy anisole, butylated hydroxy toluene and propyl gallate are primarily used in semi/non-aqueous vehicles because of their low aqueous solubility. Ascorbic acid/sodium ascorbate may serve as an antioxidant, buffer, and chelating agent in the same formulation.

Benzyl alcohol was the most common antimicrobial preservative present in parenteral formulations (Table V). This is consistent with other surveys (9). Parabens are the next most common preservatives. Thirty-nine products had a combination of methyl and propyl parabens; eleven had only methyl, and one had only propyl paraben. Thimerosal was surprisingly common, especially in vaccines, even though some individuals have sensitivity to mercurics. Chlorocresol is purported to be a good preservative for parenterals, but our survey did not find any examples of commercial products containing chlorocresol.

Table VI lists buffers and chemicals used to adjust the pH of formulations. Phosphate, citrate, and acetate are the most common buffers used in parenteral products. Mono and diethanolamine are added to adjust pH and form corresponding salts. Hydrogen bromide, sulfuric acid, benzene sulfonic acid and methane sulfonic acids are added to drugs which are bromide (Scopolamine HBr, Hyoscine HBr, UDL), sulfate (Nebcin, Tobramycin sulfate, Lilly), besylate

TABLE IV
Antioxidants and Reducing Agents

Excipient	Frequency	Range	Example
Acetone sodium bisulfite	4	0.2–0.4% w/v	Novocaine® (Sanofi-Winthrop) 0.4% w/v
Ascorbate (sodium/acid)	7	0.1–4.8% w/v	Vibramycin® (Roerig) 4.8% w/v
Bisulfite sodium	28	0.02–0.66% w/v	Amikin® (Bristol Myers) 0.66% w/v
Butylated hydroxy anisole (BHA)	3	0.00028–0.03% w/v	Aquasol® (Astra) 0.03%
Butylated hydroxy toluene (BHT)	3	0.00116–0.03% w/v	Aquasol® (Astra) 0.03%
Cystein/Cysteinate HCl	2	0.07–0.10% w/v	Acthar Gel® (Rhone-Poulanc) 0.1% w/v
Dithionite sodium (Na hydrosulfite, Na sulfoxylate)	1	0.10%	Numorphan® (DuPont) 0.10%
Gentisic acid	1	0.02% w/v	OctreoScan® (Mallinckrodt)
Gentisic acid ethanolamine	1	2%	M.V.I. 12® (Astra) 2%
Glutamate monosodium	2	0.1% w/v	Varivas® (Merck) 0.1% w/v
Formaldehyde sulfoxylate sodium	9	0.075–0.5% w/v	Terramycin Solution (Roerig) 0.5% w/v
Metabisulfite potassium	1	0.10%	Vasoxyl® (Glaxo-Wellcome) 0.10%
Metabisulfite sodium	29	0.02–1% w/v	Intropin® (DuPont) 1% w/v
Monothioglycerol (Thioglycerol)	6	0.1–1%	Terramycin Solution (Roerig) 1%
Propyl gallate	2	0.02%	Navane® (Roerig)
Sulfite sodium	7	0.05–0.2% w/v	Enion® (Ohmeda) 0.2% w/v
Thioglycolate sodium	1	0.66% w/v	Sus-Phrine® (Forest) 0.66% w/v

TABLE V
Antimicrobial Preservatives

Excipient	Frequency	Range	Example
Benzalkonium chloride	1	0.02% w/v	Celestone Soluspan® (Schering) 0.02% w/v
Benzethonium chloride	4	0.01%	Benadryl® (Parke-Davis) 0.01% w/v
Benzyl alcohol	74	0.75–5%	Dimenhydrinate® (Steris) 5%
Chlorobutanol	17	0.25–0.5%	Codine phosphate (Wyeth-Ayerst) 0.5%
m-Cresol	3	0.1–0.3%	Humatrope® (Lilly) 0.30%
Myristyl gamma-picolinium chloride	2	0.0195–0.169% w/v	Depo-Provera® (Upjohn) 0.169% w/v
Paraben methyl	50	0.05–0.18%	Inapsine® (Janssen) 0.18% w/v
Paraben propyl	40	0.01–0.1%	Xylocaine w/Epinephrine (Astra) 0.1% w/v
Phenol	48	0.2–0.5%	Calcimar® (Rhone Poulanc) 0.5% w/v
2-Phenoxyethanol	3	0.50%	Havrix® (SmithKline Beecham) 0.50% w/v
Phenyl mercuric nitrate	3	0.001%	Antivenin® (Wyeth-Ayerst) 0.001%
Thimerosal	46	0.003–0.01%	Atgam® (Upjohn) 0.01%

TABLE VI
Buffers and pH Adjusting Agents

Excipient	Example
Acetate	
Sodium	Miacalcin Injection® (Sandoz)
Acetic acid	Miacalcin Injection® (Sandoz)
Glacial acetic acid	Brevibioc Injection® (Ohmeda)
Ammonium	Bumex Injection® (Roche)
Ammonium hydroxide	Triostat Injection® (SmithKline Beecham)
Benzene sulfonic acid	Tracrium Injection® (Glaxo-Wellcome)
Benzoate Sodium/acid	Valium Injection® (Roche)
Bicarbonate Sodium	Cefotan Injection® (Zeneca)
Carbonate Sodium	HypoRho-D® (Bayer)
Citrate	
Acid	DTIC-Dome® (Bayer)
Sodium	Ceredase® (Genzyme)
Disodium	Cerezyme® (Genzyme)
Trisodium	Cerezyme® (Genzyme)
Diethanolamine	Bactrim IV® (Roche)
Glucono delta lactone	Quinidine® (Lilly)
Glycine	Hep-B Gammagee® (Merck)
Hydrochloric acid	Amicar® (Immunex)
Hydrogen bromide	Scopolamine (UDL)
Lactate acid/Sodium	Fentenyl citrate & Droperidol (Astra)
Lysine	Eminase Injection® (Roberts)
Maleic acid	Librium Injection® (Roche)
Methanesulfonic acid	DHE-45 Injection® (Sandoz)
Monoethanolamine	Terramycin Solution (Roerig)
Phosphate	
Acid (phosphoric)	Humegon® (Organon)
Monobasic potassium	Zantac Injection® (Glaxo-Wellcome)
Monobasic sodium*	Pregnyl® (Organon)
Dibasic sodium**	Prolastin® (Bayer)
Tribasic sodium	Synthroid® (Knoll)/
Sodium hydroxide	Optiray® (Mallinckrodt)
Sulfuric acid	Nebcin® (Lilly)
Tartrate acid/sodium	Methergine Injection® (Sandoz)
Tromethamine	Optiray® (Mallinckrodt)

* Sodium biphosphate, Sodium dihydrogen phosphate or Na dihydrogen orthophosphate.
** Sodium phosphate, Disodium hydrogen phosphate.

(Tracrium Inj., Atracurium besylate) or mesylate (DHE 45 Injection, Dihydroergotamine mesylate) salts. Glucono delta lactone is used to adjust the pH of Quinidine gluconate (Lilly). Benzoate buffer, at a concentration of 5%, is used in Valium Injection. Citrates are common buffers that can have a dual role as chelating agents. Lysine and glycine are amino acids which function as buffers and stabilize protein and peptide formulations. These amino acids are also used as lyo-additives and may prevent cold denaturation. Lactate and tartrate are occasionally used as buffer systems.

Table VII lists additives which are used to modify osmolality, and as bulking or lyo-cryo protective agents. Dextrose and sodium chloride are used to adjust tonicity in the majority of formulations. Some amino acids, glycine, alanine, histidine, imidazole, arginine, asparagine, aspartic acid, are used as bulking agents for lyophilization and may serve as stabilizers for proteins or peptides and as buffers. Monosaccharides (dextrose, glucose, lactose), disaccharide (sucrose), polyhydric alcohols (inositol, mannitol, sorbitol), glycol (PEG 3350), Povidone (polyvinylpyrrolidone), and proteins (albumin, gelatin) are commonly used as lyo-additives.

TABLE VII
Bulking Agents, Protectants, and Tonicity Adjustors

Excipient	Example
Alanine	Thrombate III® (Bayer)
Albumin	Bioclate® (Arco)
Albumin human	Botox® (Allergan)
Amino acids	Havrix® (SmithKline Beecham)
L-Arginine	Activase® (Genentech)
Asparagine	Tice BCG® (Oganon)
L-Aspartic acid	Pepcid® (Merck)
Calcium chloride	Phenergan Injection® (Wyeth-Ayerst)
Citric acid	Sensorcaine-MPF® (Astra)
Dextrose	Betaseron® (Berlex)
Gelatin hydrolyzed	Acthar® (Rhone-Poulanc Rorer)
Glucose	Iveegam® (immuno-US)
Glycerin	Tice BCG® (Oganon)
Glycine	Atgam Injection® (Upjohn)
Histidine	Antihemophilic Factor, human (Am. Red Cross)
Imidazole	Helixate® (Armour)
Inositol	OctreoScan® (Mallinckrodt)
Lactose	Caverject® (Upjohn)
Magnesium chloride	Terramycin Solution® (Roerig)
Magnesium sulfate	Tice BCG® (Oganon)
Mannitol	Elspar® (Merck)
Polyethylene glycol 3350	Bioclate® (Arco)
Polysorbate 80	Helixate® (Armour)
Potassium chloride	Varivax® (Merck)
Povidone	Alkeran® (Glaxo-Wellcome)
Sodium chloride	WinRho SD® (Univax)
Sodium succinate	Actimmune® (Genentech)
Sodium sulfate	Depo-Provera® (Upjohn)
Sorbitol	Panhematin® (Abbott)
Sucrose	Prolastin® (Bayer)

Special Additives

These additives have been included in pharmaceutical formulation to serve specific functions (Table VIII). Below is a summary of the special additives along with their intended use—

(1) Calcium gluconate injection (American Regent) is a saturated solution of 10% w/v; calcium d-saccharate tetrahydrate 0.46% w/v is added to prevent crystallization during temperature fluctuations.
(2) Cipro IV® (Ciprofloxacin, Bayer) contains lactic acid as a solubilizing agent for the antibiotic.
(3) Premarin Injection® (Conjugated Estrogens, Wyeth-Ayerst Labs) is a lyophilized product that contains simethicone to prevent formation of foam during reconstitution.
(4) Dexamethasone acetate (Dalalone DP, Forest, Decadron-LA, Merck, Dalalone DP Injection, UAD Labs) and Dexamethasone Na phosphate (Merck) are available as suspension or solution. These dexamethasone formulations contain creatine or creatinine as an additive.
(5) Adriamycin RDF® (Doxorubicin hydrochloride, Pharmacia) contains methyl paraben, 0.2 mg/mL, to increase dissolution (10).
(6) Ergotrate maleate (Ergonovine maleate, Lilly) contains 0.1% ethyl lactate as a solubilizing agent.
(7) Estradurin Injection® (Polyestradiol phosphate, Wyeth-Ayerst Labs) uses Niacinamide (12.5 mg/ml)

TABLE VIII
Special Additives

Excipient	Example
Acetyl tryptophanate	Human Albumin (American Red Cross)
Aluminum hydroxide	Recombinant HB® (Merck)
Aluminum phosphate	Tetanus Toxoid Adsorbed® (Lederle)
Aluminum potassium sulfate	TD Adsorbed Adult® (Connaught)
E-Aminocaproic acid	Eminase® (Roberts)
Calcium d-saccharate	Calcium Gluconate (American Regent)
Caprylate sodium	Human Albumin (American Red Cross)
8-Chlorotheophylline	Dimenhydrinate (Steris)
Creatine	Dalalone DP® (Forest)
Creatinine	Hydrocortone Phosphate (Merck)
Diatrizoic acid	Conray (Mallinckrodt)
Gamma Cyclodextrin	Cardiotec (Squibb)
Ethyl lactate	Ergotrate maleate® (Lilly)
Ethylenediamine	Aminophylline® (Abbott)
L-Glutamate sodium	Kabikinase® (Pharmacia)
Iron ammonium citrate	Tice BCG® (Oganon)
Lactic acid	Cipro IV® (Bayer)
D,L-Lactic and Glycolic acid copolymer	Zoladex® (Zeneca)
Maltose	Gamimune® (Bayer)
Meglumine	Magnevist® (Berlex)
Niacinamide	Estradurin® (Wyeth-Ayerst)
Paraben methyl	Adriamycin RDF® (Pharmacia)
Protamine	Insulatard NPH® (Novo Nordisk)
Simethicone	Premarin Injection® (Wyeth-Ayerst)
Sodium saccharin	Compazine Injection® (Smith-Kline Beecham)
Tri-n-butyl phosphate	Venoglobulin® (Apha Therapeutic)
von Willebrand factor	Bioclate® (Arco)
Zinc	Lente Insulin® (Novo Nordisk)

TABLE IX
List of Excipient from 1996 FDA 'Inactive Ingredient Guide'

Ammonium sulfate	Pentetate (DTPA) calcium trisodium
Benzyl chloride	Poloxamer 165
Butyl paraben	PEG 4000
Caldiamide sodium	PEG 600
Calteridol calcium	Polyglactin
Castor oil	Polylactide
Cellulose (microcrystalline)	Polyoxyethlene fatty acid esters
Cholesterol	Polyoxyethylene sorbitan monosterate
Deoxycholic acid	Polyoxyl 35 Castor oil
Diatrizoic acid	Polysorbate 40
Dicyclohexyl carbodiimide	Polysorbate 85
Diethyl amine	Potassium hydroxide
Dimyristoyl lecithin	Potassium phosphate, dibasic
Dimyristoyl phosphatidyl-glycerol	Sodium bisulfate
Disofenin	Sodium chlorate
Docusate sodium	Sodium hypochloride
Edamine	Sodium iodide
Exametazime	Sodium pyrophosphate
Gluceptate sodium	Sodium thiosulfate, anhydrous
Gluceptate calcium	Sodium trimetaphosphate
Glucuronic acid	Sorbitan monopalmitate
Guanidine HCl	Stannous chloride
Iofetamine HCl	Stannous fluoride
Lactobionic acid	Stannous tartrate
Lecithin hydrogenated soy	Starch
Lidofenin	Succimer
Medrofenin	Succinic acid
Medronate disodium	Sulfurous acid
Medronic acid	Tetrakis (1-isocyano-2-methoxy-2,methyl-propante) copper (I) Te
Methyl boronic acid	Thiazoximic acid
Methyl cellulose	Trithiazoximic acid
Methylene blue	Urea
N-(carbamoyl-methoxy polyethylene-glycol 2000)-1,2-distearoyl	Zinc acetate
N-2-hydroxyethyl piperazine N'-2' ethane sulphonic acid	Zinc chloride
Nioxime	Zinc oxide
Nitric acid	2-ethyl hexanoic acid
Oxyquinoline	PEG vegetable oil

as a solubilizing agent. Hydeltrasol® (Merck) also contains niacinamide.

(8) Aluminum in the form of aluminum hydroxide, aluminum phosphate or aluminum potassium sulfate is used as adjuvant in various vaccine formulations to elicit an increased immunogenic response.

(9) Zoladex® (Goserelin acetate, Zeneca) is administered subcutaneously as microspheres. These spheres are made of D,L-lactic and glycolic acid copolymer. Lupron Depot Injection® (TAP) are lyophilized microspheres of gelatin and glycolic-lactic acid for intramuscular injection.

(10) Gamma cyclodextrin is used as a stabilizer in Cardiotec® at a concentration of 50 mg/mL.

(11) Sodium caprylate (sodium octoate) has antifungal properties, but it is also used to improve the stability of albumin solution against effects of heat. Albumin solution can be heat pasteurized by heating at 60°C for 10 hours in the presence of sodium caprylate. Acetyl tryptophanate sodium is also added to albumin formulations.

(12) Meglumine (N-methylglucamine) is used as an excipient and to form in-situ salt. For example, diatrizoic acid, an X-ray contrast agent, is more stable when autoclaved as meglumine salt than as sodium salt (11). Meglumine is also added to Magnevist®, a magnetic resonance contrast agent, formulation.

(13) Surprisingly, sodium saccharine is used in Stelazine® and Compazine® formulations; our guess is that it serves as a stabilizer and tonicity adjuster.

(14) Tri-n-butyl phosphate is present as an excipient in human immune globulin solution (Venoglobulin®). Its exact function in the formulation is not known, but it may serve as a scavenging agent.

(15) von Willebrand factor is used to stabilize recombinant antihemophilic factor (Bioclate®).

(16) Maltose serves as a tonicity adjuster and stabilizer in immune globulin formulation (Gamimune N®).

(17) Epsilon amino caproic acid (6-amino hexanoic acid) is used as a stabilizer in anistreplase (Eminase injection®).

(18) Zinc and protamine have been added to insulin to form complexes and control the duration of action.

Recently, FDA has published 'Inactive Ingredient Guide' which lists all the excipients in alphabetical order. Each ingredient is followed by the route of administration (for example, iv, oral) and, in some cases, the range of concentration used in the approved drug product. However, this list does not provide the name of commercial product(s) corresponding to each excipient. Table IX is a summary of all the excipients which are included in the 'Inactive Ingredient Guide,' but do not appear in PDR or Handbook on Injectable Drugs.

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ATTACHMENT F - COMPILATION

TAB 9

PDR

27 EDITION

1973

Physicians' Desk Reference®

To Pharmaceutical Specialties and Biologicals

Publisher: CHARLES E. BAKER, Jr.
Production Manager: GEORGE E. QUIST, Jr.
Compilation Editor: BARBARA B. HUFF
Medical Consultant: AUSTIN JOYNER, M.D.
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...two 100 mg. tablets (150 or 200 mg.) ...ur to six hours. Once a satisfactory ...has been achieved, it may be desirable ...inister one-half to one 100 mg. PRAN... tablet (50 to 100 mg.) every four to six ...to prevent recurrence. Increase in the ...ance dosage is suggested during peri... heightened emotional stress or psychic ...and at intervals when experience in... ulcer may recur.

Supplied: PRANTAL Tablets, 100 mg., ...bottle of 100.

...GYNON®

...ol, estradiol, N.F.

...ous Suspension

...ion

...tion: Aqueous suspension of estra... isotonic solution for intramuscular in... Contains in each cc 1.0 mg. estradiol, ...mg. polysorbate 80, with 0.5% phenol ...rvative. Pellets of estradiol 25 mg. for ...aneous implantation; the pellets con... excipient or binder.

...: Estradiol, one of the more potent of ...ural estrogenic compounds, is identical ...estrogenic hormone produced by the ...ovary. Estradiol exerts a developmen... on the female generative tract, has ...ibitory effect upon the pituitary in ...doses, and produces a marked constitu... effect with an increase in muscular ...th, bodily vigor, and mental acumen. It ...s follicular hormone in cases where es... activity is depressed, insufficient, or ...

...In PROGYNON Aqueous Suspension ...ous solution is absorbed rapidly and ...re crystalline estradiol remains in the ...as a depot from which absorption be... promptly and continues for a long pe... The vials should be shaken immediately ...using in order to suspend the estradiol ...ally. It is intended for intramuscular ...istration. The PROGYNON Pellets are ...ical, with an approximate diameter of ...and length of 3.5 mm. Pellet therapy ...advantage of high efficiency from the ...oint of the quantity of hormone admin... and the further advantage that a sin... ...tment has effect continuously for sev... ...nths.

...ions: In the female—PROGYNON ...n Suspension is indicated in mono... ...syndrome, hypogenitalism and sexual ...ism, oligomenorrhea associated with ...nadism, and postpartum breast en... ...gement.

...OGYNON Aqueous Suspension is also in... ...for inoperable breast carcinoma in ...menopausal women, senile vaginitis, and ...s or kraurosis vulvae.

...OGYNON Pellets are indicated in condi... ...where constant and prolonged estrogen ...n is required. The pellets may be used ...ve symptoms of estrogen deficiency ...in the menopausal syndrome and ...adism, as replacement therapy in ...ed females; in the male—carcinoma of ...state (palliative).

...Indications: Familial or personal his... ...carcinoma (also precancerous lesions) ...dicates use of estrogens, unless spe... ...indicated as therapy for carcinoma. ...ns administered continuously are con... ...ated in thrombophlebitis, pulmonary ...s, and liver dysfunction or disease. ...ry of hypersensitivity or toxic reac... ...any of the components contraindi... ...use.

...ions: Hypercalcemia and sodium ...retention may occur with continued ...rge doses of estrogens; use cautiously ...in patients with cardiac or renal disease, or epilepsy.

As with all estrogens, undesirable uterine growth may occur; as a consequence withdrawal endometrial bleeding may occur; uterine fibroids may increase in size.

Diabetic patients should be observed carefully for regulation during medication with estrogens.

Use estrogens judiciously in young patients in whom bone growth is not complete; estrogens may effect epiphyseal closure.

Thrombophlebitis and pulmonary embolism have occasionally occurred with estrogen therapy; although no definitive relationship exists, physicians should be alert to the earliest manifestations of these conditions.

In patients with histories of psychic abnormalities, estrogen therapy should be terminated if symptoms of such abnormalities reoccur.

Adverse Reactions: Gastrointestinal disturbances (nausea, vomiting, mild diarrhea), headache, edema due to salt retention, soreness of breast or gynecomastia (may occur in treatment of prostatic carcinoma), vertigo, chloasma, cholestatic jaundice, erythema multiforme, hemorrhagic eruption, allergic rash, itching, amenorrhea, mental depression, hypercalcemia with large doses.

Dosage and Administration: Menopausal syndrome:—In average cases, 1.0 mg. of estradiol intramuscularly two or three times weekly for 2 or 3 weeks; in more severe cases, 1.0 to 1.5 mg. of estradiol. Thereafter, dosage is gradually reduced to minimum requirement, usually within the range of 0.5 to 1.0 mg. of estradiol twice weekly. In all cases the objective should be determination of the minimum amount of hormone that will maintain the patient symptom-free. With adequate clinical improvement, usually obtainable in two weeks or less, gradual reductions in dosage are advisable. Subcutaneous implantation—implant one 25 mg. PROGYNON Pellet and repeat when necessary. The pellets provide constant estrogen levels for approximately 3 months.

Hypogenitalism and Sexual Infantilism:—1.5 mg. of estradiol intramuscularly two or three times weekly. Subcutaneous implantation—Implant one 25 mg. pellet and repeat when necessary.

Amenorrhea and Oligomenorrhea Associated with Hypogonadism: 1.5 mg. of estradiol intramuscularly two or three times weekly during the first two weeks of an arbitrary 28-day menstrual cycle; progesterone is given during the last two weeks of the theoretical cycle. This regimen is continued for 3-6 months. The patient then is allowed to go untreated for 2 months to determine whether or not she can maintain the cycle without hormonal therapy. If not, additional courses of therapy as outlined should be prescribed.

Postpartum Breast Engorgement:—1.5 mg. of estradiol is administered intramuscularly daily beginning at the first sign of engorgement and continuing until symptoms are controlled. Restriction of fluids and a tight binder should also be employed.

Inoperable Breast Carcinoma in Postmenopausal Women:—1.5 mg. of estradiol intramuscularly three or more times weekly according to the severity of the pain.

Carcinoma of the Prostate:—1.5 mg. of estradiol intramuscularly three times weekly. Subcutaneous implantation—implant one 25 mg. pellet and repeat when necessary.

Senile Vaginitis; Pruritus Vulvae; Kraurosis vulvae:—Initially, 1.0 to 1.5 mg. of estradiol intramuscularly three times weekly for two or three injections, then 0.5 to 1.0 mg. of estradiol twice weekly for maintenance. Oral estrogen therapy may be preferred for maintenance.

PROGYNON (estradiol) Aqueous Suspension should be injected intramuscularly. Never intravenously. A 21-gauge 1½-inch needle is best suited for injecting the suspension well into the muscle.

The pellets may be implanted conveniently and quickly by means of an injector or they may be administered by making an incision in the skin. Either method, though readily carried out in the physician's office, is a minor surgical procedure, and all aseptic precautions must be observed. *BY INJECTOR:* The pellet may be quickly and easily implanted by means of the Kearns or Perloff Pellet Injectors. The areas usually selected for implantation are the infrascapular region or the posterior axillary line. Aseptic precautions must be observed as for any surgical procedure. The skin is carefully cleaned, followed by the application of iodine and alcohol. The area is infiltrated with procaine 1:100. Make a very small incision (about 2 mm. long and 1 mm. deep) into the skin with a sharp scalpel to allow free passage of the large injector needle. The injector needle of the Kearns injector, with sharp plunger in place, is inserted into the incision and gently forced into the subcutaneous tissue at the desired site of implantation. The sharp plunger is withdrawn, and the pellet inserted into the hollow needle. The simplest method for placing the pellet in the needle is to allow the pellet to slide from the vial in which it is packed into the slot provided in the needle. The pellet is pushed as far as possible through the needle by means of the blunt plunger and held in place with the plunger while the needle is gently withdrawn. When the needle comes in contact with the knob of the plunger, both are withdrawn together. When the injector has been withdrawn, the wound may be closed with a single stitch or a skin clip. In many instances, apposition of the edges of the wound with adhesive tape is sufficient. *BY INCISION:* The infrascapular region or the posterior axillary line are convenient sites for implanting pellets. The operative field is prepared in the usual manner with iodine and alcohol and the area is infiltrated with procaine 1:100 solution. An incision about one centimeter in length is made. With blunt dissection, a pocket about two centimeters in depth is prepared in the subcutaneous tissue below and away from the incision. The edges of the pocket may be held apart by a small dilator and the pellet inserted into the bottom of the pocket with small forceps. Force should not be used in inserting pellets. The incision is closed with one or two sutures.

How Supplied: Aqueous Suspension—multiple-dose vials of 10 cc., 1.0 mg./cc., boxes of 1 and boxes of 6 are available. Store away from heat. **Pellets**—vial of one 25 mg. pellet, box of 3.

PROLUTON®

brand of progesterone injection, N.F.

Injection

Description: PROLUTON achieves all of the definitely established effects of the corpus luteum hormone on the uterus. It causes the secretory phase of the endometrium to devel-

Continued on next page

Information on Schering products appearing on these pages is effective as of September 30, 1972. Schering products whose active ingredients are listed in Medicare-approved pharmaceutical compendia appear at the beginning of the Schering Product Information Section.

Schering—Cont.

op and attain up to ten times its original thickness, with distention and activity of the glands and profound hyperemia. Greatest effectiveness of progesterone depends on previous priming of the endometrium with estrogens. PROLUTON for intramuscular administration contains in each cc. of solution progesterone, N.F., 50 mg.; benzyl alcohol, N.F., 50 mg.; benzyl benzoate, U.S.P., 150 mg.; propylparaben, U.S.P., 1.0 mg.; and sesame oil, U.S.P.

Indications: PROLUTON is indicated in habitual and threatened abortion, premature labor, functional uterine bleeding, functional dysmenorrhea, premenstrual tension, primary and secondary amenorrhea and female hypogonadism.

Contraindications: Hypersensitivity or toxic reactions to any of the components contraindicates its use. Progesterone is also contraindicated in patients with impaired renal function, missed or incomplete abortion, carcinoma of the breast, and undiagnosed genital bleeding.

A history or the presence of thrombophlebitis, thromboembolic disorders, cerebrovascular accident, or pulmonary embolism also contraindicates the use of this product.

Precautions: Administer cautiously in patients who have had periodic attacks of asthma, migraine, or epilepsy; these conditions may be exacerbated by progesterone. Patients with a history of psychic depression should be carefully observed; the drug should be discontinued if the depression recurs to a serious degree. Fluid retention may occur; observe patients with cardiac or renal dysfunction carefully.

Adverse Reactions: Edema, urticaria, pruritus vulvae, gastrointestinal disturbances (nausea, vomiting, diarrhea), ulcerative stomatitis, headache, weight gain, and local irritation.

Dosage and Administration: *Habitual Abortion*—PROLUTON 5 to 20 mg., should be given three times a week, commencing therapy with the early diagnosis of pregnancy and continuing through the eighth month. At times of stress and calculated menses, 25 mg. should be given daily. *Threatened Abortion*—In addition to usual measures, PROLUTON 25 to 50 mg. daily should be administered as long as there are pains and bleeding. When symptoms have subsided, the dosage is reduced to 10 to 25 mg. daily, and maintained at this level through the eighth month of pregnancy. When estrogen therapy is preferred during crises, PROGYNON® (estradiol Benzoate, 1.666 mg. may be given at two-hour intervals until symptoms are controlled. *Premature Labor*—PROLUTON 25 to 50 mg., may be given daily until symptoms subside. *Functional Uterine Bleeding*—5 to 10 mg. daily or 25 mg. on alternate days, should be administered starting eight to ten days before the patient is expected to menstruate. In severe cases, 50 mg. daily may be used. *Functional Dysmenorrhea, Premenstrual Tension*—Recommended dosage is 10 to 25 mg. daily during the last eight to ten days before the patient is expected to menstruate. *Primary and Secondary Amenorrhea, Female Hypogonadism*—Recommended dosage is 25 mg. three times weekly during the last two weeks of a calculated menstrual cycle after estrogen therapy during the first two weeks of the calculated cycle.

PROLUTON should be injected intramuscularly, never intravenously. Subcutaneous injection at times may give rise to painful local reactions. Immersion of the vial momentarily in warm water will facilitate aspiration into the syringe. A 21-gauge, 1½-inch needle is best suited for injecting the oil solution well into the muscular tissue. For obese patients, a 20-gauge, 2-inch needle may be used. The site usually selected for injection is the upper outer quadrant of the gluteal region. Aspiration should be done before expelling the contents of the syringe in order to make certain a blood vessel has not been entered.

How Supplied: PROLUTON Injection, 10 cc. multiple-dose vials, boxes of 1 and 6.

NOTE: In cool weather, crystals may appear in the vials, in which case the vials should be warmed to bring the crystals back into solution before using.

RELA®

brand of carisoprodol

Tablets

Description: Carisoprodol is N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate.*

Actions: Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord. There are no peripheral or autonomic effects. Relief of symptoms usually begins within 30 minutes and lasts four to six hours.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: for symptomatic relief in conditions characterized by skeletal muscle spasm and mild to moderate pain.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Carisoprodol is contraindicated in patients who have had allergic or idiosyncratic reactions to it or to related compounds such as meprobamate or mebutamate and also in patients who have porphyria or in whom porphyria is suspected.

Warnings: The patient should be warned that carisoprodol may impair the mental and/or physical abilities required for the performance of hazardous tasks such as driving a motor vehicle or operating machinery.

Use carisoprodol with caution in addiction-prone individuals. Withdrawal symptoms including abdominal cramps, insomnia, chilliness, headache, and nausea have occurred following abrupt cessation of higher than recommended dosage. There have been rare instances of psychological dependence.

On very rare occasions, the first dose of carisoprodol has been followed by idiosyncratic symptoms appearing within minutes or hours. Symptoms reported include extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Symptoms usually subside over the course of the next several hours. Supportive and symptomatic therapy, including hospitalization, may be necessary.

Usage in pregnancy: Safe usage of this drug in pregnant women has not been established. Therefore, the expected benefits must be weighed against the potential hazards. In lactating mothers receiving carisoprodol, the concentration in breast milk is two to four times that of maternal plasma. This factor should be taken into account when use of the drug is contemplated in nursing mothers.

Use of this drug in children is not recommended.

Since the effects of carisoprodol and alcohol or carisoprodol and other CNS depressants may be additive, appropriate caution should be exercised.

Precautions: Carisoprodol is metabolized in the liver and excreted by the kidney; to avoid its excess accumulation, caution should be exercised in administration to patients with compromised liver or kidney function.

Adverse Reactions: *Central nervous system reactions:* Drowsiness and other CNS effects may require dosage reduction. Other adverse reactions include dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia.

Allergic or idiosyncratic reactions: Allergic or idiosyncratic reactions occasionally develop. They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug. Skin rash, erythema multiforme, pruritus, eosinophilia, and fixed drug eruption with cross reaction to meprobamate have been reported with carisoprodol. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock.

If such reactions do occur, discontinue carisoprodol and initiate appropriate symptomatic therapy, utilizing epinephrine, antihistamines, and possibly corticosteroids. In evaluating possible allergic reactions, also consider allergy to excipients.

Cardiovascular reactions: Tachycardia, postural hypotension, and facial flushing have been reported.

Gastrointestinal reactions: Nausea, vomiting, hiccup, and epigastric distress have been reported.

Hematologic reactions: Leukopenia, for which other drugs or viral infection may have been responsible, and pancytopenia, attributed to phenylbutazone, have been reported. No serious blood dyscrasias have been attributed to carisoprodol.

Dosage and Administration: The recommended dosage for adults is one RELA® 350 mg. four times daily, the last dose taken at bedtime. Use of this drug in children is not recommended.

Overdosage: Overdosage of carisoprodol produced stupor, coma, shock, respiratory depression, and, very rarely, death. Any drug remaining in the stomach should be removed and symptomatic therapy given. If respiration or blood pressure becomes compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously as indicated.

Carisoprodol is metabolized in the liver and excreted by the kidney. Although carisoprodol overdosage experience is limited, the following types of treatment have been used successfully with the related drug meprobamate: diuresis, osmotic (mannitol), peritoneal dialysis, and hemodialysis (carisoprodol is dialysable).

Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Carisoprodol can be measured in biological fluids by gas chromatography (Douglas JF, et al; J Pharm Sci 1968).

How Supplied: RELA Tablets are round, sugar-coated, pink tablets imprinted with a brown Schering trademark and product identification letters, AHRI on the tablets.

*Licensed under U.S. Pat. No. 2,937,...

[Shown in Product Identification...

Squibb—Cont.

dumone has been discontinued for 60 days before the test. Because of osteoblastic action of estrogens, patients with metabolic bone disease or renal disease should be carefully observed. Because of a possible decrease in glucose tolerance, diabetic patients should be followed closely. Any effect of prolonged use of this drug on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further studies.

Adverse Reactions: In therapeutic doses, undesirable hormonal effects are generally minimal. However, because of excessive androgenic or estrogenic stimulation, they may occur.

The following adverse reactions have been observed following Deladumone therapy:

Virilization, manifested by hirsutism, changes in the voice (hoarseness or deepening), and acne. The phenomena of virilization appear to be reversible except for some instances of voice changes. Virilization may be controlled by use of supplementary injections of estradiol valerate; excessive endometrial or breast stimulation may be controlled by the use of supplemental injections of testosterone enanthate.

Other adverse reactions which have been reported are delayed menses followed by profuse bleeding, excessive and prolonged vaginal bleeding, mastodynia, edema, erythema and edema of the vulva, convulsions, pain at the site of injection, sterile abscess, incomplete suppression of lactation and/or breast engorgement, and localized dermatitis.

Dosage and Administration: The usual dosage for all indications except prevention of postpartum lactation, breast engorgement, and subsequent pain is 1 cc. every 4 weeks, depending on the clinical response. To alter the amount of therapy, it is recommended that the change be made in the quantity per injection (range 1 to 4 cc.) rather than in the time interval between injections.

For the prevention of postpartum lactation, breast engorgement, and subsequent pain, 4 cc. should be given as a single injection just prior to the onset of the second stage of labor because the percentage of favorable results has been shown to decline when the dose is administered at a later time. A second injection is not recommended.

Care should be taken to inject Deladumone deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Storage: Vials of Deladumone may be stored at room temperature. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming. Deladumone in Unimatic® single-dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Deladumone, vials of 5 cc.; Unimatic® single dose preassembled syringes of 1 cc. and cartridge-needle units of 1 cc.

DELADUMONE® OB

Testosterone Enanthate [360 mg.] And Estradiol Valerate [16 mg.] Injection

Description: Deladumone OB is a sterile, long-acting preparation for the prevention of lactation, providing a precisely balanced combination of the naturally-occurring testicular and follicular hormones in ester form dissolved in a vehicle of sesame oil with 2% (w/v) benzyl alcohol as a preservative. Each 2 cc. Deladumone OB contains 360 mg. testosterone enanthate and 16 mg. estradiol valerate. (180 mg. testosterone enanthate and 8 mg. estradiol valerate per cc.).

Actions: Deladumone OB is a long-acting androgen-estrogen preparation. When used for the prevention of lactation, a single 2 cc. injection, administered as directed, effectively inhibits the release of lactogenic hormone from the pituitary, thereby preventing lactation and the painful breast engorgement which accompanies it. However, if breast feeding is desired after Deladumone OB has been administered, satisfactory release of the lactogenic hormone and lactation may be induced by the stimulus of suckling by the infant. Involution of the uterus and resumption of menstrual cycles are generally not affected by Deladumone OB.

Deladumone OB contains the same hormonal agents as Deladumone (Testosterone Enanthate and Estradiol Valerate Injection) but at twice the potency, in order to provide a high dosage concentration in a low volume. The optimal balance of androgenic and estrogenic hormones obviates the disadvantages inherent in single hormone therapy, minimizing the likelihood of virilization, withdrawal bleeding, or other unwanted effects.

Indications: Deladumone OB is specifically indicated for the prevention of postpartum lactation, breast engorgement, and subsequent pain.

Contraindications: Deladumone OB is contraindicated in patients with a history of established or suspected mammary or genital malignancy, or hepatic dysfunction or disease.

Precautions: Because normal endogenous hormone production varies individually, certain patients may be unusually responsive and may exhibit undesirable manifestations of excessive androgenic or estrogenic stimulation (see *ADVERSE REACTIONS*).

Although edema has not been found to be a problem when Deladumone OB is used as recommended in the control of postpartum lactation and breast engorgement, nevertheless, caution should be taken in administering the drug to patients with cardiac or renal disease, and to patients with epilepsy, migraine, or asthma.

Adverse Reactions: When properly given, injections of Deladumone OB are generally well tolerated. In therapeutic doses, undesirable hormonal effects are generally minimal. The following adverse reactions have been reported: Virilization, manifested by hirsutism, changes in the voice (hoarseness or deepening), and acne. The phenomena of virilization appear to be reversible except for some instances of voice changes. Virilization may be controlled by use of supplementary injections of estradiol valerate. Excessive endometrial or breast stimulation has been reported; these effects may be controlled by the use of supplemental injections of testosterone enanthate.

Other adverse reactions that have been reported are pain at the site of injection, convulsions, sterile abscess, incomplete suppression of lactation and/or breast engorgement, uterine bleeding, mastodynia, and localized dermatitis.

Dosage and Administration: For the prevention of postpartum lactation, breast engorgement, and subsequent pain, 2 cc. of Deladumone OB should be given as a single intramuscular injection. It appears that the optimal time for administration of Deladumone OB is just prior to the onset of the second stage of labor. It is worthwhile noting, however, that the preparation has been successfully used from the early first stage of labor to as late as 10 hours after expulsion of the placenta. A second injection is not recommended.

Care should be taken to inject Deladumone OB deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Because of the viscosity of the preparation, and since Deladumone OB provides a high concentration in a small volume, particular care should be taken to administer the full dose. A slow, steady pressure on the syringe plunger is recommended.

Storage: Vials of Deladumone OB should be stored at room temperature. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming. Deladumone OB in Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Vials of 2 cc. (Military Stock #FSN-6505-823-7903). Unimatic® single dose preassembled syringes of 2 cc. and cartridge-needle units of 2 cc.

DELALUTIN®

(Hydroxyprogesterone Caproate Injection U.S.P.)

Description: Delalutin is a sterile, long-acting preparation of the caproate ester of the naturally occurring progestational hormone, hydroxyprogesterone, in an oil solution for intramuscular use.

Actions: Hydroxyprogesterone is a potent, long-acting, progestational steroid ester which transforms proliferative endothelium into secretory endothelium, induces mammary gland duct development, and inhibits the production and/or release of gonadotropic hormone; it also shows slight estrogenic, androgenic, or corticoid effects as well, but should not be relied upon for these effects.

In advanced adenocarcinoma of the uterine corpus, Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) in a dosage of 100 mg. or more, one or more times each week, often induces regressive changes.

Indications

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

Effective: In non-pregnant women, Delalutin is indicated for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV) and in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) is also indicated for use as a test for continuous endogenous progesterone production (a presumptive test for pregnancy), as a test for endogenous estrogen production ("Medical D and C"), and for the production of secretory endometrium and desquamation.

Probably effective: Habitual and threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hydroxyprogesterone caproate is contraindicated in patients with markedly impaired liver function, carcinoma of the breast, undiagnosed abnormal genital

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ing, missed abortion, and in th
ry of hypersensitivity to the d
ge regimens requiring estroge
dicated in women with a kno
d genital malignancy, and i
thrombophlebitis, thromboe
rs, cerebral apoplexy, or a past
e conditions.
nings: Discontinue the medica
examination if there is a sudd
mplete loss of vision, or if the
onset of proptosis, diplopia, or
ication should be stopped if ex
als papilledema or retinal v
e.
ctable amounts of progestins
ified in the milk of mother
drug. The effect of this on t
nt has not been determined.
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ed when progestins have be
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physician should watch for
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If these occur or are suspect
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ONTRAINDICATIONS).
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management of sexually-ma
h regular normal menses, dur
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inistered with caution to those
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e pretreatment physical
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ome compounds with progestat
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atients who have a history c
ression should be carefully obs
ug discontinued if the depres
serious degree.
aboratory test results, parti
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d by progesterone and/or estr
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ion should not be considered
as therapy has been discon
east 60 days.
Adverse Reactions: The follo
ion is pertinent whenever
preparations are used with est
known at the present time if th
re applicable to progesterone:
A. A statistically significant
been demonstrated betwe
trogen-progesterone com
thrombophlebitis, pulmor
and cerebrovascular accid
B. Although such a relatio
neither confirmed nor re
evidence is suggestive of
between the use of prog
estrogens and the followi
fects: neuro-ocular lesio

bleeding, missed abortion, and in those with a history of hypersensitivity to the drug.

Dosage regimens requiring estrogens are contraindicated in women with a known or suspected genital malignancy, and in patients with thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions.

Warnings: Discontinue the medication pending examination if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine. Medication should be stopped if examination reveals papilledema or retinal vascular lesions.

Detectable amounts of progestins have been identified in the milk of mothers receiving the drug. The effect of this on the nursing infant has not been determined.

Masculinization of the female fetus has occurred when progestins have been used in pregnant women.

The physician should watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). If these occur or are suspected the drug should be discontinued immediately (see CONTRAINDICATIONS).

Precautions: Like other progestogens, hydroxyprogesterone caproate may inhibit production and/or release of gonadotropic hormones, particularly the luteinizing and luteotropic hormones; this should be considered in the management of sexually-mature women with regular normal menses, during the first part of the ovarian cycle.

Hydroxyprogesterone caproate should be administered with caution to those patients in whom periodic attacks of certain medical conditions such as asthma, migraine, epilepsy, or cardiac or renal dysfunction, are known to be exacerbated by progesterone.

The pretreatment physical examination should include examination of the breasts and pelvic organs, and a Papanicolaou smear.

In relation to irregular bleeding which does not respond predictably to the hormone therapy, nonfunctional causes should be borne in mind and adequate diagnostic measures instituted.

Some compounds with progestational activity may induce fluid retention.

Any influence of prolonged sex hormone medication on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

The pathologist should be advised of progesterone therapy when relevant specimens are submitted.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

Laboratory test results, particularly of hepatic and endocrine functions, may be affected by progesterone and/or estrogen therapy. Tests to evaluate endocrine and liver function should not be considered definitive unless therapy has been discontinued for at least 60 days.

Adverse Reactions: The following information is pertinent whenever progesterone preparations are used with estrogens; it is not known at the present time if these statements are applicable to progesterones alone.

A. A statistically significant association has been demonstrated between the use of estrogen-progesterone combinations and thrombophlebitis, pulmonary embolism, and cerebrovascular accidents.

B. Although such a relationship has been neither confirmed nor refuted, available evidence is suggestive of an association between the use of progesterones with estrogens and the following untoward effects: neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis); nausea; vomiting; anorexia; gastrointestinal symptoms (such as abdominal cramps or bloating); edema; breakthrough bleeding, spotting, or withdrawal bleeding; breast tenderness and enlargement; changes in body weight (increase or decrease); headache; increase in cervical mucus; allergic rash; sterile abscess; pain at the injection site; post-injection flare; reactivation of endometriosis; aggravation of migraine headaches; and hepatic cutaneous porphyria becoming manifest.

C. The following adverse reactions are known to occur in patients receiving both progesterones and estrogens: chloasma or melasma, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, and amenorrhea during or after treatment.

D. The following adverse reactions have been reported with the concomitant use of progesterones and estrogens; a cause and effect relationship has been neither confirmed nor refuted: post-treatment anovulation, cystitis-like syndrome, hirsutism, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, and hypomenorrhea, oligomenorrhea, or amenorrhea.

E. The following laboratory tests may give altered results by the concomitant use of progesterones and estrogens: hepatic function (increased sulfobromophthalein retention and other tests); coagulation tests (increase in prothrombin and Factors VII, VIII, IX, and X); metyrapone test; pregnanediol determination; and thyroid function tests (increase in PBI and butanol extractable protein-bound iodine, decrease in T3 uptake values, and possible diminution in lactation when given immediately post-partum).

Female fetal masculinization has been observed in patients who received hydroxyprogesterone caproate.

A few instances of coughing, dyspnea, constriction of the chest, and/or allergic-like reactions have occurred following hydroxyprogesterone caproate therapy; the likelihood of these occurring may be increased at higher dosage levels.

Dosage and Administration: Suggested dosages are presented below. Because of the low viscosity of the vehicle, Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) may be administered with a small gauge needle. (The Unimatic single dose syringe contains a 20 gauge needle.) Care should be taken to inject the preparation deeply into the upper outer quadrant of the gluteal muscle following the usual precautions for intramuscular injection. Since the 250 mg. potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

Note: Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

Cyclic therapy is a 28-day cycle repeated every 4 weeks. The Cyclic Therapy Schedule is as follows: 20 mg. Estradiol Valerate Injection U.S.P. is administered on Day 1 of each cycle; two weeks after Day 1, 250 mg. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) and 5 mg. Estradiol Valerate Injection U.S.P. are administered; four weeks after Day 1 is Day 1 of next cycle.

Suggested Cyclic Regimen—Non-Pregnant Women: *Amenorrhea (primary and secondary); Abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer.* Administer 375 mg. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) any time. After 4 days of desquamation or, if there is no bleeding, 21 days after Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) alone, start Cyclic Therapy Schedule; repeat Cyclic Therapy Schedule every 4 weeks; stop after 4 cycles. Genital malignancy should be excluded before hormone therapy is started. Hydroxyprogesterone caproate is used as a "Medical D and C" to eliminate any proliferated endometrium from previous estrogenic action by conversion to secretory endometrium and desquamation. To determine onset of normal cyclic function, patient should be observed for 2 to 3 cycles after cessation of therapy.

Production of secretory endometrium and desquamation. In patients not on estrogen therapy, start Cyclic Therapy Schedule any time; repeat every 4 weeks; stop when cyclic therapy is no longer required. If estrogen deficiency has been prolonged, menstruation may not occur until estrogen has been given for several months. In patients currently on estrogen therapy, administer 375 mg. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) any time; start Cyclic Therapy Schedule after 4 days of desquamation or, if there is no bleeding, 21 days after Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) alone; repeat Cyclic Therapy Schedule every 4 weeks; stop when cyclic therapy is no longer required. If estrogen deficiency has been prolonged, menstruation may not occur until estrogen has been given for several months.

Suggested Non-Cyclic Regimen—Non-Pregnant Women: *Adenocarcinoma of uterine corpus in advanced stage (Stage III or IV).* 1000 mg. or more at once; repeat one or more times each week (1-7 grams per week); stop when relapse occurs, or after 12 weeks with no objective response. Should not be used in early stage (Stage I or II) in place of established anti-cancer therapy. May be used in advanced stage concomitantly with other anti-cancer therapy (surgery, or radiation, or chemotherapy, or a combination of these). Treatment results reported to date have been better in histologically well-differentiated forms of endometrial adenocarcinoma.

Pregnant Women: *Habitual Abortion.* 250 mg. or more as soon as possible after start of pregnancy; repeat once each week; stop 2 weeks before expected delivery. A single injection is of limited value.

Threatened Abortion. 250 mg. or more at once; repeat one or more times daily; stop when symptoms are controlled; thereafter treat as for habitual abortion (see above). In threatened abortion, large amounts of hydroxyprogesterone caproate are required.

Tests: *As a Test for Endogenous Estrogen Production ("Medical D and C").* 250 mg. as a single injection. In non-pregnant patients with responsive endometrium, bleeding 7 to 14 days after injection indicates endogenous estrogen. The test may be confirmed by a second injection 4 weeks after the first.

As a Test for Continuous Endogenous Progesterone Production. (This procedure is a presumptive test for pregnancy) 250 mg. as a single injection; in the patient with a responsive endometrium and endogenous estrogen production, failure to bleed indicates an endogenous source of progesterone, as in pregnancy; to confirm this test, a second dose may be given 4 weeks after first injection.

Storage: Delalutin (Hydroxyprogesterone

Continued on next page

For information on Squibb products write to: Squibb Professional Services Department, Lawrenceville-Princeton Rd., Princeton, N.J. 08540.

Squibb—Cont.

Caproate Injection U.S.P.) should be stored at room temperature. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on heating the vials in boiling water. Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) in Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Delalutin (Hydroxyprogesterone Caproate Injection U.S.P.) is available in vials providing hydroxyprogesterone caproate in potencies of 125 mg. and 250 mg. per cc. The 125 mg. potency is formulated in sesame oil and 30% benzyl benzoate and the 250 mg. potency is formulated in castor oil and 46% benzyl benzoate; both potencies also contain 2% (w/v) benzyl alcohol as a preservative. The 125 mg. potency is supplied in vials of 10 cc. (Military Stock # FSN-6505-656-1022) and vials of 2 cc. The 250 mg. potency is supplied in vials of 5 cc. (Military Stock # FSN-6505-864-5221), Unimatic® single dose preassembled syringes of 1 cc. and cartridge-needle units of 1 cc.

DELATESTRYL®

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(Testosterone Enanthate Injection U.S.P.)

Description: Delatestryl (Testosterone Enanthate Injection U.S.P.) is a sterile solution of testosterone enanthate for intramuscular use.

Actions: Delatestryl is intended for androgen therapy, particularly when prolonged action is desirable. Following a single intramuscular injection, the androgenic effect is sustained over a period of about 4 weeks. This continous flow of hormone is thought to resemble closely the endogenous production of testosterone.

Testosterone enanthate is primarily used for its protein anabolic effect and its catabolic inhibiting effect on tissue. Nitrogen balance is improved with anabolic agents but only when there is sufficient intake of calories and protein. Whether this positive nitrogen balance is of primary benefit in the utilization of protein-building dietary substances has not been established.

Enhancement of protein anabolism is manifest by conservation of sodium, nitrogen, phosphorus, potassium, sulfur, and water in the proportions of physiologic protein tissues, and of calcium with additional phosphorus in the proportions of physiologic osseous tissues.

Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. They suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

Indications: In males, Delatestryl (Testosterone Enanthate Injection U.S.P.) is indicated in the treatment of eunuchism, eunuchoidism, deficiency after castration, male climactericlike symptoms when these are secondary to androgen deficiency, and oligospermia.

Contraindications: Androgens are contraindicated in male patients with prostatic or breast cancer, in those elderly patients in whom overstimulation is to be avoided, and in those cases of benign prostatic hypertrophy with obstructive symptoms. Androgens are also contraindicated in patients with nephrosis or the nephrotic phase of nephritis.

Precautions: If symptomatic hypercalcemia occurs, discontinue androgen therapy and institute appropriate measures.

Caution is required in administering androgens to patients with cardiac, renal, or hepatic disease. Edema may occur occasionally. Concomitant administration with adrenal steroids or ACTH may add to the edema.

Anabolic steroids may increase sensitivity to anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain the prothrombin time at the desired therapeutic level.

Anabolic steroids have been shown to alter glucose tolerance tests. Diabetics should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly.

Serum cholesterol may increase or decrease during therapy. Because of its hypercholesterolemic effects, caution is required when administering this drug to patients with a history of myocardial infarction or coronary artery disease. Serial determinations of serum cholesterol should be made and therapy adjusted accordingly. A cause and effect relationship between myocardial infarction and hypercholesterolemia has not been established.

Inhibition of testicular function and decrease in ejaculatory volume may occur when the drug is administered in doses greater than those used for replacement therapy in hypogonadal males.

Adverse Reactions: In males, the following post-pubertal adverse reactions have occurred: inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, gynecomastia, epididymitis, and bladder irritability. In addition, the following reactions are known to occur with anabolic steroids: increased or decreased libido, flushing of the skin, acne, habituation, excitation and sleeplessness, chills, leucopenia, and bleeding in patients on concomitant anticoagulant therapy.

Intramuscular preparations of anabolic steroids have been associated with urticaria at the injection site, post-injection induration, and furunculosis.

Alterations may occur in the following clinical laboratory tests: metyrapone test, fasting blood sugar (FBS) and glucose tolerance test, thyroid function tests [decrease in protein bound iodine (PBI), thyroxine-binding capacity, and radioactive iodine uptake, and an increase in T^3 uptake by the red blood cells or resin: free thyroxine levels remain normal and the altered tests usually persist for 2-3 weeks after stopping anabolic therapy], electrolytes (retention of sodium, chloride, water, potassium, calcium, and inorganic phosphates), blood coagulation tests (increase in clotting factors II, V, VII, and X), and miscellaneous laboratory tests (decreased creatinine and creatine excretion lasting up to two weeks after discontinuing therapy and increased 17-ketosteroid excretion).

Dosage and Administration: When properly given, injections of Delatestryl (Testosterone Enanthate Injection U.S.P.) are well tolerated. Care should be taken to inject the preparation deeply into the gluteal muscle following the usual precautions for intramuscular administration. In general, total doses above 400 mg. per month are not required because of the prolonged action of the preparation. Injections more frequently than every two weeks are rarely indicated. NOTE: Use of a wet needle or wet syringe may cause the solution to become cloudy: however, this does not affect the potency of the material.

In male hypogonadism (i.e., eunuchism, eunuchoidism, severe deficiency after castration, male climacteric-like symptoms when secondary to androgen deficiency), the suggested dosage is 200-400 mg. every four weeks. Androgen therapy is regarded as replacement therapy, being effective only as long as continued; prolonged treatment with chorionic gonadotropin is also recommended.

In the treatment of oligospermia, the suggested dosage is 100-200 mg. every 4-6 weeks for the development and maintenance of testicular tubular function: for suppression and rebound stimulation, the recommended dosage is 200 mg. every week for 6-12 weeks.

Storage: Vials should be stored at room temperature. Warming and shaking the vial will redissolve any crystals that may have formed during storage at low temperatures. Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: Delatestryl (Testosterone Enanthate Injection U.S.P.) is available in vials of 5 cc. and Unimatic® single dose preassembled syringes of 1 cc. and cartridge-needle units of 1 cc. Each cc. of sterile solution provides 200 mg. testosterone enanthate in sesame oil with 0.5% chlorobutanol (chloral derivative) as a preservative.

DELESTROGEN®

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(Estradiol Valerate Injection U.S.P.)

Description: Delestrogen (Estradiol Valerate Injection U.S.P.) is a long-acting sterile estrogen preparation for intramuscular use. It is available in potencies of 10 mg., 20 mg., and 40 mg. per cc. The 10 mg. potency is formulated in a sesame oil vehicle with 0.5% chlorobutanol (chloral derivative) as a preservative. The 20 mg. potency is formulated in castor oil and 20% benzyl benzoate and the 40 mg. potency is formulated in castor oil and 40% benzyl benzoate; both also contain 2% (w/v) benzyl alcohol as a preservative.

Actions: Estradiol valerate is a hormone with a potent and prolonged estrogenic effect. It promotes the growth of the endometrium; promotes thickening, stratification, and cornification of the vagina; causes growth of mammary gland ducts; and inhibits the anterior pituitary gland. The estrogenic effect occurs soon after administration and lasts for approximately two to three weeks after a single intramuscular injection.

Indications: Delestrogen (Estradiol Valerate Injection U.S.P.) is indicated for replacement therapy of estrogen deficiency associated with menopausal syndrome, amenorrhea, female castration, primary ovarian failure, senile vaginitis, and kraurosis vulvae with or without pruritus. Delestrogen is also indicated for the prevention of postpartum breast engorgement and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. Delestrogen (Estradiol Valerate Injection U.S.P.) may also be used to treat inoperable, progressing prostatic cancer (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred).

Contraindications: Estradiol valerate is contraindicated in patients with a known or suspected mammary or genital malignancy (except prostatic carcinoma). It is also contraindicated in thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions, as well as in patients with pulmonary embolism, liver dysfunction or disease, undiagnosed abnormal genital bleeding, or a history of hypersensitivity to estradiol valerate.

Warnings: The physician should watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). If these occur or are suspected, the drug should be discontinued immediately.

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discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Medication should be stopped if examination reveals papilledema or retinal vascular lesions.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Since the safety of estrogens and progestogens given in conjunction with each other in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the regimen.

Because normal endogenous hormone production varies individually, certain patients may be unusually responsive to estrogenic therapy and may respond with undesirable manifestations of excessive estrogenic stimulation such as abnormal or excessive uterine bleeding, mastodynia, edema, etc.

When large doses of estrogens are used, urinary stress incontinence may occur in nonpregnant females.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the nursing infant has been described. The long range effect on the nursing infant is not known at this time.

Pre-existing fibroid tumors of the uterus may enlarge during therapy.

Precautions: The pretreatment physical examination should include examination of the breasts and pelvic organs, and a Papanicolaou smear. In cases of irregular bleeding which does not respond predictably to the hormone therapy, non-functional causes should be borne in mind and adequate diagnostic measures instituted.

Estrogen therapy may induce fluid retention. Its use in cardiac failure, in disease states associated with edema, and with epilepsy should be carefully controlled. Estrogen therapy should be used with caution in patients with a history of cerebrovascular accident.

A decrease in glucose tolerance has been observed in patients receiving estrogenic drugs. Diabetic patients should be carefully observed for regulation during medication with estrogenic therapy.

Because of the effects of estrogens on epiphyseal closure, estradiol valerate should be used judiciously in young patients in whom bone growth is not complete.

Any influence of prolonged sex hormone medication on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. It is known, however, that prolonged high doses of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with certain metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

Medication should be discontinued in patients with a history of psychic abnormalities if exaggeration of symptoms occurs.

Endocrine and liver function may be influenced by estrogen therapy. Estrogens may cause an elevation in the PBI and the BEI, and a decrease in the T3 uptake. Tests to evaluate endocrine and liver function should not be considered definitive unless therapy has been discontinued for at least 60 days. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Adverse Reactions: The following information is pertinent whenever estrogen preparations are used with progesterones; it is not known at the present time if these statements are applicable to estrogens alone.

A. A statistically significant association has been demonstrated between the use of estrogen-progesterone combinations and thrombophlebitis, pulmonary embolism, and cerebrovascular accidents.

B. Although such a relationship has been neither confirmed nor refuted, available evidence is suggestive of an association between the use of estrogens with progesterones and the following untoward effects: neuro-ocular lesions (e.g. retinal thrombosis and optic neuritis); nausea; vomiting; anorexia; gastrointestinal symptoms (such as abdominal cramps or bloating); edema; breakthrough bleeding, spotting, or withdrawal bleeding; breast tenderness and enlargement; changes in body weight (increase or decrease); headache; increase in cervical mucus; allergic rash; loss of libido and gynecomastia in the male; sterile abscess; pain at the injection site; post-injection flare; reactivation of endometriosis; aggravation of migraine headaches; and hepatic cutaneous porphyria becoming manifest.

C. The following adverse reactions are known to occur in patients receiving both estrogens and progesterones: chloasma or melasma, cholestatic jaundice, rise in blood pressure in susceptible individuals, mental depression, and amenorrhea during and after treatment.

D. The following adverse reactions have been reported with the concomitant use of estrogens and progesterones; a cause and effect relationship has been neither confirmed nor refuted: post-treatment anovulation, cystitis-like syndrome, hirsutism, loss of scalp hair, erythema nodosum, hemorrhagic eruption, premenstrual-like syndrome, changes in libido, changes in appetite, nervousness, dizziness, fatigue, backache, erythema multiforme, itching, hypomenorrhea, oligomenorrhea, or amenorrhea.

E. The following laboratory tests may give altered results by the concomitant use of estrogens and progesterones: hepatic function (increased sulfobromophthalein retention and other tests); coagulation tests (increase in prothrombin and Factors VII, VIII, IX, and X); metyrapone test; pregnanediol determination; and thyroid function tests (increase in PBI and butanol extractable protein-bound iodine, decrease in T3 uptake values, and possible diminution in lactation when given immediately post-partum).

When estrogens are used for the treatment of prostatic carcinoma, hypercalcemia may develop.

Dosage and Administration: Care should be taken to inject deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicles, the various preparations of Delestrogen (Estradiol Valerate Injection U.S.P.) may be administered with a small gauge needle. Since the 40 mg. potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

Note: A dry needle and syringe should be used. Use of a wet needle or syringe may cause the solution to become cloudy; however, this does not affect the potency of the material.

For Castration; Primary ovarian failure; Menopausal syndrome; Senile vaginitis; Kraurosis vulvae with or without pruritus. Administer 10-20 mg. Delestrogen (Estradiol Valerate Injection U.S.P.) any time; repeat 2-3 weeks after initial injection; stop after second injection. Continuous therapy with estrogen alone may induce dysfunctional uterine bleeding.

For Inoperable, progressing prostatic carcinoma (for palliation only when castration is not feasible or when castration failures or delayed escape following a response to castration have not occurred). 30 mg. or more every 1 to 2 weeks. Close medical supervision is mandatory. Suspend therapy if there is a relapse. Soreness of the breasts or gynecomastia may occur; hypercalcemia may develop.

For Prevention of postpartum breast engorgement. 10-25 mg. as a single injection at the end of the first stage of labor.

As Part of Cyclic Therapy Schedule. The Cyclic Therapy Schedule is as follows: 20 mg. Delestrogen (Estradiol Valerate Injection U.S.P.) is administered on Day 1 of each cycle; two weeks after Day 1, 250 mg. Hydroxyprogesterone Caproate Injection U.S.P. and 5 mg. Delestrogen (Estradiol Valerate Injection U.S.P.) are administered; four weeks after Day 1 is Day 1 of next cycle.

Amenorrhea; Abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology. Administer 375 mg. Hydroxyprogesterone Caproate Injection U.S.P. any time. After 4 days of desquamation or, if there is no bleeding, 21 days after hydroxyprogesterone caproate alone, start Cyclic Therapy Schedule; repeat Cyclic Therapy Schedule every 4 weeks; stop after 4 cycles. Genital malignancy should be excluded before hormone therapy is started. Hydroxyprogesterone caproate is used as a "Medical D and C" to eliminate any proliferated endometrium from previous estrogenic action by conversion to secretory endometrium and desquamation. To determine onset of normal cyclic function, patient should be observed for 2 to 3 cycles after cessation of therapy.

Storage: Vials should be stored at room temperature. Storage at low temperature may result in the separation of some crystalline material which redissolves readily on warming. Unimatic single dose preassembled syringes and cartridge-needle units should be stored at room temperature.

How Supplied: The 10 mg. potency is available in 1 cc. and 5 cc. vials. The 20 mg. potency is available in 5 cc. vials and in 1 cc. Unimatic® single dose preassembled syringes and cartridge-needle units. The 40 mg. potency is available in 5 cc. vials.

DELUTEVAL® 2X

(Hydroxyprogesterone Caproate and Estradiol Valerate Injection)

Description: Deluteval 2X is a long-acting sterile preparation for intramuscular use providing an esterified derivative of the naturally-occurring progestational hormone, hydroxyprogesterone, and the valeric acid ester of naturally-occurring estradiol. Each cc. of Deluteval 2X provides 250 mg. hydroxyprogesterone caproate and 5 mg. estradiol valerate in castor oil and 45% benzyl benzoate with 1.6% (w/v) benzyl alcohol as a preservative.

Continued on next page

...range flavored and colored) in 60 cc. ... assembly bottles with dropper cali... at 0.5 cc. (0.25 mg.), 1 cc. (0.5 mg.), 1.5 ... mg.), and 2 cc. (1 mg.); and in pint ... bottles.

...—Multiple-dose vials of 10 cc., Uni... single dose preassembled syringes of 1 ... cartridge-needle units of 1 cc.

...own in Product Identification Section]

...LIXIN® ENANTHATE

...enazine Enanthate Injection N.F.)

...iption: Prolixin Enanthate (Fluphena... Enanthate Injection N.F.) is an esterified ...romethyl phenothiazine derivative, ...ically designated as 4-[3-[2-(trifluorome... phenothiazin-10-yl]propyl]-1-piperazino... heptanoate (enanthate). It is a highly ... behavior modifier with a markedly ex... duration of effect, available for intra... or subcutaneous administration in ... Unimatic® single dose preassembled sy... and cartridge-needle units providing ... fluphenazine enanthate per cc. in a ... oil vehicle, with 1.5% (w/v) benzyl al... as a preservative. At the time of manu... the air in the vials is replaced by ni...

...ions: The basic effects of fluphenazine ...anthate appear to be no different from ... of fluphenazine hydrochloride, with the ...ception of duration of action. The esterifi... of fluphenazine markedly prolongs the ...drug's duration of effect without unduly at... its beneficial action. The onset of ...ction generally appears between 24 to 72 ...hours after injection, and the effects of the ...drug on psychotic symptoms become signifi... within 48 to 96 hours. Amelioration of ...symptoms then continues for 1 to 3 weeks or ...longer, with an average duration of effect of ...about 2 weeks.

Fluphenazine has activity at all levels of the ...central nervous system as well as on multiple ...organ systems. The mechanism whereby its ...therapeutic action is exerted is unknown.

Fluphenazine differs from other phenothia... derivatives in several respects: it is more ...potent on a milligram basis; it has less poten...tiating effect on central nervous system de...pressants and anesthetics than do some of the ...phenothiazines and appears to be less sedat...ing; and it is less likely than some of the older ...phenothiazines to produce hypotension (nev...ertheless, appropriate cautions should be ob...served—see sections on "Precautions" and "Adverse Reactions").

...dications: Prolixin Enanthate (Fluphena... Enanthate Injection N.F.) is indicated in ...the management of manifestations of psy...chotic disorders. In the treatment of these ...conditions, the drug often maintains relief of ...such target symptoms as agitation, hostility, ...and anxiety. Prolixin Enanthate (Fluphena... Enanthate Injection N.F.) finds useful ...application not only in the hospital milieu, ...but also in the long-term maintenance ther...apy of chronically psychotic patients who are ...treatable on an out-patient basis.

Contraindications: Phenothiazines are con...traindicated in patients with suspected or es...tablished subcortical brain damage.

Phenothiazine compounds should not be used ...in patients receiving large doses of hypnotics.

Prolixin Enanthate (Fluphenazine Enanthate ...Injection N.F.) is contraindicated in comatose ...or severely depressed states.

The presence of blood dyscrasia, liver dam...age, or renal insufficiency precludes the use ...of fluphenazine enanthate.

Fluphenazine enanthate is not indicated for ...use in children under 12 years of age.

Prolixin Enanthate is contraindicated in pa...tients who have shown hypersensitivity to ...fluphenazine; cross-sensitivity to phenothia...zine derivatives may occur.

Warnings: The use of this drug may impair ...the mental and physical abilities required for ...driving a car or operating heavy machinery.

Physicians should be alert to the possibility ...that severe adverse reactions may occur ...which require immediate medical attention.

Potentiation of the effects of alcohol may oc...cur with the use of this drug.

Usage in Pregnancy:—The safety for the use ...of this drug during pregnancy has not been ...established; therefore, the possible hazards ...should be weighed against the potential bene...fits when administering the drug to pregnant ...patients.

Precautions: Because of the possibility of ...cross-sensitivity, fluphenazine enanthate ...should be used cautiously in patients who ...have developed cholestatic jaundice, derma...toses, or other allergic reactions to phenothia...zine derivatives.

Psychotic patients on large doses of a pheno...thiazine drug who are undergoing surgery ...should be watched carefully for possible hy...potensive phenomena. Moreover, it should be ...remembered that reduced amounts of anes...thetics or central nervous system depressants ...may be necessary.

The effects of atropine may be potentiated in ...some patients receiving fluphenazine because ...of added anti-cholinergic effects.

Fluphenazine enanthate should be used cau...tiously in patients exposed to extreme heat or ...phosphorus insecticides or in patients who ...have a history of ulcer disease, since aggrava...tion of peptic ulcer has occurred.

The preparation should be used with caution ...in patients with a history of convulsive disor...ders, since grand mal convulsions have been ...known to occur.

Use with caution in patients with special ...medical disorders such as mitral insufficiency ...or other cardiovascular diseases and pheo...chromocytoma.

The possibility of liver damage, pigmentary ...retinopathy, lenticular and corneal deposits, ...and development of irreversible dyskinesia ...should be remembered when patients are on ...prolonged therapy.

Outside state hospitals or other psychiatric ...institutions, fluphenazine enanthate should ...be administered under the direction of a phy...sician experienced in the clinical use of ...psychotropic drugs, particularly phenothia...zine derivatives. Furthermore, facilities ...should be available for periodic checking of ...hepatic function, renal function, and the ...blood picture. Renal function of patients on ...long-term therapy should be monitored; if ...BUN (blood urea nitrogen) becomes abnor...mal, treatment should be discontinued.

As with any phenothiazine, the physician ...should be alert to the possible development of ...“silent pneumonias” in patients under treat...ment with fluphenazine enanthate.

Adverse Reactions: *Central Nervous Sys...tem:* The side effects most frequently report...ed with phenothiazine compounds are extra...pyramidal symptoms including pseudopar...kinsonism, dystonia, dyskinesia, akathisia, ...oculogyric crises, opisthotonos, and hyper-re...flexia. Most often these extrapyramidal ...symptoms are reversible; however, they may ...be persistent (see below). The frequency of ...such reactions is related in part to chemical ...structure: one can expect a higher incidence ...with fluphenazine enanthate than with less ...potent piperazine derivatives or with ...straight-chain phenothiazines such as chlor...promazine. With any given phenothiazine de...rivative, the incidence and severity of such ...reactions depend more on individual patient ...sensitivity than on other factors; but dosage ...level and patient age are also determinants.

Extrapyramidal reactions may be alarming, ...and the patient should be forewarned and re...assured. These reactions can usually be con...trolled by administration of anti-parkinsonian ...drugs such as Benztropine Mesylate or In...travenous Caffeine and Sodium Benzoate In...jection U.S.P. and by subsequent reduction of ...dosage.

A persistent pseudo-parkinsonian syndrome ...may develop after chronic administration of ...phenothiazine compounds. The syndrome is ...characterized by rhythmic, stereotyped dyski...netic involuntary movements, particularly of ...the face, mouth, tongue and jaw, resembling ...the facial grimaces of encephalitis. These ...may be accompanied by choreiform move...ments of the limbs. The symptoms persist af...ter drug withdrawal and in some patients ap...pear to be irreversible. Anti-parkinsonian a...gents are seldom of benefit. The risk ap...pears to be greatest in elderly female patients ...with organic brain disease or damage who ...have been receiving fairly large doses of phe...nothiazines for a prolonged period.

Drowsiness or lethargy, if they occur, may ...necessitate a reduction in dosage; the induc...tion of a catatonic-like state has been known ...to occur with dosages of fluphenazine far in ...excess of the recommended amounts. As with ...other phenothiazine compounds, reactivation ...or aggravation of psychotic processes may be ...encountered.

Phenothiazine derivatives have been known ...to cause, in some patients, restlessness, ex...citement, or bizarre dreams.

Autonomic Nervous System: Hypertension ...and fluctuations in blood pressure have been ...reported with fluphenazine enanthate.

Hypotension has rarely presented a problem ...with fluphenazine. However, patients with ...pheochromocytoma, cerebral vascular or re...nal insufficiency, or a severe cardiac reserve ...deficiency such as mitral insufficiency appear ...to be particularly prone to hypotensive reac...tions with phenothiazine compounds and ...should therefore be observed closely when ...the drug is administered. If severe hypoten...sion should occur, supportive measures in...cluding the use of intravenous vasopressor ...drugs should be instituted immediately. Lev...arterenol Bitartrate Injection U.S.P. is the ...most suitable drug for this purpose; *epineph...rine should not be used* since phenothiazine ...derivatives have been found to reverse its ac...tion, resulting in a further lowering of blood ...pressure.

Autonomic reactions including nausea and ...loss of appetite, salivation, polyuria, perspira...tion, dry mouth, headache, and constipation ...may occur. Autonomic effects can usually be ...controlled by reducing or temporarily discon...tinuing dosage.

In some patients, phenothiazine derivatives ...have caused blurred vision, glaucoma, blad...der paralysis, fecal impaction, paralytic ileus, ...tachycardia, or nasal congestion.

Metabolic and Endocrine: Weight change, pe...ripheral edema, abnormal lactation, gynecco...mastia, menstrual irregularities, false results ...on pregnancy tests, impotency in men and in...creased libido in women have all been known ...to occur in some patients on phenothiazine ...therapy.

Allergic Reactions: Skin disorders such as ...itching, erythema, urticaria, seborrhea, pho...tosensitivity, eczema and even exfoliative ...dermatitis have been reported with phenothi...azine derivatives. The possibility of anaphy...lactoid reactions occurring in some patients ...should be borne in mind.

Hematologic: Routine blood counts are advis...

Continued on next page

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Squibb—Cont.

able during therapy since blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazine derivatives. Furthermore, if any soreness of the mouth, gums, or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage as manifested by cholestatic jaundice may be encountered, particularly during the first months of therapy; treatment should be discontinued if this occurs. An increase in cephalin flocculation, sometimes accompanied by alterations in other liver function tests, has been reported in patients receiving fluphenazine enanthate who have had no clinical evidence of liver damage.

Others: Sudden, unexpected and unexplained deaths have been reported in hospitalized psychotic patients receiving phenothiazines. Previous brain damage or seizures may be predisposing factors; high doses should be avoided in known seizure patients. Several patients have shown sudden flare-ups of psychotic behavior patterns shortly before death. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions.

Although this is not a general feature of fluphenazine, potentiation of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) may occur.

The following adverse reactions have also occurred with phenothiazine derivatives: hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use—skin pigmentation, and lenticular and corneal opacities.

Injections of fluphenazine enanthate are extremely well tolerated, local tissue reactions occurring only rarely.

Dosage and Administration: Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) may be given intramuscularly or subcutaneously. A dry syringe and needle of at least 21 gauge should be used. Use of a wet needle or syringe may cause the solution to become cloudy.

To begin therapy with Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) the following regimens are suggested:

For most patients a dose of 25 mg. (1 cc.) every 2 weeks should prove to be adequate, and therapy may be started on that basis. Subsequent adjustments in the amount and the dosage interval may be made, if necessary, in accordance with the patient's response.

It may be advisable that patients who have had no history of taking phenothiazines should be treated initially with a shorter acting form of fluphenazine before administering the enanthate to determine the patient's response to fluphenazine and to establish appropriate dosage. Since the dosage comparability of the shorter-acting forms of fluphenazine to the longer-acting enanthate is not known, special caution should be exercised when switching from the shorter-acting forms to the enanthate.

Severely agitated patients may be treated initially with a rapid-acting phenothiazine compound such as Prolixin Injection (Fluphenazine Hydrochloride Injection N.F.—see package insert accompanying that product for complete information). When acute symptoms have subsided, 25 mg. (1 cc.) of Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) may be administered; subsequent dosage is adjusted as necessary.

"Poor risk" patients (those with known hypersensitivity to phenothiazines, or with disorders that predispose to undue reactions): Therapy may be initiated cautiously with oral or parenteral fluphenazine hydrochloride (see package inserts accompanying these products for complete information). When the pharmacologic effects and an appropriate dosage are apparent, an equivalent dose of Prolixin Enanthate (Fluphenazine Enanthate Injection N.F.) may be administered. Subsequent dosage adjustments are made in accordance with the response of the patient.

The optimal amount of the drug and the frequency of administration must be determined for each patient, since dosage requirements have been found to vary with clinical circumstances as well as with individual response to the drug. Although in a large series of patients the optimal dose was usually 25 mg. every 2 weeks, the amount required ranged from 12.5 to 100 mg. (0.5 to 4 cc.). The interval between doses ranged from 1 week to 3 weeks in most instances, but some patients required doses as often as once a day for the first few days of treatment, while the response to a single dose was found to last as long as 6 weeks in a few patients on maintenance therapy.

Dosage should not exceed 100 mg. If doses greater than 50 mg. are deemed necessary, the next dose and succeeding doses should be increased cautiously in increments of 12.5 mg.

How Supplied: Vials of 5 cc., Unimatic Single Dose Pronssomixed Syringes of 1 cc., and cartridge-needle units of 1cc.

PRONESTYL® CAPSULES
(Procainamide Hydrochloride Capsules U.S.P.)

PRONESTYL INJECTION
(Procainamide Hydrochloride Injection U.S.P.)

Description: Pronestyl is the amide analogue of procaine hydrochloride. It is available as gelatin capsules supplying 250 mg., 375 mg., and 500 mg. for oral use and as a 10% sterile aqueous solution (100 mg./cc.) for parenteral use.

The parenteral solution contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives; the pH has been adjusted to 4.0-6.0 with hydrochloric acid or sodium hydroxide. The solution, which is colorless initially, may in time develop a slightly yellow color. This does not indicate a change which would prevent its use, but a solution any darker than light amber or discolored in any other way should not be used.

Actions: Procainamide depresses the excitability of cardiac muscle to electrical stimulation, and slows conduction in the atrium, the bundle of His, and the ventricle. The refractory period of the atrium is considerably more prolonged than that of the ventricle. Contractility of the heart is usually not affected nor is cardiac output decreased to any extent unless myocardial damage exists. In the absence of any arrhythmia, the heart rate may occasionally be accelerated by conventional doses, suggesting that the drug possesses anticholinergic properties. Larger doses can induce atrioventricular block and ventricular extrasystoles which may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram; a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged, and the QRS and T waves show some decrease in voltage.

The action of procainamide begins almost immediately after intramuscular or intravenous administration. Plasma levels after intramuscular injection are at their peak in 15 to 60 minutes. Following oral administration plasma levels of the drug are comparable to those obtained parenterally and are maximal within an hour; therapeutic levels are usually attained in half that time.

Procainamide is less readily hydrolyzed than procaine, and plasma levels decline slowly—about 10% to 20% per hour. The drug is excreted primarily in the urine, about 10% as free and conjugated *p*-aminobenzoic acid and about 60% in the unchanged form. The fate of the remainder is unknown.

Indications: The effects of Pronestyl (Procainamide Hydrochloride), are more beneficial in ventricular than in auricular arrhythmias. Ventricular extrasystoles and ventricular tachycardia are controlled within an hour after oral or intramuscular administration or within a few minutes after intravenous infusion. Digitalis-induced ventricular extrasystoles and tachycardia may at times be suppressed by careful and judicious administration of the drug. Pronestyl may also be of value in the control of an auricular arrhythmia particularly if the condition is of recent development. Atrial fibrillation of short duration may be converted to a normal sinus rhythm, and chronic atrial fibrillation may occasionally benefit as well. The drug is also worthy of trial in paroxysmal atrial tachycardia that cannot be controlled by reflex vagal stimulation or other measures.

The correction of cardiac arrhythmias which may occur during anesthesia constitutes an important indication for procainamide. The drug is especially valuable with cyclopropane anesthesia and for intrathoracic surgery; endotracheal intubation, or surgery in cardiac patients for whom the incidence of potentially severe arrhythmias is high. It may be given prophylactically before surgery to patients with known heart conditions or to those undergoing thoracic surgery.

Contraindications: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block.

Precautions: During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation with resultant forceful contractions of the atrium, may cause a dislodgement of atrial thrombi and produce an embolic episode. However, it has been suggested that the patient who is already discharging emboli procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as heart block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or cardiac arrest.

Parenteral administration should be monitored electrocardiographically when practicable. If electrocardiograms g

ATTACHMENT F - COMPILATION

TAB 10

Compendium of Excipients for Parenteral Formulations

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Overview

The selection of excipients in parenteral formulation design is often both rational and empirical. It is rational in the sense that certain types of excipients are added to alter the formulation properties: i) buffers of appropriate pKa are added to control hydrogen ion concentration at a desired pH, ii) tonicifiers are added for biocompatibility, iii) surfactants are added when necessary to prevent aggregation, adsorption to surfaces, or increase solubility, iv) antioxidants are included to prevent unwanted oxidation of the drug, and so on. The inclusion of various classes of formulation components, and the concentration used is often quite rational, in that their behavior and properties are known, and they are added to prevent specific problems that would arise in their absence. On the other hand, however, the selection of the *exact* excipient used is far from rational; it is empirical in the first order, satisfying only one question, "Has it been used previously in a similar parenteral formulation?"

Many prototype formulations have been terminated because one or more of the selected excipients was not found in a previously approved parenteral product. In fact, there have been a handful of excipients with striking favorable properties, such as trehalose with its ability to confer solid state stabilization of several types of proteins, or EDTA and its antioxidants by metal ion chelation. These excipient compounds, and many others, have not been used widely, largely because of concerns with unknown toxicity, continued production supply, or cost.

Thus, the formulation scientist is often faced with a dilemma—which excipients are truly available for use (based on what has been used previously), and which are not? For example, PEG 400 has been added to several parenteral formulations, but what about PEG 1200, or PEG 4000? And at what concentrations, and by what route? Sodium citrate is an excellent buffer for many formulations at 5 mM, but is too painful in most instances for subcutaneous use at 50 mM. High concentrations of propylene glycol may be used in a slow intravenous infusion, but would produce unwanted hemolysis and pain if given by subcutaneous or intramuscular injection. It is often the case that the "safe level" of an excipient may depend on the route of administration. These are only a few examples of factors which must be considered when designing a formulation; there are dozens more based on empirical information required for efficient formulation design, but thus far a compendium has not been published. This review was written to fill this void.

Herein are listed the excipients found in most of the approved and marketed parenteral formulations, given systematically by excipient name. In this format it is easy to determine what concentrations were used, the route of administration, the main rationale for addition of that excipient, the drug that was formulated, the manufacturer, brand name, etc. The information found in this table comes from several sources, including package inserts, the Physician's Desk Reference (PDR '97), as well as personal correspondence from the companies supplying the products. The published excipient concentration was often given in different units, including: mg/mL, mOs, Molar, sodium equivalents, biological Units, Molal, weight percent, etc., and provided one of the greatest challenges in putting this compendium together. We sought to list all the excipients (where possible) in common units (i.e., mg/mL), so that a rapid comparison of the different formulations could be made at a glance. (This is not easy to do, for example, when comparing Tween 20 concentrations at 0.0001 M, 0.01% and 1 mg/mL; fortunately, the average molecular weight is known for most excipients, permitting a standardization of excipient concentrations). This standardization of excipient concentrations is perhaps the greatest value of this compendium, but also represents one of the greatest sources of potential error. The recalculation of excipient concentrations, often from scant or nondescriptive data, is not trivial and there may be an occasional discrepancy despite cross-checking with the original sources.[1] Nevertheless, this compendium represents a comprehensive survey of parenteral excipients used today, and is a resource for the parenteral formulation scientist.

Notes

In putting together this excipient compendium, there were a number of points that should be noted, so that the reader understands the limitations and assumptions in some of the calculations.

1) Concentrations are listed in weight/volume% unless otherwise noted. In some cases values are listed in volume/volume% or the manufacturer did not specify what kind of percentage they were using (and in this case it was assumed weight/volume %).

2) Sterile water for injection is included in the excipient list when used in solution formulations; however, in most

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[1] If discrepancies are found, e-mail them to nguyen.tue@gene.com for correction to subsequent compendiums of this nature.

cases the quantity or percentage of water in the formulation was not indicated by the manufacturer or identified only as q.s. We have kept the same conventions here.

3) Excipients listed are present in the drug formulation itself, and do not include excipients present in diluent (for example, when a lyophilized formulation is diluted with bacteriostatic water containing benzyl alcohol). In some cases, a diluent is supplied that contains several additional excipients and, in the case or provided diluent, these excipients are listed in the excipient category and designated with a "D" in addition to their usual excipient type (the D stand for present in diluent).

4) If no excipients are listed, it means that no excipients were revealed by the manufacturer. In some cases, this is because there are no excipients in the formulation, but this should not be assumed. In some cases, there may be excipients present but the manufacturer has not disclosed them to us, largely for proprietary reasons. Specific follow-up about these drugs should be referred to the manufacturer.

5) The given drug concentration is usually the concentration of the compound listed in the drug name category, unless identified as otherwise. For example, many drugs are formulated as salts such that the salt name is listed in the drug name category (for example, mitoxantrone hydrochloride). However, in the drug concentration category, the concentration of the active component is usually listed (for example, equivalent to 2 mg/mL mitoxantrone free base), so as to have a correct concentration of the active drug form.

6) When concentrations of excipients and drugs are listed as a range it implies that these values could only be approximated. Frequently, a range is given because the product is available in a variety of storage containers, or having several dilution schemes. The ranges given are approximations only, based on the available information. In no way should these ranges be assumed to encompass all possible dilution schemes or configurations.

7) Preservatives (such as benzyl alcohol) that are present only in one configuration of a drug (for example in the multiple-dose product, but not in the single-use product) may be listed as a range (0–x%). This was to avoid making two or more records for essentially the same product configuration.

8) For drugs that are given as a salt form, the counter ion may not be listed as an excipient. To search for counter ions (like sodium or potassium) one may look in the drug name fields (where the entire salt is often listed) or in the comments section (where the quantity of the counter ion per gram of drug is often provided) as well as in the excipient section.

9) If a pH value is listed for a lyophilized product, in most cases, it is the pH of the drug after its initial reconstitution with diluent, not the pH at lyophilization.

10) The concentration values given for excipients and active drug product in lyophilized products are usually those present at the initial reconstitution step, and are not necessarily the concentrations present at delivery (often further dilution occurs). This applies to solution formulations as well. Further, excipient concentrations may not take into account additive effects from the diluent (for example, a drug containing sodium chloride and reconstituted with 0.9% Sodium Chloride usually lists the concentration of sodium chloride present in the undiluted state).

11) When the excipient concentration is calculated for a lyophilized product, it is usually done by dividing the weight of the material by the volume of liquid added. Note that this does not take into account the additive volume of mixing that occurs, so such values are to be considered only approximations. In cases where the manufacturer provided the total volume after mixing, this final volume was used for calculations.

12) For drugs requiring reconstitution/dilution, in most cases a diluent recommended by the manufacturer is identified. In cases where multiple compatible diluents are possible, or when dilution schemes are complicated, one will see the note "Consult PDR for appropriate dilution." In some cases, often when the recommended diluent is provided, the manufacturer would not reveal the identity of the diluent for proprietary reasons.

13) Finally, most of the entries herein have been sent to the manufacturer for their correction and final notes. Many manufacturers participated in checking the data; others did not. We want to make this compendium as correct as possible, and so if errors are found, please e-mail them to nguyen.tue@gene.com for correction.

Acknowledgments

This compendium would not have been possible without the diligent work of Milianne Chin. She compiled much of the data, engineered the database, and contacted dozens of different companies to ensure that the listings are up to date.

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
			paravertebral	sarracenia purpurea, pitcher plant distillate	Sarapin	High Chemical Company	Solution	multidose vial
		6.0 - 7.0	IV - intravenous	Provides Rose's recommended daily intake of essential	5.4% NephrAmine "	R&D Laboratories Inc.	Solution	glass containers
acacia	7.0		ID - intradermal	Old Tuberculin	Tuberculin, Old, Tine Test	Lederle Laboratories	Solution	disposable
acacia (gum arabic)	7.0		ID - intradermal	tuberculin, purified protein derivative	(PPD) Tine Test	Lederle Laboratories	Solution	multiple-puncture
acetate	0.059	4.0	IV - intravenous	filgrastim (recombinant methionyl human	Neupogen ®	Amgen, Inc.	Solution	single dose vial
acetate		neutral	SC - subcutaneous	Lente (R) human insulin zinc suspension	Novolin ® L	Novo Nordisk Pharmaceuticals	Suspension	vials
acetate		neutral	SC - subcutaneous	Lente (L) Purified Pork Insulin Zinc Suspension, USP	Lente (L) Purified Pork Insulin Zinc Suspension,	Novo Nordisk Pharmaceuticals	Suspension	vials
acetic acid	0.435		IV - intravenous	ritodrine hydrochloride	Yutopar	Astra USA, Inc.	Solution	vial
acetic acid			SC - subcutaneous	leuprolide acetate	Lupron Injection	TAP Pharmaceuticals	Solution	multidose vial
acetic acid			IM - intramuscular	calcitonin-salmon	Calcimar ® Injection; Synthetic	Rhone-Poulenc Rorer	Solution	vials
acetic acid			IV - intravenous	albumin (human), 25%	Albuminar ®-25	Armour Pharmaceutical	Solution	vials
acetic acid		6.9 ± 0.5	IV - intravenous	albumin (human) 5%	Albuminar ®-5	Armour Pharmaceutical	Solution	bottles
acetic acid		3.5 - 5.5	IV - intravenous	vincristine sulfate, USP	Oncovin ®	Eli Lilly & Company	Solution	vials
acetic acid	0.01	~4.0	IV - intravenous	flumazenil	Romazicon ™	Roche Laboratories	Solution	vials
acetic acid	<2.5 (w/w)		SC - subcutaneous	goserelin acetate implant	Zoladex ®	Zeneca Pharmaceuticals	Solid Implant	disposable
acetic acid	0.46	3.0 - 4.5	IV - intravenous	mitoxantrone hydrochloride	Novantrone	Immunex Corporation	Solution	multidose vials
acetic acid		2.5 - 4.5	IM - intramuscular	oxytocin	Oxytocin Injection	Wyeth-Ayerst	Solution	sterile cartridge
acetic acid			IM - intramuscular	promethazine hydrochloride	Phenergan Injection (ampuls)	Wyeth-Ayerst	Solution	ampuls
acetic acid			IM - intramuscular	promethazine hydrochloride	Phenergan Injection	Wyeth-Ayerst	Solution	sterile cartridge
acetic acid		~5.9	IM - intramuscular	neostigmine methylsulfate	Prostigmin Injectable	ICN Pharmaceuticals	Solution	multidose vial
acetic acid	0.225		IM - intramuscular	calcitonin-salmon	Miacalcin ®	Sandoz Pharmaceuticals	Solution	vial
acetic acid		6.4 - 7.2	IM - intramuscular	tetanus immune globulin (human) primarily IgO	Hyper-Tet ®	Bayer Corporation-Biologi	Solution	prefilled
acetic acid		4.0	IV - intravenous	rocuronium bromide	Zemuron ™ Injection	Organon	Solution	multidose vial
acetic acid (ampul)			IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals,	Lyophilized	single dose vials
acetic acid (glacial)	0.2	4.2 ± 0.3	IV - intravenous	octreotide acetate injection	Sandostatin ®	Sandoz Pharmaceuticals	Solution	ampuls

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
acetic acid NF			IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
acetic acid NF		4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
acetone sodium	0.1	4.0 - 5.0	IM - intramuscular	pentazocine lactate	Talwin Injection (cartridge needle)	Sanofi Winthrop	Solution	cartridge needle
acetone sodium	0.2	4.0 - 5.0	IM - intramuscular	pentazocine lactate	Talwin Injection (multidose vial)	Sanofi Winthrop	Solution	multidose vials
acetone sodium	0.4		spinal anesthesia	procaine hydrochloride	Novocain	Sanofi Winthrop	Solution	ampuls
acetone sodium	≤ 0.2	3.2 - 6.0	spinal anesthesia	tetracaine hydrochloride	Pontocaine Hydrochloride 1% Solution	Sanofi Winthrop	Solution	ampuls
alanine	0.668 - 1.11	6.0 - 7.5	IV - intravenous	antithrombin III (human)	Thrombate III ®	Bayer Corporation-Biologi	Lyophilized	single dose vials
albumin	0.25	5.8 - 7.2	IV - intravenous	epoetin alfa	Procrit	Ortho Biotech, Inc.	Solution	single dose vial
albumin	<10.0		IM - intramuscular	rabies virus prepared from strain	Imovax ® Rabies Vaccine	Connaught Laboraties Inc.	Freeze-dried	single dose vial
albumin (human)	≤1.25		IV-intravenous	Antihemophilic Factor (recombinant)	Bioclate ™	Armour Pharmaceutical	Lyophilized	single-dose
albumin (human)	≤0.3	6.8 ± 0.4	IV-intravenous	Immune Globulin Intravenous (human) (IGIV)	Gammagard ® S/D	Baxter Healthcare Corporation	Lyophilized	single use bottles
albumin (human)	0.04-1.0		IV - intravenous	antihemophilic factor (recombinant)	Kogenate ®	Bayer Corporation-Biologi	Lyophilized	single dose vial
albumin (human)	≤1.0		IV - intravenous	antihemophilic factor (Human)	Koate ®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
albumin (human)	0.4-1.0		IV - intravenous	antihemophilic factor (recombinant)	Helixate ™	Armour Pharmaceutical	Lyophilized	single dose
albumin (human)	0.0063 - 0.05		IM - intramuscular	botulinum toxin type A	Botox ®	Allergan Inc.	Lyophilized	ampuls
albumin (human)	5.0		IV - intravenous	urokinase for injection	Abbokinase	Abbott Laboratories	Lyophilized	vial
albumin (human)	0.25	6.9 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ®	Amgen, Inc.	Solution	single dose vial
albumin (human)	0.25	6.1 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ® - multidose	Amgen, Inc.	Solution	multidose vial
albumin (human)	3.0	6.8 ± 0.4	IV - intravenous	immune globulin IV (human) primarily IgG	Gammar ®-IV	Armour Pharmaceutical	Lyophilized	single dose vials
albumin (human)	1.0 - 2.0		IV - intravenous	monotional antibody purified human	Monoclate-P ® Factor VIII: C Pasteurized	Armour Pharmaceutical	Lyophilized	single dose vial
albumin (human)	1.25		SC - subcutaneous	interferon beta-1b	Betaseron ®	Berlex Laboratories	Lyophilized	single use vial
albumin (human)	1.0		IV - intravenous	cytomegalovirus immune globulin intravenous	CytoGam ®	MedImmune, Inc.	Sterile Liquid	single dose vial
albumin (human)	0.5		SC - subcutaneous	poliovirus vaccine inactivated; type 1 (Mahoney), type 2	Poliovax ®	Connaught Laboratories, Inc.	Suspension	ampoules
albumin (human)	0.5		IM - intramuscular	interferon alfa-2a, recombinant	Roferon ®-A	Roche Laboratories	Solution	vial

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
albumin (human)	0.167		IM - intramuscular	interferon alfa-2a, recombinant	Roferon ®-A (powder)	Roche Laboratories	Powder (sterile)	vial
albumin (human)	0.1		IL - intralesional	interferon alfa-2b, recombinant	Intron A	Schering Corporation	Powder	vial
albumin (human)	0.1		IM - intramuscular	interferon alfa-2b, recombinant	Intron A (solution)	Schering Corporation	Solution	vials
albumin (human)	0.6		IV - intravenous	anistreplase	Eminase ®	Roberts Pharmaceutical	Lyophilized	vial
albumin (human)	0.4 - 0.8		IV - intravenous	antihemophilic factor (human) (Factor VIII, AHF)	Humate-P ™	Armour Pharmaceutical	Lyophilized	single dose vial
albumin human USP	1.0		IV - intravenous	alglucerase injection	Ceredase ®	Genzyme Corporation	Solution	glass bottle
alcohol	30.5 (v/v%)	3.0 - 4.0	IV-intravenous	Etoposide	VePesid	Bristol-Myers Squibb-Oncology	Solution	multiple dose
alcohol	6.8 (v/v)		IV - intravenous	liothyronine sodium injection (T3)	Triostat	SmithKline Beecham Pharmaceuticals	Solution	amber-glass vials
alcohol	10.0	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin	Glaxo-Wellcome	Solution	ampul
alcohol	6.1 (v/v)	3.6 ± 0.4	IM - intramuscular	dihydroergotamine mesylate	D.H.E. 45 ®	Sandoz	Solution	ampuls
alcohol	10.0	~9.5	IM - intramuscular	pentobarbital sodium injection	Nembutal Sodium Solution	Abbott Laboratories	Solution	ampul
alcohol	10.0	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin (Digoxin) Injection	Glaxo Wellcome	Solution	ampuls
alcohol	10.0	12.0	IV - intravenous	phenytoin sodium injection, USP	Dilantin	Parke-Davis	Solution	steri-vials
alcohol	10.0		IM - intramuscular	ketorolac tromethamine	Toradol	Syntex Laboratories	Solution	Tubex cartridge
alcohol (Ph. Helv)	32.9 (v/v)		IV - intravenous	cyclosporine concentrate for injection USP	Sandimmune ®	Sandoz Pharmaceuticals	Solution	Ampul
alcohol (USP)	0.61 (v/v)	4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
alcohol (USP)	6.1 (v/v%)	3.6 ± 0.4	IM - intramuscular	dihydroergotamine mesylate injection, USP	D.H.E. 45 ® or Dyhdergot ®	Sandoz	Solution	ampuls
alpha	1.0		IM - intramuscular	oxytetracycline	Terramycin	Roerig	Solution	multidose vial
aluminum	≤0.17		IM-intramuscular	Diphtheria and Tetanus Toxoids and Acellular	Acel-Imune	Lederle Laboratories	Suspension(aft	multidose vial
aluminum	≤0.0001		IV - intravenous	antihemophilic factor (Human)	Koate ®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
aluminum	≤0.034	~ 7.4	IM-intramuscular	Diphtheria & Tetanus Toxoids and Acellular	Tripedia ™	Connaught Laboratories, Inc.	Solution/Suspe	vial
aluminum	≤0.16		IM - intramuscular	combination of refined tetanus & diphtheria toxoids	Tetanus & Diphtheria Toxoids Adsorbed (Adult	Lederle Laboratories	Suspension	vial
aluminum	≤0.16		IM - intramuscular	refined tetanus toxoid	Tetanus Toxoid Adsorbed, aluminum	Lederle Laboratories	Suspension	vial
aluminum	≤0.16		IM - intramuscular	diphtheria & tetanus toxoids & Pertussis Vaccine	Tri-Immunol	Lederle Laboratories	Suspension(aft	multidose vials

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc, %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
aluminum	0.05		IM - intramuscular	hepatitis A vaccine	Havrix (Hepatitis A Vaccine, Inactivated)	SmithKline Beecham Biologicals	Suspension	single dose vial
aluminum	0.04 - 0.12		IM - intramuscular	combination of purified tetanus & diphtheria	Diphtheria & Tetanus Toxoids & Pertussis	SmithKline Beecham Pharmaceuticals	Suspension	vials
aluminum	≤0.034		IM - intramuscular	combines diphtheria & tetanus toxoids	Diphtheria & Tetanus Toxoids & Pertussis	Connaught Laboratories, Inc.	Turbid Liquid	vial
aluminum	≤0.16		IM - intramuscular	combination of refined diphtheria & tetanus toxoids	Diphtheria & Tetanus Toxoids Adsorbed,	Lederle Laboratories	Suspension(aft	vial
aluminum	≤0.17		IM - intramuscular	Diphtheria & Tetanus Toxoids and Pertussis	Tetramune, (DTP-HbOC)	Lederle Laboratories	Suspension(aft	vial
aluminum	0.045		IM - intramuscular	haemophilus b conjugate vaccine (meningococcal	PedvaxHIB	Merck & Company	Lyophilized	single dose vials
aluminum	~0.05		IM - intramuscular	hepatitis B vaccine (recombinant)	Recombivax HB	Merck & Company	Suspension	single dose vial
aluminum	0.05		IM - intramuscular	hepatitis B vaccine (recombinant)	Engerix-B	SmithKline Beecham Pharmaceuticals	Suspension	single dose vial
aluminum	2.0		IM - intramuscular	aurothioglucose	Solganal	Schering Corporation	Suspension	multidose vial
aluminum phosphate	≤0.2		IM - intramuscular	inactivated CVS Kissling/MDPII rabies virus	Rabies Vaccine Adsorbed	SmithKline Beecham Pharmaceuticals	Suspension	vial
amino acid	0.3		IM - intramuscular	hepatitis A vaccine	Havrix (Hepatitis A Vaccine, Inactivated)	SmithKline Beecham Biologicals	Suspension	single dose vial
ammonia	0.219		IV - intravenous	liothyronine sodium injection (T3)	Triostat	SmithKline Beecham Pharmaceuticals	Solution	amber-glass vials
ammonium acetate	0.4	~7.0	IM - intramuscular	bumetanide	Bumex ®	Roche Laboratories	Solution	ampuls
ammonium hydroxide			SC - subcutaneous	pentagastrin	Peptavlon	Wyeth-Ayerst	Solution	ampules
anhydrous citric acid	0.0175		IV - intravenous	liothyronine sodium injection (T3)	Triostat	SmithKline Beecham Pharmaceuticals	Solution	amber-glass vials
anhydrous citric acid	0.08	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin	Glaxo-Wellcome	Solution	ampul
anhydrous citric acid		3.0 - 4.0	IV - intravenous	dacarbazine	DTIC-Dome Sterile	Bayer Corporation-Pharma	Solid	vials
anhydrous citric acid	0.08	6.8 - 7.2	IM - intramuscular	digoxin	Lanoxin (Digoxin) Injection	Glaxo Wellcome	Solution	ampuls
anhydrous dextrose	4.5	3.0 - 4.0	IV - intravenous	labetalol hydrochloride	Trandate Injection ®	Glaxo Wellcome	Solution	vials
anhydrous dextrose	4.5	3.0 - 4.0	IV - intravenous	labetalol HCl	Normodyne	Schering Corporation	Solution	multidose vial
anhydrous dextrose	5.0		IM - intramuscular	buprenorphine hydrochloride	Buprenex	Reckitt & Colman Pharmaceuticals	Solution	glass snap-ampuls
anhydrous sodium	6.0	9.5 - 11.0	IV - intravenous	Methohexital Sodium for injection	Brevital Sodium	Eli Lilly & Company	Freeze-dried	vials
arginine	1.56 - 26.0	4.5 - 7.5	IM - intramuscular	aztreonam for injection	Azactam for Injection	Bristol-Myers Squibb-Oncology	Lyophilized	vials
ascorbic acid	0.048 - 0.48		IV - intravenous	doxycycline hyclate for injection	Vibramycin Intravenous	Roerig	Powder	vial

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
ascorbic acid	0.1		IM - intramuscular	imipramine hydrochloride USP	Tofranil	CibaGeneva Corporation	Solution	ampuls
ascorbic acid	0.2		IM - intramuscular (see	chlorpromazine hydrochloride	Thorazine-ampule	SmithKline Beecham	Solution	ampule
ascorbic acid	0.2		IM - intramuscular (see	chlorpromazine hydrochloride	Thorazine	SmithKline Beecham	Solution	multidose vials
ascorbic acid	0.2	3.4 - 4.5	various	bupivacaine hydrochloride and epinephrine	Marcaine Hydrochloride with Epinephrine	Sanofi Winthrop	Solution	single dose vials
ascorbic acid	1.0		SC - subcutaneous	Epinephrine	Sus-phrine ®	Forest Pharmaceuticals Inc.	Suspension	ampul
ascorbic acid USP	0.1		IM - intramuscular	thiethylperazine malate USP	Torecan ®	Roxane Laboratories, Inc.	Solution	ampul
asparagine			IVS - intravesical	an attenuated live culture preparation of BCG vaccine	TICE ® BCG	Organon	Freeze-dried	ampules
benzalkonium	0.02	6.8 - 7.2	ID - intradermal	betamethasone sodium phosphate & betamethasone	Celestone Soluspan Suspension	Schering Corporation	Suspension	multidose vial
benzenesulfonic acid		3.25 - 3.65	IV - intravenous	atracurium besylate	Tracrium	Glaxo Wellcome	Solution	single use vial
benzethonium	0.0 - 0.01*	5.0 - 6.0	IM - intramuscular	diphenhydramine hydrochloride	Benadryl	Parke Davis	Solution	ampules
benzethonium	0.0 - 0.01		IM - intramuscular	butorphanol tartrate	Stadol ® Injection	Apotheeon/Bristol-Myers Squibb	Solution	vial
benzyl alcohol	3.0	3.0 - 4.0	IV-intravenous	Etoposide	VePesid	Bristol-Myers Squibb-Oncology	Solution	multiple dose
benzyl alcohol	0.9	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
benzyl alcohol	0.9	5.0 - 7.0	IM-intramuscular	Cortisone Acetate	Cortone Acetate	Merck & Company	Suspension	vials
benzyl alcohol	0.9	5.0 - 7.5	IM-intramuscular	dexamethasone acetate	Decadron-LA	Merck & Company	Suspension	vials
benzyl alcohol	0.9	6.0 - 8.0	IAR - intraarticular	Prednisolone Tebutate	Hydeltra T. B. A.	Merck & Company	Suspension	vials
benzyl alcohol	0.9	5.0 - 7.0	IAR - intraarticular	Hydrocortisone acetate	Hydrocortone Acetate	Merck & Company	Suspension	vials
benzyl alcohol	0.89-0.93	3.5 - 7.0	IM - intramuscular	Methylprednisolone acetate	Depo-Medrol	The Upjohn Company	Suspension	single dose vial
benzyl alcohol	0.90	~6.0	IM - intramuscular	triamcinolone diacetate	Aristocort Forte (P)	Fujisawa	Micronized	vial
benzyl alcohol	0.90	~6.0	IL - intralesional	triamcinolone diacetate	Aristocort	Fujisawa USA, Inc.	Micronized	vial
benzyl alcohol	0.90	4.5 - 6.5	IL - intralesional	triamcinolone hexacetonide suspension	Aristospan Suspension 5 mg/ml	Fujisawa USA, Inc.	Suspension	vial
benzyl alcohol	2.02		IV - intravenous	amiodarone Hcl	Cordarone Intravenous (Cordarone IV)	Wyeth-Ayerst	Solution	ampuls
benzyl alcohol	0.9		IV - intravenous	Enalaprilat	Vasotec I.V.	Merck & Company	Solution	vial
benzyl alcohol	1.0	~3.0	IV - intravenous	midazolam hydrochloride	Versed	Hoffman - LaRoche Inc.	Solution	vials

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
benzyl alcohol	0.9		IM - intramuscular	hydroxyzine hydrochloride	Vistaril	Roerig	Solution	multidose vials
benzyl alcohol	0.5	5.8 - 6.5	IM - intramuscular	gold sodium thiomalate	Myochrysine	Merck & Company	Solution	ampuls
benzyl alcohol	1.0	3.5 - 6.0	IM - intramuscular	netilmicin sulfate, USP	Netromycin Injection	Schering Biochem. Corporation	Solution	vials
benzyl alcohol	0.9	3.9 - 5.0	IV - intravenous	doxacurium chloride	Nuromax	Glaxo Wellcome	Solution	multidose vial
benzyl alcohol	1.2		IM - intramuscular	haloperidol decanoate	Haldol Decanoate 50 and 100	McNeil Pharmaceutical	Solution (in	ampuls
benzyl alcohol	3.0	~5.0	IV - intravenous	teniposide	Vumon Injection Concentrate (VM-26)	Bristol-Myers Squibb-Oncology	Solution	ampules
benzyl alcohol	1.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra I.V. Infusion	Glaxo Wellcome	Solution	multidose vials
benzyl alcohol	2.0		IM - intramuscular	lorazepam	Ativan	Wyeth-Ayerst	Solution	sterile cartridge
benzyl alcohol	0.9	~4.5	IM - intramuscular	methotrimeprazine as the hydrochloride salt	Levoprome	Immunex Corporation	Solution	vials
benzyl alcohol	1.5	~3.0	IM - intramuscular	chlordiazepoxide hydrochloride	Librium Injectable (IM)	Roche Products, Inc.	Crystalline	amber ampuls
benzyl alcohol	0.945		IM - intramuscular	lincomycin hydrochloride	Lincocin sterile solution	The Upjohn Company	Solution	vials
benzyl alcohol	0.9		SC - subcutaneous	leuprolide acetate	Lupron Injection	TAP Pharmaceuticals,	Solution	multidose vial
benzyl alcohol	0.84		ICN - intracavernosal	alprostadil	Caverject Sterile Powder	The Upjohn Company	Freeze-dried	vial
benzyl alcohol	0.9	~6.8	IV - intravenous	aminocaproic acid	Amicar Injection, USP	Immunex Corporation	Solution	vial
benzyl alcohol	2.0		IM - intramuscular	physostigmine salicylate	Antilirium	Forest	Solution	ampuls
benzyl alcohol	1.0	~7.0	IM - intramuscular	bumetanide	Bumex ®	Roche Laboratories	Solution	ampuls
benzyl alcohol	0.945		IM - intramuscular	clindamycin phosphate	Cleocin Phosphate Sterile Solution	The Upjohn Company	Solution	vials
benzyl alcohol	1.5		IM - intramuscular	diazepam	Valium Injectable	Roche Products	Solution	ampuls
benzyl alcohol	2.0		IM - intramuscular (see	chlorpromazine hydrochloride	Thorazine	SmithKline Beecham	Solution	multidose vials
benzyl alcohol	0.75		IM - intramuscular	prochlorperazine as the edisylate	Compazine	SmithKline Beecham Pharmaceuticals	Solution	vials
benzyl alcohol	1.0	6.1 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ® - multidose	Amgen, Inc.	Solution	multidose vial
benzyl alcohol	1.2		IM - intramuscular	fluphenazine decanoate injection	Prolixin Decanoate	Apothecon/Bristol-Myers Squibb	Solution	single dose
benzyl alcohol	1.5		IM - intramuscular	fluphenazine Enanthate Injection	Prolixin Enanthate	Apothecon/Bristol-Myers Squibb	Solution	vials
benzyl alcohol	0.9	5.0 - 7.0	IM - intramuscular	phytonadione (vitamin K1)	AquaMephyton	Merck & Company	Aqueous	ampuls

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
benzyl alcohol	0.9		IM - intramuscular	chorionic gonadotropin for injection, USP	Pregnyl ®	Organon	Powder	multidose vials
benzyl alcohol	0.9	~8.5	IA - intraarterial	methotrexate sodium	Methotrexate Sodium Injection	Immunex Corporation	Solution	vial
benzyl alcohol	1.0	~10.0	IV - intravenous	trimethoprimand sulfamethoxazole	Septra IV Infusion	Glaxo Wellcome	Solution	vial
benzyl alcohol	1.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra IV Infusion ADD	Glaxo Wellcome	Solution	vial
benzyl alcohol	0.0 - 0.91	7.0 - 8.0	IM - intramuscular	hydrocortisone sodium succinate	Solu-Cortef Sterile Powder	The Upjohn Company	Powder	Act-O-vial
benzyl alcohol	0.02 (v/v)	7.9	IV - intravenous	sodium tetradecyl sulfate injection	Sotradecol ®	Elkins-Sinn Inc.	Solution	ampul
benzyl alcohol	0.75		IM - intramuscular	trifluoperazine hydrochloride	Stelazine	SmithKline Beecham Pharmaceuticals	Solution	multidose vial
benzyl alcohol	2.0 (v/v)	8.0 - 9.0	IV - intravenous	ethanolamine oleate	Ethamolin ® Injection	Schwarz Pharmaceutical	Solution	ampules
benzyl alcohol	2.0		IV - intravenous	gonadorelin hydrochloride	Factrel	Wyeth-Ayerst	Lyophilized	single dose Secule
benzyl alcuhol	≤1.0		IV - intravenous	heparin sodium	Heparin Lock Flush Solution, USP	Wyeth-Ayerst	Solution	Tubex Blunt
benzyl alcohol	≤1.0	5.0 - 7.5	IV - intravenous	heparin sodium	Heparin Sodium Injection USP	Wyeth-Ayerst	Solution	Tubex sterile
benzyl alcohol	0.945	5.0 - 7.5	IV - intravenous	heparin sodium	Heparin Sodium Injection	The Upjohn Company	Solution	vial
benzyl alcohol	1.0		IV - intravenous	heparin sodium	Heparin Sodium Injectio -Eli Lilly	Eli Lilly & Company	Solution	multidose vial
benzyl alcohol NF	0.9	3.5 - 5.0	IV - intravenous	doxapram hydrochloride injection USP	Dopram Injectable	A. H. Robins Company	Solution	multidose vials
benzyl alcohol NF	0.9	2.0 - 3.0	IM - intramuscular	glycopyrrolate, USP	Robinul Injectable	A. H. Robins Company	Liquid	multidose vial
benzyl alcohol	0.90	4.5 - 6.5	IAR - intrarticular	triamcinolone hexacetonide	Aristospan Suspension 20 mg/ml	Fujisawa	Micronized	vials
benzyl alcohol (see	0 - 0.9	3.25 - 3.65	IV - intravenous	atracurium besylate	Tracrium	Glaxo Wellcome	Solution	single use vial
benzyl alcohol (see	0.0 - 0.9	3.5 - 5.0	IV - intravenous	mivacurium chloride	Mivacron Injection	Glaxo Wellcome	Solution	single dose vials
benzyl alcohol (see	0.0 - 0.9		IM - intramuscular	furosemide	Lasix ®	Hoechst-Roussel Pharmaceuticals	Solution	ampuls
benzyl alcohol (see	0.0 - 0.104	6.5 - 8.5	IV - intravenous	mesna	Mesnex Injection	Bristol-Myers Squibb-Oncology	Solution	multidose vial
benzyl alcohol (see	0.0 - 0.9		IV - intravenous	famotidine	Pepcid Injection	Merck & Company	Solution	multidose vial
benzyl alcohol (see	0.0 - 1.0	5.8 - 7.2	IV - intravenous	epoetin alfa	Procrit	Ortho Biotech, Inc.	Solution	single dose vial
benzyl alcohol (see	0.0 - 8.92	7.0 - 8.0	IM - intramuscular	methylprednisolo ne sodium succinate, USP	Solu-Medrol Sterile Powder	The Upjohn Company	Powder	Act-O-vial
bovine serum	<0.0001		SC - subcutaneous	poliovirus vaccine inactivated; type 1 (Mahoney), type 2	Poliovax ®	Connaught Laboratories, Inc.	Suspension	ampoules
buffered sodium			SC - subcutaneous	typhoid vaccine	Typhoid Vaccine USP	Wyeth-Ayerst	Suspension	vials

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
buffered sodium			ID - intradermal	equal parts of Ogawa and Inaba serotypes of killed	Cholera Vaccine USP	Wyeth-Ayerst	Suspension	vials
butylated	0.03		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
butylated	0.03		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
calcium	≤0.02		IV-intravenous	Antihemophilic Factor (recombinant)	Recclate ™	Armour Pharmaceutical	Lyophilized	single-dose
calcium chloride	0.022-0.056		IV - intravenous	antihemophilic factor (recombinant)	Kogenate ®	Bayer Corporation-Biologi	Lyophilized	single dose vial
calcium chloride	≤0.03327		IV - intravenous	antihemophilic factor (Human)	Koate ®-HP	Bayer Corporation-Biologi	Lyophilized	single dose bottle
calcium chloride	0.022-0.05		IV - intravenous	antihemophilic factor (recombinant)	Helixate ™	Armour Pharmaceutical	Lyophilized	single dose
calcium chloride	0.033	4.5 - 6.8	various	mepivacaine hydrochloride	Carbocaine Hydrochloride-single	Sanofi Winthrop	Solution	single dose vials
calcium chloride	0.048	7.0 - 7.5	ITO - intraocular	sodium hyaluronate	Amo ® Vitrax ®	Allergan Inc.	Solution	disposable glass
calcium chloride	0.022 - 0.056		IV - intravenous	monoclonal antibody purified human	Monoclate-P ® Factor VIII: C Pasteurized	Armour Pharmaceutical	Lyophilized	single dose vial
calcium chloride	0.048	7.2 ± 0.4	ITO - intraocular	purified hydroxypropylmethylcellulose	Ocucoat	Storz Ophthalmics	Solution	syringes
calcium chloride	0.004		IM - intramuscular	promethazine hydrochloride	Phenergan Injection (ampuls)	Wyeth-Ayerst	Solution	ampuls
calcium chloride	0.004		IM - intramuscular	promethazine hydrochloride	Phenergan Injection	Wyeth-Ayerst	Solution	sterile cartridge
calcium chloride	0.004		IM - intramuscular	meperidine hydrochloride & promethazine	Mepergan	Wyeth-Ayerst	Solution	sterile cartridge
carbon dioxide		8.0 - 9.0	IV - intravenous	cyclophosphamide for injection, USP	Lyophilized Neosar ®	Pharmacia	Lyophilized	vials
carbon dioxide gas			IM - intramuscular	thiethylperazine malate USP	Torecan ®	Roxane Laboratories, Inc.	Solution	ampul
carbon dioxide gas			IM - intramuscular	mesoridazine besylate USP	Serentil ®	Boehringer Ingelheim	Solution	ampuls
carboxymethylcellul	0.55		IM - intramuscular	penicillin G benzathine and penicillin G	Bicillin C-R 900/300	Wyeth-Ayerst	Suspension	sterile cartridge
carboxymethylcellul	0.6		IM - intramuscular	penicillin G benzathine suspension	Bicillin L-A	Wyeth-Ayerst	Suspension	disposable
carboxymethylcellul	0.55		IM - intramuscular	penicillin G benzathine and penicillin G	Bicillin C-R	Wyeth-Ayerst	Suspension	disposable
carboxymethylcellul	0.05	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot-3 month, 22.5	TAP Pharmaceuticals	Lyophilized	vial

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
carboxymethylcellul	0.5		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials
chloride	0.355-0.46 1		IV - intravenous	antihemophilic factor (recombinant)	Kogenate ®	Bayer Corporation-Biologi	Lyophilized	single dose vial
chloride	0.355-0.46		IV - intravenous	antihemophilic factor (recombinant)	Helixate ™	Armour Pharmaceutical	Lyophilized	single dose
chloride	0.213 - 0.638	6.6 - 7.4	IV - intravenous	alpha1-proteinase inhibitor (human)	Prolastin ®	Bayer Corporation-Biologi	Lyophilized	single dose vials
chloride	0.390-0.744	6.0 - 7.5	IV - intravenous	antithrombin III (human)	Thrombate III ®	Bayer Corporation-Biologi	Lyophilized	single dose vials
chlorobutanol	0.5		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
chlorobutanol	0.25	6.0 - 7.0	IM - intramuscular		Nydrazid Injection	Apothecon/Bristol-Myers Squibb	Solution	vial
chlorobutanol	≤0.5		IM - intramuscular	L-epinephrine hydrochloride (injection),	Ana-Kit	Bayer Corporation-Pharma	Solution	syringe
chlorobutanol	0.5	2.5 - 4.5	IM - intramuscular	oxytocin	Oxytocin Injection	Wyeth-Ayerst	Solution	sterile cartridge
chlorobutanol	0.5		IM - intramuscular	testosterone enanthate 200mg/mL	Delatestryl	BioTechnology General Corp.-BTG	Solution	single dose
chlorobutanol	0.5		IM - intramuscular	dicyclomine hydrochloride	Bentyl Injection	Merrell Dow Pharmaceuticals	Solution	multidose vial
chlorobutanol, NF	0.5	4.0 ± 0.3	IM - intramuscular	oxytocin	Syntocinon ®	Sandoz	Solution	ampul
chlorobutanol (see	0.0-0.5	4.0	IV - intravenous	desmopressin acetate	DDAVP ® Injection	Rhone-Poulenc Rorer	Solution	ampuls
chlorobutanol (see	0.0 - 0.5		IM - intramuscular	papverine hydrochloride	Papverine Hydrochloride Injection, USP	Eli Lilly & Company	Solution	multidose vials
citrate	~1.0		IV - intravenous	alglucerase injection	Ceredase ®	Genzyme Corporation	Solution	glass bottle
citric acid	0.1		IM-intramuscular	Vitamin A Palmitate as retinol	Aquasol A Parenteral	Astra USA, Inc.	Solution	single-dose vial
citric acid	0.2	3.0 - 4.0	IV-intravenous	Etoposide	VePesid	Bristol-Myers Squibb-Oncology	Solution	multiple dose
citric acid		~6.1	IV - intravenous	imiglucerase	Cerezyme ™	Genzyme Corporation	Lyophilized	vial
citric acid	0.02	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-ampuls	Roberts Pharmaceuticals	Solution	ampuls
citric acid	0.02	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-vials	Roberts Pharmaceuticals	Solution	multiple dose vial
citric acid	0.02	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-syringe	Roberts Pharmaceuticals	Solution	disposable
citric acid		5.5 - 6.5	IV - intravenous	atenolol	Tenormin I. V. Injection	Zeneca Pharmaceuticals	Solution	ampules
citric acid		~ 5.4	IV - intravenous	edrophonium chloride	Tensilon	ICN Pharmaceuticals	Solution	multidose vials
citric acid			IVS - intravesical	an attenuated live culture preparation of BCG vaccine	TICE ® BCG	Organon	Freeze-dried	ampules

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
citric acid	0.02	3.3 - 5.5	various	lidocaine hydrochloride and epinephrine at	Xylocaine with Epinephrine	Astra USA, Inc.	Solution	multidose vials
citric acid	0.02	3.3 - 5.5	various	lidocaine hydrochloride and epinephrine at	Xylocaine MPF with epinephrine	Astra USA, Inc.	Solution	ampules
citric acid	0.2		IM - intramuscular	hydromorphone hydrochloride	Dilaudid	Knoll Laboratories	Solution	ampules
citric acid	0.2		IM - intramuscular	hydromorphone hydrochloride	Dilaudid-HP Injection	Knoll Laboratories	Solution	amber ampules
citric acid			IV - intravenous	propranolol hydrochloride	Inderal	Wyeth-Ayerst	Solution	ampuls
citric acid	1.0		IM - intramuscular	oxytetracycline	Terramycin	Roerig	Solution	multidose vial
citric acid	0.075	3.7 - 4.1	IV - intravenous	diltiazem hydrochloride	Cardizem	Marion Merrell Dow Inc.	Solution	vial
citric acid			IV - intravenous	perphenazine	Trilafon Injection	Schering Corporation	Solution	ampul
citric acid	0.006	6.9 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ®	Amgen, Inc.	Solution	single dose vial
citric acid	0.011	6.1 ± 0.3	IV - intravenous	epoetin alfa (recombinant human	Epogen ® - multidose	Amgen, Inc.	Solution	multidose vial
citric acid		6.8 ± 0.4	IV - intravenous	immune globulin IV (human) primarily IgG	Gammar ®-IV	Armour Pharmaceutical	Lyophilized	single dose vials
citric acid	0.02	3.0 - 4.5	various	etidocaine HCl and epinephrine as bitartarate	Duranest Injections	Astra USA, Inc.	Solution	single dose vial
citric acid		6.0 - 8.5	IM - intramuscular	penicillin G potassium	Buffered Pfizerpen for Injection	Roerig	Powder	vials
citric acid	0.006 - 0.011	5.8 - 7.2	IV - intravenous	epoetin alfa	Procrit	Ortho Biotech, Inc.	Solution	single dose vial
citric acid		~5.0	IM - intramuscular	pyridostigmine bromide	Mestinon Injectable	ICN Pharmaceuticals	Solution	ampuls
citric acid	0.33		IM - intramuscular	butorphanol tartrate	Stadol ® Injection	Apothecon/Bristol-Myers Squibb	Solution	vial
citric acid	0.03	6.7 - 7.3	IV - intravenous	ranitidine hydrochloride	Zantac Injection Premixed	Glaxo Wellcome	Solution	flexible plastic
citric acid	0.052	3.0 - 4.0	IV - intravenous	ondansetron hydrochloride dihydrate	Zofran ® Injection Premixed	Glaxo Wellcome	Solution	single dose
citric acid	0.023	5.0 - 7.0	IV - intravenous	metronidazole	Flagyl IV RTU	SCS	Solution	single dose
citric acid (additional)		3.5	IV - intravenous	nicardipine HCl	Cardene	Wyeth-Ayerst	Solution	ampuls
citric acid anhydrous	1.0	6.5 - 6.9	LI - local injection	dexamethasone sodium phosphate-lidocai	Decadron Phosphate with Xylocaine Injection	Merck & Company	Solution	vials
citric acid anhydrous	0.21	4.0	IV - intravenous	vecuronium bromide	Norcuron ®	Organon	Freeze-dried	vials
citric acid	0.02	3.3 - 5.5	various	bupivacaine hydrochloride and epinephrine as	Sensorcaine ®-MPF with epinephrine	Astra USA, Inc.	Solution	single dose vials
citric acid anhydrous	0.5		IV - intravenous	methyldopate HCl	Aldomet Ester Hydrochloride	Merck & Company	Solution	vials

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
citric acid anhydrous	0.3		IM - intramuscular	metboxamine hydrochloride	Vasoxyl	Glaxo Wellcome	Solution	ampuls
citric acid anhydrous	1.26		IM - intramuscular	nalbuphine hydrochloride	Nubain	DuPont Pharma	Solution	ampuls
citric acid anhydrous	1.26		IM - intramuscular	nalbuphine hydrochloride	Nubain (ampules)	DuPont Pharma	Solution	ampules
citric acid anhydrous	2.2	3.5 - 3.5	IV - intravenous	streptozocin	Zanosar Sterile Powder	The Upjohn Company	Freeze-dried	vial
citric acid	0.1		SC - subcutaneous	phenylephrine hydrochloride injection	Neo-Synephrine hydrochloride	Sanofi Winthrop	Solution	ampuls
citric acid		3.0 - 4.0	IV - intravenous	labetalol HCl	Normodyne	Schering Corporation	Solution	multidose vial
citric acid	0.053	3.5	IV - intravenous	nicardipine HCl	Cardene	Wyeth-Ayerst	Solution	ampuls
citric acid	0.05	3.3 - 4.0	IV - intravenous	ondansetron hydrochloride dihydrate	Zofran ® Injection	Glaxo Wellcome	Solution	single dose vial
citric acid		3.0 - 4.0	IV - intravenous	labetalol hydrochloride	Trandate Injection ®	Glaxo Wellcome	Solution	vials
citric acid US,		~4.5	IM - intramuscular	methotrimeprazine as the hydrochloride salt	Levoprome	Immunex Corporation	Solution	vials
colloidal silicon	9.6		ICV - intracervical	dinoprostone	Prepidil Gel	The Upjohn Company	Viscous Gel	syringe
creatinine	0.5	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
creatinine	0.5	5.0 - 7.5	IM-intramuscular	dexamethasone acetate	Decadron-LA	Merck & Company	Suspension	vials
creatinine	0.8	7.5 - 8.0	IV - intravenous	Dexamethasone sodium phosphate , USP	Decadron Phosphate Injection	Merck & Company	Solution	vials
creatinine	0.8	6.5 - 6.9	LI - local injection	dexamethasone sodium phosphate-lidocai	Decadron Phosphate with Xylocaine Injection	Merck & Company	Solution	vials
creatinine	0.8	7.5 - 8.5	IM - intramuscular	hydrocortisone sodium phosphate	Hydrocortone Phosphate	Merck & Company	Solution	multidose vial
Cremophor ® EL	52.7		IV - intravenous	paclitaxel	Taxol	Bristol-Myers Squibb-Oncology	Nonaqueous	single dose vials
Cremophor(R) EL	50.0	~5.0	IV - intravenous	teniposide	Vumon Injection Concentrate (VM-26)	Bristol-Myers Squibb-Oncology	Solution	ampules
Cremophor(R) EL	65.0		IV - intravenous	cyclosporine concentrate for injection USP	Sandimmune ®	Sandoz Pharmaceuticals	Solution	Ampul
crosslinked gelatin	0.5 - 1.25		IV - intravenous	streptokinase	Streptase	Astra USA, Inc.	Lyophilized	vial
D,L-lactic + glycolic	74.3 - 84.6 (w/w)		SC - subcutaneous	goserelin acetate implant	Zoladex ®	Zeneca Pharmaceuticals	Solid Implant	disposable
D-mannitol	0.66		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
D-mannitol	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
D-mannitol	1.32		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
D-mannitol	1.32-2.64		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
D-mannitol	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
d-mannitol	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot-3 month, 22.5	TAP Pharmaceuticals	Lyophilized	vial
d-mannitol	2.59		IM - intramuscular	leuprolide acetate	Lupron Depot-3 month, 22.5	TAP Pharmaceuticals	Lyophilized	vial
D-mannitol (ampul)	5.0		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials
d-sorbitol	45.0	6.0 - 8.0	IAR - intraarticular	Prednisolone Tebutate	Hydeltra T. B. A.	Merck & Company	Suspension	vials
dehydrated alcohol	42.7 (v/v)	~5.0	IV - intravenous	teniposide	Vumon Injection Concentrate (VM-26)	Bristol-Myers Squibb-Oncology	Solution	ampules
dehydrated alcohol	49.7 (v/v)		IV - intravenous	paclitaxel	Taxol	Bristol-Myers Squibb-Oncology	Nonaqueous	single dose vials
dehydrated alcohol			IV - intravenous	alprostadil, (prostaglandin E1)	Prostin VR Pediatric Sterile Solution	The Upjohn Company	Solution	ampoules
dehydrated alcohol,	80.0 (v/v)		IV - intravenous	tacrolimus injection	Prograf	Fujisawa USA, Inc.	Solution	ampules
dextrose	8.25	3.3 - 5.5	spinal anesthesia	bupivacaine hydrochloride	Sensorcaine ®-MPF Spinal	Astra USA, Inc.	Solution	ampules
dextrose	4.4		IM - intramuscular	amitriptyline HCl	Elavil	Zeneca Pharmaceuticals	Solution	vials
dextrose	5.0		IV - intravenous	clindamycin phosphate	Cleocin Phosphate IV Solution	The Upjohn Company	Premixed	Galaxy (R) plastic
dextrose	1.25		SC - subcutaneous	interferon beta-1b	Betaseron ®	Berlex Laboratories	Lyophilized	single use vial
dextrose	5.0	3.5 - 4.6	IV - intravenous	ciprofloxacin	Cipro ® IV	Bayer Corporation-Pharma	Ready-to-Use	flexible
dextrose	8.25	4.0 - 6.5	SA - subarachnoid	bupivacaine hydrochloride	Marcaine Spinal	Sanofi Winthrop	Solution	single dose ampul
dextrose	3.75	5.0 - 7.0	IM - intramuscular	phytonadione (vitamin K1)	AquaMephyton	Merck & Company	Aqueous	ampuls
dextrose	30.0		ID - intradermal	tuberculin, purified protein derivative	(PPD) Tine Test	Lederle Laboratories	Solution	multiple-puncture
dextrose	10.0		IU - intrauterine	dextran 70	Hyskon ® Hysteroscopy Fluid	Medisan Pharmaceuticals	Solution	bottles
dextrose	5.0	3.0 - 4.0	IV - intravenous	ondansetron hydrochloride dihydrate	Zofran ® Injection Premixed	Glaxo Wellcome	Solution	single dose
dextrose	5.0	3.8 - 5.8	IV - intravenous	ofloxacin injection	Floxin ® IV - premixed	Ortho Pharmaceutical	Premixed	single use flexible
dextrose	3.2 - 4.4	5.0 - 7.5	IV - intravenous	ceftazidime sodium injection	Fortaz ® Injection	Glaxo Wellcome	Frozen	Galaxy plastic
dextrose anhydrous	4.7 - 4.94	3.2 - 4.0	IV - intravenous	milrinone lactate injection	Primacor	Sanofi Winthrop	Solution	single dose vials
dextrose (D-glucose)	7.5	5.5 - 7.0	spinal anesthesia	lidocaine hydrochloride	Xylocaine MPF 1.5%/5% with 7.5%	Astra USA, Inc.	Solution	ampules
dextrose hydrous	5.6	3.5 - 6.5	IV - intravenous	fluconazole	Diflucan Injection	Roerig	Solution	Viaflex Plus

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
dextrose hydrous	1.4 - 3.4	5.0 - 7.5	IV - intravenous	cefotaxime sodium injection	Premixed Claforan ® Injection	Hoechst-Roussel Pharmaceuticals	Frozen	Galaxy single
dextrose hydrous	2.4 - 3.8		IV - intravenous	ceftriaxone sodium injection	Rocephin Injection	Roche Laboratories	Premixed	Galaxy single
dextrose hydrous	2.2 - 4.0	~6.5	IV - intravenous	cefoxitin sodium injection	Premixed Intravenous Solution Mefoxin	Merck & Company	Solution	single dose
dextrose hydrous	2.2 - 3.8	4.2 - 6.2	IV - intravenous	cefmetazole sodium injection	Zefazone ® IV solution	The Upjohn Company	premixed	plastic Galaxy
dextrose hydrous	0.0 - 2.8	5.0 - 7.5	IV - intravenous	cefuroxime sodium injection	Zinacef ®	Glaxo Wellcome	Frozed	Galaxy plastic
dextrose hydrous USP	1.9 - 3.8	5.5 - 8.0	IV - intravenous	ceftizoxime sodium injection	Ceftizox	Fujisawa USA, Inc.	frozen	single dose
dextrose hydrous USP	4.0 - 4.8		IV - intravenous	cefazolin sodium injection	Ancef (solution)	SmithKline Beecham Pharmaceuticals	Solution	single dose
dextrose hydrous USP	3.6 - 4.6		IV - intravenous	cefoperazone sodium injection	Cefobid	Roerig Division of Pfizer	Premixed	plastic containers
dextrose injection	5.0	3.5 - 5.0	IV - intravenous	mivacurium chloride	Mivacron Premixed Infusion	Glaxo Wellcome	Solution	flexible plastic
dextrose USP	2.2 - 3.8	4.0 - 6.5	IV - intravenous	cefotetan disodium injection	Cefotan ®	Zeneca Pharmaceuticals	Premixed	Galaxy (R) plastic
diabasic sodium	0.44 - 1.1	7.0 - 8.0	IM - intramuscular	hydrocortisone sodium succinate	Solu-Cortef Sterile Powder	The Upjohn Company	Powder	Act-O-vial
diacetylated	5.0	~8.0	IV - intravenous	diazepam emulsified injection	Dizac	Ohmeda PPD, Inc.	Emulsion	single dose vial
dibasic potassium	0.24	6.7 - 7.3	IM - intramuscular	ranitidine hydrochloride	Zantac Injection	Glaxo Wellcome	Solution	single dose vial
dibasic sodium	0.18	7.0 ± 0.5	IV - intravenous	muromonab-CD3 biochemically purified IgG2a	Orthoclone OKT3	Ortho Biotech Inc.	Solution	ampule
dibasic sodium	0.0226	~7.5	IM - intramuscular	somatropin rDNA origin for injection	Humatrope ®	Eli Lilly & Company	Lyophilized	vials
dibasic sodium		6.3 ± 0.6	IV - intravenous	cladribine	Leustatin Injection	Ortho Biotech, Inc.	Solution	single use vials
dibasic sodium	0.71	6.8 - 7.2	ID - intradermal	betamethasone sodium phosphate & betamethasone	Celestone Soluspan Suspension	Schering Corporation	Suspension	multidose vial
dibasic sodium	0.558	7.2 - 7.4	IM - intramuscular	pegademase bovine	Adagen ®	Enzon	Solution	single dose vials
dibasic sodium	0.530 - 0.585	7.3	IM - intramuscular	pegaspargase	Oncaspar ®	Rhone-Poulenc Rorer	Solution	single dose vials
dibasic sodium	0.044 - 0.44		IM - intramuscular	chorionic gonadotropin for injection, USP	Pregnyl ®	Organon	Powder	multidose vials
dibasic sodium	0.16 - 0.8		IM - intramuscular	human chorionic gonadotropin (HCG) for	Profasi	Serono Laboratories, Inc.	Lyophilized	multidose vial
dibasic sodium	0.089	7.2 - 7.8	IV - intravenous	aldesleukin (recombinant human	Proleukin ®	Chiron Therapeutics	Lyophilized	single use vial
dibasic sodium	0.18	6.7 - 7.3	IV - intravenous	ranitidine hydrochloride	Zantac Injection Premixed	Glaxo Wellcome	Solution	flexible plastic
dibasic sodium	0.003		IV - intravenous	sermorelin acetate for injection	Geref ®	Serono Laboratories, Inc.	Lyophilized	ampule

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
dibasic sodium	0.072	7.9	IV - intravenous	sodium tetradecyl sulfate injection	Sotradecol ®	Elkins-Sinn Inc.	Solution	ampul
dibasic sodium	0.87 - 1.75	7.0 - 8.0	IM - intramuscular	methylprednisolone sodium succinate, USP	Solu-Medrol Sterile Powder	The Upjohn Company	Powder	Act-O-vial
dibasic sodium	0.137-0.144	3.5 - 7.0	IM - intramuscular	Methylprednisolone acetate	Depo-Medrol	The Upjohn Company	Suspension	single dose vial
diethanolamine	0.3	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra I.V. Infusion	Glaxo Wellcome	Solution	multidose vials
diethanolamine	0.3	~10.0	IV - intravenous	trimethoprimand sulfamethoxazole	Septra IV Infusion	Glaxo Wellcome	Solution	vial
diethanolamine	0.3	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra IV Infusion ADD	Glaxo Wellcome	Solution	vial
dimethylsulfoxide	<0.06		IV - intravenous	anistreplase	Eminase ®	Roberts Pharmaceutical	Lyophilized	vial
disodium edetate	0.05	5.0 - 7.5	IM-intramuscular	dexamethasone acetate	Decadron-LA	Merck & Company	Suspension	vials
disodium edetate	0.05	6.5 - 6.9	LI - local injection	dexamethasone sodium phosphate-lidocai	Decadron Phosphate with Xylocaine Injection	Merck & Company	Solution	vials
disodium edetate	0.01	~5.0	IM - intramuscular	trimethobenzamide HCl	Tigan ®-syringe	Roberts Pharmaceuticals	Solution	disposable
disodium edetate	0.01	~3.0	IV - intravenous	midazolam hydrochloride	Versed	Hoffman - LaRoche Inc.	Solution	vials
disodium edetate	0.05		IV - intravenous	methyldopate HCl	Aldomet Ester Hydrochloride	Merck & Company	Solution	vials
disodium edetate	0.05		IM - intramuscular	clindamycin phosphate	Cleocin Phosphate Sterile Solution	The Upjohn Company	Solution	vials
disodium edetate	0.004		IV - intravenous	clindamycin phosphate	Cleocin Phosphate IV Solution	The Upjohn Company	Premixed	Galaxy (R) plastic
disodium edetate	0.05	7.0 - 8.0	IM - intramuscular	prednisolone sodium phosphate	Hydeltrasol	Merck & Company	Solution	vial
disodium edetate USP	0.065	~4.5	IM - intramuscular	methotrimeprazine as the hydrochloride salt	Levoprome	Immunex Corporation	Solution	vials
disodium EDTA	0.011	2.7 - 4.0	IF - infiltration &	chloroprocaine hydrochloride	Nesacaine Injection	Astra USA, Inc.	Solution	multidose vials
disodium EDTA	0.011	2.7 - 4.0	IF - infiltration &	chloroprocaine hydrochloride	Nesacaine-MPF Injection	Astra USA, Inc.	Solution	single dose vials
disodium hydrogen	0.34	~6.1	IV - intravenous	imiglucerase	Cerezyme ™	Genzyme Corporation	Lyophilized	vial
disodium hydrogen	0.25		IVS - intravesical	BCG Live (intravesical)	TheraCys ®	Connaught Laboratories	Freeze-dried	vial
disodium hydrogen	0.028	7.0 - 7.5	ITO - intraocular	sodium hyaluronate	Healon ®	Pharmacia, Inc. Ophthalmics Inc.	Viscoelastic	Disposable glass
disodium hydrogen	0.028	7.0 - 7.5	ITO - intraocular	sodium hyaluronate 7000	Healon GV	Pharmacia Inc. Ophthalmics	Viscoelastic	disposable glass
disodium phosphate		7.0	IV - intravenous	plicamycin	Mithracin	Bayer Corporation-Pharma	Freeze-dried	vials
disodium phosphate	0.013	7.0 ± 0.3	IM - intramuscular	typhoid Vi polysaccharide vaccine	Typhim Vi ™	Connaught Laboratories	Solution	syringe

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
disodium phosphate	0.0265	~6.7	SC - subcutaneous	somatropin (rDNA origin) for injection	Genotropin ™	Pharmacia Inc.	Lyophilized	Intra-Mix two
disodium phosphate	0.027	~6.7	SC - subcutaneous	somatropin (rDNA origin) for injection	Genotropin ™ Injection	Pharmacia, Inc.	Lyophilized	Intra-Mix two
disodium phosphate	0.0125 - 0.025		IM - intramuscular	menotropins for injection	Humegon™	Organon Inc.	Lyophilized	vial
disodium phosphate	0.098		IM - intramuscular	hepatitis B vaccine (recombinant)	Engerix-B	SmithKline Beecham Pharmaceuticals	Suspension	single dose vial
DL-lactic acid &	3.31		IM - intramuscular	leuprolide acetate	Lupron Depot 3.75	TAP Pharmaceuticals	Lyophilized	single dose vial
DL-lactic acids &	6.62		IM - intramuscular	leuprolide acetate	Lupron Depot 7.5	TAP Pharmaceuticals	Lyophilized	single dose vials
DL-lactic acids &	6.62-13.24		IM - intramuscular	leuprolide acetate	Lupron Depot-Ped	TAP Pharmaceuticals	Lyophilized	single dose vial
E-aminocaproic acid	0.026		IV - intravenous	anistreplase	Eminase ®	Roberts Pharmaceutical	Lyophilized	vial
edetate calcium	0.01	3.4 - 4.5	various	bupivacaine hydrochloride and epinephrine	Marcaine Hydrochloride with Epinephrine	Sanofi Winthrop	Solution	single dose vials
edetate disodium	0.05	5.0 - 7.5	IM-intramuscular	Dexamethasone Acetate Suspension	Dalalone D.P. ®	Forest Pharmaceuticals	Suspension	vials
edetate disodium	0.01	3.0 - 6.5	IM - intramuscular	tobramycin sulfate	Tobramycin Sulfate Injection, USP	Elkins-Sinn	Solution	multidose vials
edetate disodium	0.01	3.0 - 4.0	IV - intravenous	labetalol hydrochloride	Trandate Injection ®	Glaxo Wellcome	Solution	vials
edetate disodium	0.01	3.5 - 6.0	IM - intramuscular	netilmicin sulfate, USP	Netromycin Injection	Schering Biochem. Corporation	Solution	vials
edetate disodium	0.01	3.0 - 4.0	IV - intravenous	labetalol HCl	Normodyne	Schering Corporation	Solution	multidose vial
edetate disodium	0.05		IM - intramuscular	hydromorphone hydrochloride	Dilaudid-vials	Knoll Laboratories	Solution	multidose vials
edetate disodium	0.01	~7.0	IM - intramuscular	bumetanide	Bumex ®	Roche Laboratories	Solution	ampuls
edetate disodium	0.01	6.8 - 7.2	ID - intradermal	betamethasone sodium phosphate & betamethasone	Celestone Soluspan Suspension	Schering Corporation	Suspension	multidose vial
edetate disodium	0.05		IM - intramuscular	mesoridazine besylate USP	Serentil ®	Boehringer Ingelheim	Solution	ampuls
edetate disodium	0.025	6.5 - 8.5	IV - intravenous	mesna	Mesnex Injection	Bristol-Myers Squibb-Oncology	Solution	multidose vial
edetate disodium	0.01	~4.0	IV - intravenous	flumazenil	Romazicon ™	Roche Laboratories	Solution	vials
edetate disodium	0.01		IM - intramuscular	tobramycin sulfate injection	Nebcin ®	Eli Lilly & Company	Solution	multidose vials
edetate disodium	0.005		IM - intramuscular	papverine hydrochloride	Papverine Hydrochloride Injection, USP	Eli Lilly & Company	Solution	multidose vials
edetate disodium	0.01		IM - intramuscular	promethazine hydrochloride	Phenergan Injection (ampuls)	Wyeth-Ayerst	Solution	ampuls
edetate disodium	0.01		IM - intramuscular	promethazine hydrochloride	Phenergan Injection	Wyeth-Ayerst	Solution	sterile cartridge

EXCIPIENTS FOR PARENTERAL FORMULATIONS

Excipient	Conc. %W/V	pH where applicable	Administration Route	Drug Name	Brand Name	Manufacturer	Dosage Form	Storage Container
edetate disodium	0.01		IM - intramuscular	meperidine hydrochloride & promethazine	Mepergan	Wyeth-Ayerst	Solution	sterile cartridge
edetate disodium	0.01		IM - intramuscular	gentamicin sulfate USP	Garamycin Injectable	Schering Corporation	Solution	vial
EDTA	trace		SC - subcutaneous	Varicella Virus Vaccine Live (Oka/Merck)	Varivax	Merck & Company	Lyophilized	single-dose vial
egg lecithin	1.2	7.0 - 8.5	IV - intravenous	propofol	Diprivan ® Injection 1%	Zeneca Pharmaceuticals	Emulsion	ampules
ethanol	10.0 (v/v)	5.6 - 6.0	IV - intravenous	sterile carmustine (BCNU)	BiCNU	Bristol-Myers Squibb-Oncology	Lyophilized	single dose vials
ethanol	70.0 (v/v)		IV - intravenous	nitroglycerin injection, USP	Nitro-Bid ®	Marion Merrell Dow Inc.	Solution	vials
ethanol (96%)	5.2 (v/v)		IV - intravenous	melphalan hydrochloride	Alkeran for Injection	Glaxo Wellcome	Freeze-dried	single use vial
ethyl alcohol	10.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra I.V. Infusion	Glaxo Wellcome	Solution	multidose vials
ethyl alcohol	10.0		IM - intramuscular	diazepam	Valium Injectable	Roche Products	Solution	ampuls
ethyl alcohol	10.0	~10.0	IV - intravenous	trimethoprimand sulfamethoxazole	Septra IV Infusion	Glaxo Wellcome	Solution	vial
ethyl alcohol	10.0	~10.0	IV - intravenous	trimethoprim and sulfamethoxazole	Septra IV Infusion ADD	Glaxo Wellcome	Solution	vial
fetal bovine serum	trace		SC - subcutaneous	Varicella Virus Vaccine Live (Oka/Merck)	Varivax	Merck & Company	Lyophilized	single-dose vial
formaldehyde	≤0.02		IM-intramuscular	Diphtheria and Tetanus Toxoids and Acellular	Acel-Imune	Lederle Laboratories	Suspension(afi	multidose vial
formaldehyde	≤0.02	~ 7.4	IM-intramuscular	Diphtheria & Tetanus Toxoids and Acellular	Tripedia ™	Connaught Laboratories, Inc.	Solution/Suspe	vial
formaldehyde	<0.0125		ID - intradermal	Mumps Skin Test Antigen (suspension killed	MSTA ™	Connaught Laboratories, Inc.	Suspension	vial
formaldehyde	<0.001		IM - intramuscular	combination of purified tetanus & diphtheria	Diphtheria & Tetanus Toxoids & Pertussis	SmithKline Beecham Pharmaceuticals	Suspension	vials
formaldehyde	≤0.02		IM - intramuscular	combines diphtheria & tetanus toxoids	Diphtheria & Tetanus Toxoids & Pertussis	Connaught Laboratories, Inc.	Turbid Liquid	vial
formaldehyde	≤0.02		IM - intramuscular	Diphtheria & Tetanus Toxoids and Pertussis	Tetramune, (DTP-HbOC)	Lederle Laboratories	Suspension(afi	vial
formaldehyde	0.0027		SC - subcutaneous	poliovirus vaccine inactivated; type 1 (Mahoney), type 2	Poliovax ®	Connaught Laboratories, Inc.	Suspension	ampoules
formaldehyde			IM - intramuscular	hepatitis B vaccine (recombinant)	Recombivax HB	Merck & Company	Suspension	single dose vial
formaldehyde	≤0.04		SC - subcutaneous	combination of type 1 (Mahoney), type2 (MEF-1),	Ipol ™	Connaught Laboratories	Suspension	syringe
formaldehyde	<0.01		SC - subcutaneous	Japanese encephalitis virus vaccine	Je-Vax ™	Connaught Laboratories, Inc.	Lyophilized	vial
fractionated egg yolk	1.2	~8.0	IV - intravenous	diazepam emulsified injection	Dizac	Ohmeda PPD, Inc.	Emulsion	single dose vial
fractionated soybean	15.0	~8.0	IV - intravenous	diazepam emulsified injection	Dizac	Ohmeda PPD, Inc.	Emulsion	single dose vial

ATTACHMENT F - COMPILATION

TAB 11

definite bearing on the usefulness of any column packing prepared. The performances of the seven supports mentioned previously were examined under the same operating conditions. The supports that can be used for lightly loaded packings are: glass beads, Gas Chrom-P, and Chromosorb W-HMDS. The other four supports cannot be used for lightly loaded column packing since their interaction with the antihistamines causes excessive peak tailing.

The hydrogen flame detector used in conjunction with the 0.010-in. stainless capillary column would not respond to compounds with boiling points above 330°. This limitation prevented evaluation of this column for the analysis of these antihistamines.

The 100-ft. 0.065-in. copper open tubular column was coated with XF-1150 and evaluated using the above group of antihistamines. The Sr^{90} ionization detector was used with a column flow of 36 ml./minute. The retention times obtained were comparable to the 6-ft.-XF-1150 packed column, but the peak base widths were considerably wider. Because of this increase in base width, the 0.065-in. column was less efficient than the 6-ft. packed column.

A 250-ft. 0.065-in. column wound on a $1^1/_4$-in. diameter mandrel has been reported to be more efficient than a packed column (15). There are two possible reasons why efficiency was less than previously reported: (*a*) the column was shorter (100 ft.), and (*b*) the winding configuration was markedly different. The column was wound on a $1^1/_4 \times {}^1/_4$-in. bar which resulted in a definite flattening of the tube around the edge of the bar.

CONCLUSIONS

The antihistamines investigated, except for meclizine, can be separated, identified, and concentration estimated using the Carbowax 20M, PDEAS, and XF-1150 columns described. The PDEAS column is the most efficient of the three for the analysis of antihistamines.

The usefulness of the 0.010-in. capillary and the 0.065-in. open tubular columns cannot be properly evaluated until the mentioned limitations are removed.

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Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones

By C. RIFFKIN, R. HUBER, and C. H. KEYSSER

Steroid hormones may be administered parenterally in high concentrations as oil solutions. In this form they exhibit a prolonged action and reduce the number of injections required. To accommodate the demand for increasingly greater concentrations of hormones in solution, castor oil in combination with other suitable oil-miscible solvents, has been found to fulfill a need. The development of several formulations together with the results of animal testing, as well as clinical trials in humans, attest to the acceptability of this oil for the purposes intended.

FIXED OILS are included in the "United States Pharmacopeia XVI" as nonaqueous vehicles for injection and are characterized as being of vegetable origin, essentially odorless, and without suggestion of rancidity. They must also comply with certain measurable physical limits specified for the saponification, acid, and iodine values.

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The authors are indebted to the Chemical Control Laboratories for their assistance with the assays; to Dr. N. Coy and H. Roberts of the Physical and Analytical Section, for their development of special assays; to G. Lockwood of the Pharmacology Section for the animal muscle irritation tests; and especially to Dr. E. C. Reifenstein, Jr., of the medical staff, for the information concerning the clinical trials.

After subcutaneous injection, Deanesly and Parkes (1) observed the persistence of olive oil and castor oil in animal tissue. Comparing other oils Brown, *et al.* (2), reported that sesame and corn oils were superior to cottonseed and peanut oils because they were less irritating, less antigenic, more quickly released from tissue, and possessed superior physical properties.

More recently the use of steroid hormone medication has expanded considerably. Due to limited water solubility, hormones have been administered as aqueous suspensions or solutions in oil. It has been claimed that the latter provided the slow release preferred in cyclical

TABLE I.—ANALYSIS OF COMMERCIAL OILS AND COMPARISON TO U.S.P. XVI SPECIFICATIONS

Oil	Lot No.	ml. 0.02 *N* NaOH Equiv. to Free Fatty Acid in 10-Gm. Sample	Sapon. Value	Iodine Value
Castor Oil	U.S.P. specs.	35.0[a]	179–185	83–88
	23946	14.0	183.3	84.8
	25589	4.6	179.8	87.0
	23463	7.9	182.7	84.5
	33742	9.2	180.4	84.2
Sesame Oil	U.S.P. specs.	3.0	188–195	103–116
	23549A	0.5	189.6	106.9
	26953	1.4	194.0	111.8
	33646	0.75	189.6	104.7
	29981	0.45	191.7	108.2
Cottonseed Oil	U.S.P. specs.	2.0	190–198	109–116
	49684	...	195.9	111.8
	44441	...	196.3	113.1
Corn Oil	U.S.P. specs.	2.0	187–193	102–128
	52148	1.0	194.5	119.1
	36716	1.2	191.4	124.4
	33436	1.2	189.3	125.0
	33715	1.0	189.3	123.0
Peanut Oil	U.S.P. specs.	2.0	185–195	84–100
	22160	1.2	192.0	94.4
	20993	1.4	191.7	93.2
	33622	0.8	193.1	87.8
	26147	1.2	190.4	93.9

[a] The U.S.P. specifies that the titration of free fatty acids in oral grade castor oil shall not exceed 7 ml. of 0.1 *N* NaOH which is equal to 35.0 ml. of 0.02 *N* NaOH.

TABLE II.—SOLUBILITY OF STEROIDS IN U.S.P. OILS AT 25°

Steroid	mg./ml. Castor Oil	Sesame Oil	Peanut Oil
17-Hydroxyprogesterone caproate	55.6	23.4	27.9
Testosterone	38.6	5.4	8.1
Estradiol valerate	60.6	16.1	18.8
Progesterone	52.0	22.9	23.5

therapy (3). Using withdrawal bleeding in human females as the criterion, Master, *et al.* (4), compared the duration of action of an aqueous suspension of progesterone with an oil solution, and confirmed the superiority of the latter. The prolongation of activity was generally related to storage in the fatty depots of the body (5).

In 1952 Junkmann (6) determined that a testosterone ester dissolved in sesame oil prolonged the androgenic effects in castrated rats. Davis and Wied (7) demonstrated that prolonged activity was also obtained in humans when oil solutions of a progesterone derivative were injected. There was still a limiting factor, however, in that only a relatively small amount of hormone could be dissolved in the traditional oils. To increase the solvent power of the oil it was necessary to add compatible and nonirritating cosolvents. Such additions consisted of benzyl benzoate, benzyl alcohol, ethyl lactate, ethyl oleate, etc. The U.S.P. recognized the need for such "other vehicles," with the restrictions that they must be safe in the volume of injection administered, and that they should not interfere with the therapeutic efficacy of the preparation or its testing.

Demand for increased hormone concentrations per dose, furthered the search for an acceptable oil with greater solubilizing power *per se*. Boschann (8) in 1954, observed that 17-hydroxyprogesterone caproate in a castor oil–ethyl lactate vehicle was well tolerated. In addition, private communications from clinicians in West Germany[1] reported good tolerance to Proluton-Depot containing a castor oil–benzyl benzoate vehicle. Since then other hormones have been used as solutions in ricinoleic acid esters, as well as in castor oil (9–11). Accordingly, an investigation was undertaken into the suitability of castor oil as a vehicle for parenteral administration of steroid hormones.

METHODS AND RESULTS

Representative samples of U.S.P. oils obtained from commercial sources were tested in accordance with the official method for free fatty acid content, saponification, and iodine values. The results are listed in Table I along with the U.S.P. XVI specifications for these oils.

Solubility of selected steroids in various oils was determined in the following manner. An excess of steroid was stirred for 4 hours at room temperature (25°) in the test oil, after which the undissolved solids were removed by filtration, and the clear solution assayed for steroid content. Table II shows the results obtained.

An attempt was made to reduce the free fatty acids in castor oil by treatment with alumina and anhy-

[1] Dr. Napp, Universitats-Krankenhaus, Hamburg; Dr. Pots, Humboldt-Universitat-Charite Frauenklinik, Berlin; Dr. Prill, Universitats-Frauenklinik, Wurzburg; and Dr. Rauscher, Universitats-Frauenklinik, Vienna.

TABLE III.—ABSORPTION OF OIL FROM ANIMAL MUSCLE[a]

Days after Injection	Oil	ml. 0.02 N NaOH Equiv.	Residual Oil in Muscle (estd.)
1–3	Castor oil (aged)	50	1 day —50% 3 days—20%
1–3	Castor oil U.S.P.	13	1 day —30% 3 days—10%
1–3	Sesame oil U.S.P.	1.4	1 day —30% 3 days—30%
7–60	All oils	...	Declining 10 to 2%

[a] 1 ml. injected into back muscle of rabbit.

drous sodium sulfate. Three grams of dried, powdered, amorphous aluminum oxide (Merck No. 1097) and 6 Gm. of anhydrous sodium sulfate, reagent grade, were suspended in 120 ml. of oil and heated at 80° under a blanket of nitrogen for 1.5 hours. After allowing the oil to cool to room temperature, the solids were filtered off and the acids titrated in the usual manner. A significant reduction in free fatty acid was not obtained.

The absorption characteristics of oils with varying fatty acid content were examined and compared on a biological basis. Aged castor oil with a high free fatty acid content was compared to fresh U.S.P. castor oil with a low acid content and U.S.P. sesame oil by injecting 1 ml. of oil into the back muscles of rabbits, approximately 2 in. from the iliac crest. A rotational pattern of injection was used and the oil samples were stained to aid visibility in the tissues. The animals were sacrificed and the muscles excised and examined grossly. The results were averaged and appear in Table III.

The test disclosed that oil migrated or was carried to the fascia, and very small amounts remained for 60 days. Localized degeneration produced by the high acid value castor oil was essentially healed in 7 days, and the low acid value castor oil appeared to be no more irritating than sesame oil.[3]

In a specific test for irritation 0.25 ml. of the above oil samples were also injected into the *vastus lateralis* muscles of rabbits. After 2 days the animals were sacrificed and the injected muscles examined grossly for evidence of irritation. It was found that the castor oil containing a high level of free fatty acid produced a lesion size measuring approximately 121 mm.[2]. The lesion itself was characterized mainly by degeneration of local tissue without necrosis. Castor oil with low free fatty acid and sesame oil, on the other hand, produced no measurable lesion at the injection site.

Combinations of benzyl alcohol and benzyl benzoate with both castor oil and sesame oil were also injected into the *vastus lateralis* muscles of rabbits and Table IV lists the lesion sizes produced.

Solutions which were formulated for clinical trials in humans were prepared by dissolving the steroid hormones in appropriate vehicles at 60° under nitrogen. The solutions were then filtered through a coarse sintered-glass filter with the aid of nitrogen pressure, filled into vials, and sterilized by autoclaving for 2 hours at 121° (15 lb. steam pressure). The products were then submitted for assay, safety, and animal muscle irritation testing prior to release for clinical investigation.

[3] Due to the apparent increase in free fatty acids with aging, subsequent work utilized fresh oils which required for neutralization less than 3 ml. of 0.1 N NaOH (15 ml. of 0.2 N NaOH) per 10 Gm. of sample.

DISCUSSION

Throughout the investigation it was desirable to have a reference oil to serve as a basis for comparison. Since sesame oil is universally accepted as a parenteral oil vehicle, it was chosen as the "standard" vegetable oil to be compared to castor oil, with and without other cosolvents. The physical, chemical, and biological properties of sesame oil are well documented and require no comments here.

Chemically, castor oil consists of the triglycerides of ricinoleic acid, together with small quantities of glycerides of other acids. The quantitative composition is given by Eckey (12) as follows: ricinoleic acid 87%, oleic acid 7.4%, linoleic acid 3.1%, dihydroxyricinoleic acid 0.6%, and miscellaneous acids 2.4%. Two grades are commonly recognized in this country—U.S. No. 1 which is cold pressed oil, and U.S. No. 3 which is oil extracted from the pressed cake. Only the former is used for medicinal purposes.

The high viscosity of castor oil compared to other vegetable oils is undoubtedly related to hydrogen bonding and it is probably the hydroxy groups which contribute to the greater polarity and superior solvent power of the oil. As indicated in Table I, the saponification and iodine values of commercial castor oil appear to be slightly lower than the U.S.P. XVI limits for oils used for injection. On the other hand, the content of free fatty acids even in fresh oil, varies considerably and exceeds the traditional limits for injectable oils. The significance of this is somewhat obscure, although "Remington's Practice of Pharmacy, 12th edition," page 387, states "a low free fatty acid content is essential since it indicates a fresh and pure product and not one that is likely to have become old and heavily contaminated with bacterial products."

Despite better solubility of steroids in castor oil, other cosolvents were necessary to dissolve the

TABLE IV.—LOCAL IRRITATION PRODUCED IN RABBIT MUSCLE BY INJECTION OF VARIOUS OIL VEHICLES[a]

Identification	Composition	Lesion size, mm.[2]
SHY-47-2	Sesame oil 98% Benzyl alcohol 2%	61
SHY-47-4	Castor oil 98% Benzyl alcohol 2%	Too small to measure
SHY-47-3	Sesame oil 95% Benzyl alcohol 5%	506
SHY-47-5	Castor oil 95% Benzyl alcohol 5%	106
SHY-14-2	Sesame oil 65% Benzyl benzoate 35%	291
SHY-14-5	Castor oil 65% Benzyl benzoate 35%	184
SHY-47-6	Sesame oil 63% Benzyl benzoate 35% Benzyl alcohol 2%	207
SHY-47-7	Castor oil 63% Benzyl benzoate 35% Benzyl alcohol 2%	262
SHY-14-3	Sesame oil 50% Benzyl benzoate 50%	291
SHY-14-6	Castor oil 50% Benzyl benzoate 50%	158

[a] A 0.25-ml. quantity of the oil vehicle was injected into the *vastus lateralis* muscle of the rabbit. Two days later the muscle was excised and the lesion size measured in mm.[2].

increasingly higher concentrations required by therapeutic regimens. Often these materials contributed additional advantages. For example, the addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favorable viscosity, making it easier to inject. Also, benzyl alcohol was an effective preservative and local anesthetic.

The nature of the irritative response depended on the particular hormone, its concentration in the formulations, and/or the composition of the vehicle. Although rabbit muscles are more sensitive than human muscles, they were selected primarily because local changes in the muscle were observed easily. It was not always possible, however, to correlate muscle irritation in animals to that of humans.

A numerical assignment to lesion size was used solely as a convenience for grading response. The numbers alone do not adequately describe the nature of the response, however. More completely it is characterized by the amount of hemorrhage and edema and the incidence, degree, and extent of local degeneration produced by the injection. A slight, reversible irritative response may cover a large area and a severe irreversible one may be comparatively small. A decrease in the size of the degenerated area indicates a reversible condition. The presence of necrosis, which is the most damaging situation, means that the cellular structure was destroyed and repair must take place. The debris must be removed and the original cellular mass in the area replaced with fibrous connective tissue. The extent of this fibrosis or formation of scar tissue gives an index of the amount of irreversible damage. Fortunately necrosis was not encountered, indicating the lack of permanent muscle damage. Since these changes take time, final assessment of the effects of an injection in the muscle frequently required observation for 7 days or longer.

It is unfortunate that pain cannot be measured by any known method of animal testing. The animal usually does not respond unless the painful stimulus is marked. Furthermore, the pain caused by injection into human muscle is not usually proportionate to the irritation produced either in animal muscle or in human muscle. Realizing that these limitations are inherent in animal test methods, it remained for final acceptability to be determined in man.

When it was discovered that 17-hydroxyprogesterone caproate possessed high progestational activity, potencies of the order of 65 mg./ml. were used. By increasing the dose, additional prolongation of action was obtained, and eventually concentrations of the order of 250 mg./ml. were required. Such a solution in sesame oil produced acceptable animal muscle tolerance, but the pain and local reaction in humans was so great as to prohibit the adoption of the formulation as a commercial product (see Table V, Lot Pr. 142-53/15-10).[8] Solutions were also prepared using castor oil as the vehicle, and Table V lists the formulations tested and the results obtained. Information obtained from the clinical trials (14–21) attested to the acceptability and safety of the adopted formulations.

Inherent in the development of an acceptable formulation of 17-hydroxyprogesterone caproate was the required development of a suitable assay method. This was accomplished by Roberts and Florey (13) using paper-strip chromatography.

Since estrogens are more potent than progestogens and require less per dose, an acceptable formulation of estradiol valerate was easier to prepare. Besides use in estrogen therapy, estradiol valerate has found utility in the treatment of carcinoma, and for that purpose high dosages were required. Concentrations were increased from 10 to 40 mg./ml. and

[8] Reactions in excess of 5–6% were considered unacceptable.

TABLE V.—EVALUATION OF 250 mg./ml. 17-HYDROXYPROGESTERONE CAPROATE SOLUTIONS IN VARIOUS OIL VEHICLES

Vehicle Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks on Clinical Testing
Sesame oil 50% Benzyl benzoate 50%	1049	Pr.142-53/15-7—238 injections, 20.6% reactions, rejected
Castor oil 58% Benzyl benzoate 40% Benzyl alcohol 2%	691	Pr.142-53/15-8—270 injections, 23.2% reactions, rejected
Sesame oil 60% Benzyl benzoate 35% Benzyl alcohol 5%	697	Pr.142-53/15-10—189 injections, 10.7% reactions, rejected
Castor oil 54% Benzyl benzoate 46%	258	Pr.142-53/15-11—503 injections, 4.2% reactions, accepted
Castor oil 52% Benzyl benzoate 46% Benzyl alcohol 2%	633	Pr.142-53/15-13—924 injections, 1.3% reactions, accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

TABLE VI.—EVALUATION OF ESTRADIOL VALERATE IN VARIOUS OIL VEHICLES

Composition	Animal Muscle Lesion Size, mm.[a]	Lot Number and Remarks
20 mg./ml. in Castor oil 78%, Benzyl benzoate 20%, Benzyl alcohol 2%	197	Es.31-53/15-B—Commercially available
30 mg./ml. in Sesame oil 60%, Benzyl benzoate 40%	306	DEK-98-2—Not tested clinically; dosage increased to 40 mg./ml.
30 mg./ml. in Castor oil 80%, Benzyl benzoate 20%	194	Es.31-53-V—Not tested clinically; dosage increased to 40 mg./ml.
40 mg./ml. in Sesame oil 65%, Benzyl benzoate 30%, Benzyl alcohol 5%	803	SHX-94-4—Too irritating; not tested clinically
40 mg./ml. in Sesame oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	496	Es.31-53-8—201 injections, 23.2% reactions, rejected
40 mg./ml. in Castor oil 58%, Benzyl benzoate 40%, Benzyl alcohol 2%	250	Es.31-53-A—826 injections, 2.67% reactions (all mild), accepted

[a] Injection of 0.25 ml. into *vastus lateralis* muscle of rabbits and lesion size determined 2 days after injection.

again formulations containing castor oil in the vehicle proved to be less irritating than similar preparations containing sesame oil. Physically and chemically both oil solutions were stable. Based on acceptable preliminary data, formulations such as those listed in Table VI were prepared and tested. Acceptability in humans was confirmed by clinicians and described in the literature (22, 23) and in case reports.[4]

SUMMARY

1. The development and testing of parenteral steroid hormone formulations has been described, using castor oil as a vehicle.

2. After ascertaining stability and animal muscle irritation, selected formulations were evaluated in humans. They exhibited a prolonged action, were effective and well tolerated.

3. Examples of commercially available products are the estrogen, estradiol valerate[5] at 20 mg./ml. and 40 mg./ml., and the progestogen, 17-hydroxyprogesterone caproate[6] at 250 mg./ml.

[4] Case reports: estradiol valerate, 20 mg./ml., in castor oil 78%, benzyl benzoate 20%, benzyl alcohol 2%—90 injections in 46 patients. Two mild local reactions. Estradiol valerate 40 mg./ml. in castor oil 58%, benzyl benzoate 40%, benzyl alcohol 2%—51 patients. Number of injections not completely tabulated. One report is in press.

[5] Marketed as Delestrogen by E. R. Squibb & Sons, New York, N. Y.

[6] Marketed as Delalutin by E. R. Squibb & Sons, New York, N. Y.

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Isolation of Marrubiin, a Sterol, and a Sesquiterpene from *Marrubium vulgare*

By HAROLD J. NICHOLAS*

A simple column chromatographic method for isolating the bicyclic diterpene marrubiin from acetone and ethanol extracts of *Marrubium vulgare* L. is described. An unsaturated sterol of the stigmastanol series, present in esterified form, and a sesquiterpene ($C_{15}H_{22}O_2$) have been isolated from the extracts.

IN PREPARATION for radioactive tracer work on the biosynthesis of marrubiin it was necessary to examine extracts of the plant for associated terpenoid substances. A convenient column chromatographic method was therefore devised for separating relatively pure marrubiin from crude acetone extracts. Two new terpenoid substances were detected in the extracts.

EXPERIMENTAL

Materials and Methods.—Ground *M. vulgare* L. was obtained from the Wunderlich-Diez Corp., Hasbrouck Heights, N. J.[1] This material was exhaustively extracted with hot acetone or hot ethanol. Either solution on removal of solvent by distillation (the last stages *in vacuo*) yielded black, viscous material which was used for further examination. Melting points were determined on a Fisher-Johns melting point apparatus. Optical rotations (in $CHCl_3$) and C—H analyses were determined by Drs. G. Weiler and F. B. Strauss, Microanalytical Laboratory, Oxford, England. An infrared spectrum of the unidentified diterpene was determined on a Perkin-Elmer spectrophotometer by the KBr disk method.[2] An infrared spectrum of the sterol was determined in chloroform solution in a 0.1-mm. sealed cell, compensated with $CHCl_3$, on a Beckman IR-4 recording infrared spectrophotometer,[3] and by the KBr disk method. The

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[1] This firm has given assurance that the material investigated was *M. vulgare* or white horehound, not *Ballota hirsuta* (black horehound).

[2] We are indebted to the Department of Pathology, University of Kansas, for this determination.

[3] Determined by Sadtler Research Laboratories, Philadelphia, Pa.

ATTACHMENT F - COMPILATION

TAB 12

Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999)—Part I

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Overview

The chemical structure of a molecule determines the potential successful formulation approaches available to the parenteral scientist. However, there is no comprehensive listing of parenteral products with the chemical structure and formulation. A review of domestically marketed injectable product formulations of small molecule therapeutics is presented herein with the intent of compiling a comprehensive source of public information for the formulation scientist. The compilation lists the drug name, marketed name, chemical structure of the drug, marketed injectable formulation, preadministration preparation, route of administration, company and the clinical indication (1–7).

One purpose of this compilation is to assist the formulation scientist in being able to look at a drug's chemical structure and then be able to determine possible formulation approaches. This compilation will also be useful for those interested in knowing what additives are currently used in injectable products and at what concentrations they are administered in practice. This compilation only focuses on marketed formulations and does not delve into the subject of preclinical or drug discovery formulations associated with early-stages pharmacokinetics or proof-of-concept pharmacodynamics, where the formulation scientist is not bound by regulatory constraints.

There are a few published reviews on parenteral formulations (8) and in an excellent review article (9) Lilly scientists, Sweetana and Akers, discuss the various formulation approaches with detailed tables of examples. In a compendium of excipients for parenteral formulations (10) Genentech scientists, Powell, Nguyen and Baloian, list the acceptable excipients as well as their percent's within the formulations, route of administration and pH. The compilation herein is an additional resource to the parenteral scientist by presenting the chemical structure and the formulation in a side-by-side fashion. An examination of this compilation reveals many examples of injectable formulation techniques to improve solubility or provide a sustained release. The next few sections highlight various formulation approaches with specific examples and tables, as well as general discussions of parenteral formulations.

Editor's Note: This review article on Injectable Products is being published in several parts. The next installment(s) will appear in subsequent issues of the *Journal*.

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Introduction

The word "parenteral" is Latin for "other than intestine," thus by definition the parenteral sciences not only includes injectable products but also transdermal, pulmonary, nasal, ophthalmic, and buccal routes of administration. However, in practice, parenteral usually refers to injectable products. Recently we have seen the commercialization of previously academic pursuits such as controlled-release formulations using microspheres, liposomes and polymeric gels, longer *In vivo* circulating times using PEGylated liposomes (also known as stealth liposomes) and PEGylated proteins, and new excipients such as cyclodextrin derivatives used as complexing agents for increasing water solubility of poorly soluble drugs. We have also seen the commercialization of injection devices such as prefilled syringes, dual chamber syringes containing solid drug and a liquid for reconstitution, and will likely soon see needle-free injectors and pocket-size infusion pumps.

Injectable Formulations

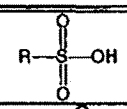
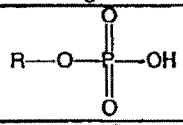
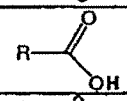
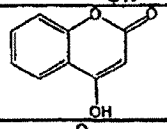
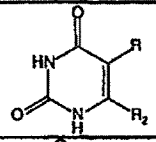
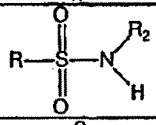
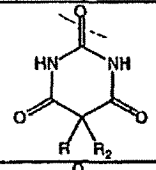
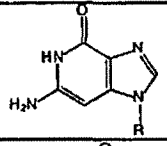
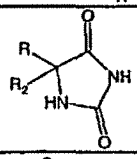
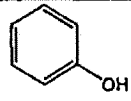
Two key aspects of any successful injectable formulation are: 1) to achieve the required drug concentration, and 2) the drug must be chemically and physically stable in order to have a sufficient shelf-life, which is generally considered to be the time for 10% degradation. The ideal injectable formulation, from an *in vivo* tolerability point-of-view, is isotonic with physiological fluids and a neutral pH (i.e., PBS: phosphate buffered saline, 0.01M sodium phosphate with 0.135M NaCl and 0.003M KCl, pH 7.4). However, in many instances the drug does not have sufficient water solubility at pH 7.4, and thus the formulation scientist must use a wide variety of solubilization techniques. If stability is insufficient to provide a two-year shelf-life, then the formulation scientist must either change the solution conditions to achieve both the solubility and stability requirements or develop a lyophilized product. This manuscript focuses on solubilization techniques for small molecules, and will not focus on stability or stabilization techniques.

I. Solubilization Techniques

1. pH Adjustment and Salts

If the drug molecule is ionizable, then pH adjustment can be utilized to increase water solubility since the ionized molecular species has higher water solubility than its neutral species. Indeed, the most common solubilization technique is pH adjustment and weak acids are normally formulated at

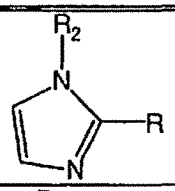
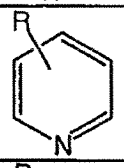
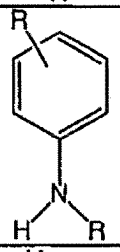
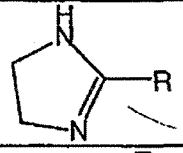
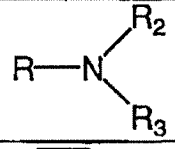
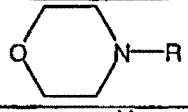
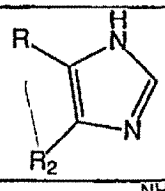
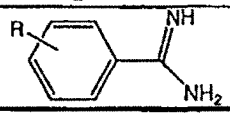
Table I. Examples of Weak Acid Chemical Functional Groups, Their Approximate pKa's and Formulation pH's.

Functional Group Name	Functional Group Structure	Functional Group pKa	Formulation pH	Selected Examples
Sulfonic acid		<1	Neutral	Aztreonam
Phosphate ester		2	Neutral	Fosphenytoin Bethamethasone Dexamethasone Fludarapine
Carboxylic acid		2.5-5	5-8	Penicillin Ketorolac
4-Hydroxy coumarin		~ 8	8.3	Warfarin
Uracil		~ 8	9.2	Flurouracil
Sulfonamide		7-9	9-11.6	Acetazolamide Clorothiazide Diazoxide
Barbituric acid		7-9	9.5-11	Methohexital Pentobarbital Phenobarbital Secobarbital
Guanine		2.2, 9.4	11	Acyclovir Gancyclovir
Hydantoin		~ 10	10-12	Phenytoin
Phenol		8-10	10.5 emulsion organic organic	Liothyronine Propofil Etoposide Teniposide

pH > 5 (Table I), weak bases at pH < 7 (Table II). Zwitterionic molecules have multiple ionizable groups and can be either cationic, anionic or neutral (positive and negative charges cancel each other, for an overall net neutral molecule) and are usually formulated at a pH in which the drug is ionic (Table III). For example, both ciprofloxacin and sufentanil have a carboxylic acid and an amine, but are formulated as the cation at pH < 7. On the other hand, both ampicillin and cephapirin have a carboxylic acid and an amine or pyridine, but are formulated as the anion at pH > 5.

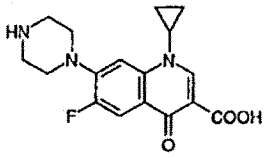
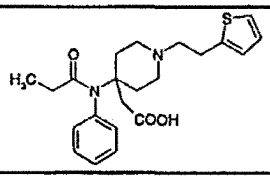
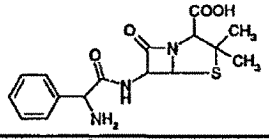
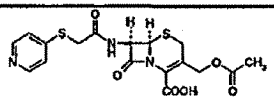
The range in pH is quite broad and is between pH 2–12, and thus any molecule with a pKa between 3–11 can be potentially solubilized by pH adjustment. However, when using extremes in pH, care must be taken to minimize buffer capacity in order for the formulation to be *in vivo* compatible. When given intravenously, the formulation components are quickly diluted by the flow of blood and neutralized by the buffer capacity of blood. When given via intramuscular injection, the rate of dilution is reduced but rapid enough to still be able to inject in the range pH ~ 3–11. However,

Table II. Examples of Weak Base Chemical Functional Groups, Their Approximate pKa's and Formulation pH's.

Functional Group Name	Functional Group Structure	Functional Group pKa	Formulation pH	Selected Examples
1H-Imidazole		~ 4-6	< 6	Miconazole Ondansetron
Pyridine		~ 5	2-4	Amronone Milrinone Papaverine Pyridoxine
Aniline		~ 5	2-6	Metoclopramide Minocycline (Procaine Procainamide also have a tertiary amine)
4,5-Imidazoline		~ 6	3-4	Tolazoline
Amine		7-10	3-7	Atenolol Codeine Daunorubicin Morphine Verapamil
N-Alky morpholine		7.4	< 5	Doxapram
Imidazole		~ 7	3-6.5	Cimetidine Dacarbazine Phentolamine
Amidine		~ 9-11	< 8	Pentamidine

when given subcutaneously the rate of dilution is reduced further with more potential for irritation at the injection site and thus the range is pH 3–6. For example, chlordiazepoxide is administered intravenously or intramuscularly and formulated at pH 3 with 20% propylene glycol and 4% TWEEN 20. Phenytoin sodium is administered either intravenously or intramuscularly and formulated at pH 10–12 with 40% propylene glycol and 10% ethanol. Subcutaneous formulations are slightly acidic such as methadone at pH 3–6, and levorphanol at pH 4.3.

Water-soluble salt forms (i.e., sodium salts of weak acids, or hydrochloride salts of weak bases) utilize the same principle of ionization, and are often the marketed form of the drug (Table IV). The most common cationic counterion is sodium which accounts for > 90% of the cations, and there are three meglumine salts, while only one salt each of

Table III. Examples of Zwitterionic Drugs, Approximate pKa's and Formulation pH's.				
Selected Example	Chemical Structure	Acidic Functional Group Name and pKa	Basic Functional Group Name and pKa	Formulation pH (ionic state)
Ciprofloxacin		Carboxylic acid ~4	Aniline ~4 Amine ~9	3-4 (Cationic)
Sufentanil		Carboxylic acid ~4	Amine ~8	3.5-6 (Cationic)
Ampicillin		Carboxylic acid ~4	Amine ~8	8-10 (Anionic)
Cephapirin		Carboxylic acid ~3	Pyridine ~5	6-8 (Anionic)

the cations potassium, tromethamine and calcium. There are many more anionic counterions and the most common is the hydrochloride salt followed by sulfate, mesylate, maleate and tartrate. When a salt is dissolved in non-buffered water, the resulting pH is generally ~2 pKa units away from the pKa, because protons are either added to (salt of a weak base) or taken away from water (salt of a weak acid). For example, gancyclovir is a weak acid with $pKa_2 = 9.4$ and dissolving its sodium salt in water results in pH ~ 11.

In order to maintain a desirable pH range, many formulations that utilize pH adjustment also use buffers to control pH (Table V). Buffers span the range of pH 2.5–11 and

Table IV. List of Counter Ion in Salt Forms of Parenteral Drugs.			
Cation	Number of instances	Anions	Number of instances
Sodium	55	Hydrochloride	64
Meglumine	3	Sulfate	16
Potassium	1	Mesylate	8
Calcium	1	Chloride	7
Tromethamine	1	Maleate	6
		Tartrate	6
		Citrate	5
		Bromide	5
		Lactate	5
		Acetate	2
		Phosphate	2
		Besylate	1
		Hydrobromide	1
		Fumarate	1
		Gluceptate	1
		Gluconate	1
		Glucuronate	1
		Lactobionate	1
		Salicylate	1
		Tosylate	1

Table V. List of Buffers Used in Parenteral Formulations				
pH	Buffer (pKa's)	Concentration in Formulation, Molarity	Concentration Administered, Molarity	Route of Administration
2.5-4.0	Tartartic acid (2.9, 4.2)	0.04	0.04	IM, IV
3	Maleic acid (1.9, 6.2)	0.14	0.14	IM
3	Glycine (2.3, 9.6)	0.2	0.05	IV infusion
3.0-4.5	Sodium lactate/ Lactic acid (3.8)	0.17 0.02	0.17 0.085 0.02	IV IV infusion, SC
3-5	Ascorbic acid (4.2, 11.6)	0.02	0.01 0.02	IM IV
3.0-7	Sodium citrates/ Citric acid (3.1, 4.8, 6.4)	0.6 0.1	0.6 0.1	IM, IV, IV infusion, SC
4-6	Sodium acetate/ Acetic acid (4.75)	0.01	0.01	IV, SC
4-6.5	Sodium bicarbonate/ Carbonic acid (6.3, 10.3)	0.08	0.08 0.001	IM IV, IV infusion
4.2-6	Sodium succinate/ Succinic acid (4.2, 5.6)	0.04	0.005 0.04	IV infusion, SC
6	Histidine (1.8, 6.0, 9.2)	0.005 0.05	0.0005 0.05	IV infusion IM
6-7	Sodium benzoate/ Benzoic acid (4.2)	0.5	0.5	IV
3-8	Sodium phosphates (2.2, 7.2, 12.4)	0.08	0.08	IV, IV infusion IM
7.4-9.0	Tris(hydroxy-methyl)amino-methane (8.3)	0.01	0.01	IM, IV infusion Intra-arterially, Intrathecal
8.7-11	Sodium bicarbonate/ Sodium carbonate (6.3, 10.3)	0.01	0.01	IV, IV infusion, Intravitreal (Fomiversen)

IM = intramuscular
IV = intravenous
SC = subcutaneous

include citrates, acetates, histidine, phosphate, tris(hydroxymethyl)aminomethane, and carbonates. The buffer concentration must be high enough to maintain the desired pH, but must be balanced by *in vivo* tolerability considerations, and thus it is good practice to minimize buffer capacity of the administered formulation.

2. Mixed Organic/Aqueous Formulations

If pH adjustment alone is insufficient in achieving the desired solution concentration, then a combination of pH and organic solvent(s) is often employed. If the drug molecule is not ionizable then pH has no effect on solubility,

but solubility enhancement can often be accomplished by a combination of aqueous and organic solvents (i.e., a cosolvent). The currently used organic solvents used in mixed organic/aqueous formulations are propylene glycol, ethanol, polyethylene glycol 300 or 400, cremophor EL, TWEEN 80, sorbitol, glycerin and dimethylacetamide (DMA) (Table VI).

As with any formulation additive, the concentration that is administered should be minimized to avoid any *in vivo* complications such as local irritation or precipitation at the injection site. Many cosolvent formulations are marketed using rather high concentrations of organic solvent, and are usually but not always diluted prior to injection. For example, propylene glycol is 50% of the fenoldopam marketed formulation, but is diluted to <1% for IV infusion. However, propylene glycol is ~70% of the oxytetracycline marketed formulation and is injected intramuscularly without dilution.

Similar to formulations using pH adjustment, of the three main routes of administration (i.e., intravenous, intramuscular and subcutaneous), the subcutaneous route has the most constraints when using cosolvent due to the reduced volume flow away from the injection site compared to intravenous and intramuscular. As a result, only three cosolvent products are administered subcutaneously and the amount of organic solvent is limited to ethanol 6% (dihydroergotamine), glycerin 32% (epinephrine), and propylene glycol 10% (hydralazine). Whereas, the intravenous bolus route can use ethanol up to 20% (paricalcitrol), PEG 300 up to 50% (methocarbamil), and propylene glycol up to 68% (phenobarbitol). The intramuscular route has similar *in vivo* constraints to the intravenous route, but can tolerate even more organic solvent (see section I.3, Totally Organic Solution Formulations).

Surfactant formulations seem to be on the increase with excipients Cremophor EL and TWEEN 80 leading the way. These formulations, in general, are supersaturated upon dilution and must be used soon after dilution into IV compatible fluids. For example, cremophor EL is 11% of the miconazole marketed formulation, but is diluted to 1% for IV infusion. Also, TWEEN 80 is 10% of the amiodarone marketed formulation, but is diluted to 0.4% for IV infusion. However, cremophor EL at 10% or TWEEN 80 at 25% can be administered by IV infusion (see section I.3).

3. Totally Organic Solution Formulations

Molecules that are non-ionizable (have pKa < 2, or pKa > 11) and non-polar are water insoluble with no effect of pH on solubility, and thus are the most challenging for the formulation scientist. These water-insoluble molecules can be formulated in 100% organic solvent, which is then usually but not always diluted prior to administration (Table VII). For example, busulfan is marketed in 33% dimethylacetamide and 67% PEG 400, but is diluted 10-fold prior to IV infusion. The lorazepam marketed formulation is 80% propylene glycol, 18% ethanol and 2% benzyl alcohol, but is diluted 2-fold for IV bolus injection, but not diluted for intramuscular injection. Paclitaxel is marketed with 51% cremophor EL and 49% ethanol, but is diluted 5- to 20-fold for IV infusion. Docetaxel is marketed in 100% TWEEN 80, but is diluted to 25% for IV infusion.

4. Cyclodextrins

Some molecules can be solubilized by forming an inclusion complex with a cyclodextrin. Cyclodextrins have a hydrophilic exterior and a hydrophobic interior core of specific dimensions, and thus molecules with a non-polar, aromatic or heterocyclic ring can potentially fit inside the core. Increased water solubility through molecular complexation with cyclodextrins has advantages over the cosolvent approach since upon dilution a 1:1 complex between cyclodextrin and drug will not precipitate, but a drug dissolved in a cosolvent often precipitates upon dilution. Two cyclodextrins have been accepted for human injectable use with the approval of alprostidol alfadex and itraconazole. Alprostidol alfadex is marketed as a lyophilized powder with α-cyclodextrin and is administered intracavernosally. Itraconazole was approved in April 1999 as a solution with 40% hydroxypropyl-β-cyclodextrin and is administered by intravenous infusion after a 2-fold dilution with saline (6). The next cyclodextrin likely to be approved is sulfobutylether-β-cyclodextrin, which is in the clinical formulation of ziprasidone for intramuscular injection (11).

5. Emulsions

Oil-soluble molecules are generally neutral uncharged and non-polar molecules, but can be formulated for intravenous administration by the use an oil-in-water emulsion. Emulsions can solubilize oil-soluble drugs since the drug partitions into the oil phase. A typical emulsion is composed of water with 10–20% soybean and/or safflower oil, 2% glycerol, 1% egg lecithin and pH 7–8, and is injected by either IV bolus or IV infusion. The only marketed emulsion formulation is propofol, which is in a typical emulsion composed of 10% soybean oil containing 10 mg/mL drug. The total parenteral nutrition (TPN) formulations are the lipid emulsions Intralipid and Liposyn, which are administered by intravenous infusion as nutritional supplements.

6. Prodrugs

Molecules which contain an alcohol, phenol, carboxylic acid, amine, hydantoin functional group can potentially be derivatized as a prodrug. Once the prodrug is administered *in vivo*, the promoiety is hydrolyzed by either esterases or phosphatases releasing the parent drug. Although prodrugs are normally associated with orally administered products for better oral bioavailability, many parenteral products are prodrugs (Table VIII).

The versatility of the prodrug approach is demonstrated with prodrugs that in design either increase or decrease water solubility. A water-soluble prodrug has an electronically charged promoiety, while a water insoluble prodrug has been derivatized to be a neutral molecule (see section II.7b). Recently, a few water-soluble phosphate ester prodrugs have been developed and marketed in order to replace the original formulations that contain high concentrations of organic solvent. The phenol-containing etoposide (etoposide phosphate) is derivatized as a water-soluble phosphate ester. Water-soluble phosphate esters are also prodrugs for alcohol-containing betamethasone, clindamycin, dexamethasone, fludarabine, hydrocortisone, and prednisolone. The hydan-

Table VI. List of Cosolvents Used in Parenteral Formulations.				
Solvent	% in Marketed Formulation	% Administered	Route of Administration	Examples
Cremophor EL	11	1	IV infusion	Miconazole
	20	0.02-0.08	IV infusion	Tacrolimus
	50	0.1-1	IV infusion	Tenoposide
	50	18	Intravesical	Valrubicin
	51	2.5-10	IV infusion	Paclitaxel
	65	0.65-3.3	IV infusion	Cyclosporin
Dimethyl-acetamide (DMA)	6	0.012-0.12	IV infusion	Tenoposide
	33	3	IV infusion	Busulfan
Ethanol	5 (diluent for LP)	0.5	IV infusion	Medroxy-progesterone
	6	6	IM, SC, IV	Dihydroergotamine
	10	10	IM, IV	Diazepam
	10	2.5-10	IV	Digoxin
	10	10	IM, IV	Ketorolac
	10	10	IM, IV	Pentobarbital
	10	10	IM, IV	Phenobarbital
	10	10	IM, IV	Phenytoin
	13 (diluent)	10 (diluent)	IV infusion	Docetaxel
	20	20	IV	Paricalcitol
	25	1	IV infusion	Esmolol
	30	0.3-0.6	IV	Etoposide
	35	0.35-1.7	IV infusion	Cyclosporin
	42	0.084-0.84	IV infusion	Teniposide
	49	2.5-10	IV infusion	Paclitaxel
	50	18	Intravesical	Valrubicin
	80	0.08-0.32	IV infusion	Tacrolimus
	100 (diluent for LP)	10	IV infusion	Carmustine
Glycerin	15	15	IM, SC, IV	Dihydroergotamine
	25	25	IV infusion	Idarubicin
	32	32	SC	Epinephrine
N-methyl-2-pyrrolidone (Pharmasolve)	100 (diluent for LP)	100	Subgingival	Doxycycline
Monothio-glycerol	10	10	IM	Oxytetracycline
PEG 300	50	50	IM, IV	Methocarbamil
	60	0.6-1.2	IV	Etoposide
PEG 400	18	18	IM	Lorazepam
	18	9	IV	Lorazepam
	67	6-7	IV infusion	Busulfan

toin-containing phenytoin prodrug (fosphenytoin) is derivatized in a unique fashion as a water-soluble hydroxymethyl phosphate ester, which after *in vivo* enzymatic phosphate ester cleavage, the resulting hydroxymethyl intermediate quickly dissociates to phenytoin and formaldehyde (12). Other water solubilizing prodrug approaches are a succinate ester of the alcohol methylprednisolone, and a piperidine carbamate in irinotecan a prodrug for a phenol drug.

Prodrugs can also be used for stability reasons. For example, alatrofloxacin is the alanine-alanine dipeptide prodrug for the primary amine trovafloxacin which is unstable in solution. The prodrug alatrofloxacin is marketed as a solution at pH 3.4–4.3.

II. Sustained-Release Techniques

The research in controlled release during the 1970s has in the 1990s become a commercial realization with the approval of liposomal, polymeric microsphere and polymeric gel formulations. However, traditional approaches are still in use such as suspensions, prodrugs and oil depots.

Table VI (cont.). List of Cosolvents Used in Parenteral Formulations.				
Solvent	% in Marketed Formulation	% Administered	Route of Administration	Examples
Propylene glycol (PG)	10	10	IM, SC	Hydralazine
	20 (diluent for LP)	20	IM	Chlordiazepoxide
	25	1	IV infusion	Esmolol
	30	30	IV	Paricalcitol
	35	35	IV	Etomidate
	40	40	IM, IV	Diazepam
	40	10-40	IV	Digoxin
	40	40	IM, IV	Pentobarbital
	40	40	IM, IV	Phenytoin
	50	50	IM	Dimenhydrinate
	50	5	IV infusion	Dimenhydrinate
	50	0.2	IV infusion	Fenoldopam
	60 (diluent for LP)	6	IV infusion	Medroxy-progesterone
	67-75	67-75	IM	Oxytetracycline
	68	68	IM, IV	Phenobarbital
	80	80	IM	Lorazepam
	80	40	IV	Lorazepam
Sorbitol	2	2	IM	Thiethylperazine
	4.5	0.1	IV infusion	Irinotecan
	5	0.2	IV infusion	Nicardipine
	7	0.7-2	IV	Diltiazem
	50	50	Intra-articular, Intralesional	Triamcinolone
TWEEN 80 (Polysorbate 80)	0.075	0.075	IM	Dexamethasone Acetate
	0.4	0.4	IV bolus	Calcitriol
	4 (diluent for LP)	4	IM	Chlordiazepoxide
	8	0.08-0.16	IV	Etoposide
	10	0.4	IV infusion	Amiodarone
	100	25	IV infusion	Docetaxel

IM = intramuscular
IV = intravenous
LP = lyophilized powder
PEG = polyethyleneglycol
SC = subcutaneous

7a. Suspension Formulations

Suspension formulations provide a sustained-release depot at the injection site that releases prodrug by dissolution. Suspensions used for sustained delivery are composed of a drug dispersion in either an aqueous or oil-based suspension (Table IX).

Almost all suspensions are administered intramuscularly, intralesionally or intra-articularly. The only subcutaneously administered suspension of a small molecule (many proteins are administered subcutaneous, e.g., human insulin) is epinephrine, which is administered every 6 hours and is formulated in 32% glycerin providing both rapid (drug in solution) and sustained activity (crystalline drug in suspension). The only sesame oil suspension is the anti-rheumatic aurothioglucose, which is administered intramuscularly every 1–4 weeks.

7b. Prodrugs in Suspension Formulations

Most of the other suspension formulations are aqueous-based and contain water-insoluble prodrugs which are lipophilic esters of alcohols. For example, hydrocortisone acetate and dexamethasone acetate are acetate esters of their alcohol-containing parent drug, and are administered intramuscularly, intralesionally or intra-articularly once every 1–3 weeks. The contraceptive medroxyprogesterone acetate is administered intramuscularly once every 13 weeks. Aqueous-based suspensions typically contain TWEEN 80 at ~0.75–4 mg/mL (0.4%) along with a suspending agent such

Table VII. List of Non-Aqueous Solution Formulations for Parenteral Administration.

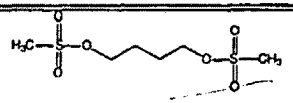
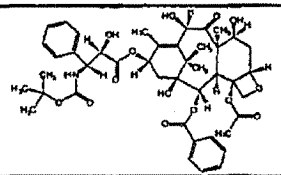
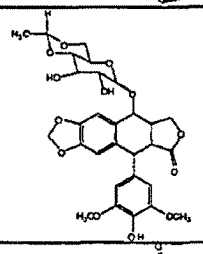
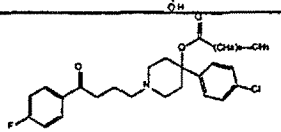
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Busulfan/ Busulfex		6 mg/mL N, N-dimethylacetamide **(DMA) 33%, PEG 400 at 67%**	Dilute with saline or dextrose 5% to 0.6 mg/mL.	IV infusion	Orphan Medical, Neoplastic
Cyclosporin/ Sandimmune	Cyclic peptide (11 amino acids), MW ~ 1200	50 mg/mL **Cremophor EL 65%, Ethanol 35%,** blanketed with nitrogen	Dilute with saline or dextrose 5% to 1-2.5 mg/mL (1 mL into 20-100 mL)	IV infusion over 2-6 hours	Novartis, Immuno-suppressant
Docetaxel/ Taxotere		40 mg/mL in **TWEEN 80** Provided **diluent of Ethyl alcohol 13%** in water	Dilute with provided diluent (13% ethyl alcohol) to 10 mg/mL.	IV infusion over 1 hour	Rhone-Poulenc Rorer , Antineoplastic
Etoposide/ Etoposide injection and VePesid		20 mg/mL **PEG 300 60%, Ethyl alcohol 30%, TWEEN 80 at 8.0%,** Benzyl alcohol 3.0 %, Citric acid 2 mg/mL pH = 3-4	Dilute with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes	Astra and Bristol-Myers Squibb, Antineoplastic
Haloperidol Decanoate/ Haldol decanoate		50-100 mg/mL in **Sesame Oil** Benzyl alcohol 1.2%	None	IM	Ortho-McNeil, psychotic disorders, Tourette's Disorder

Table VII (cont.). List of Non-Aqueous Solution Formulations for Parenteral Administration.

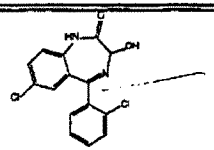
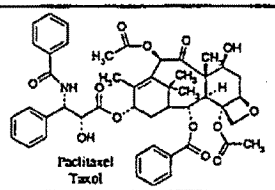
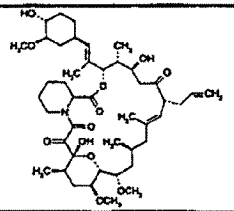
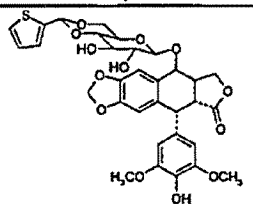
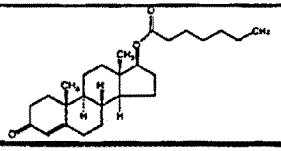
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Lorazepam/ Ativan		2-4 mg/mL **PEG 400 at 18%, in Propylene glycol** Benzyl alcohol 2%	None for IM. For IV dilute with equal volume of saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus at ≤ 2 mg/min	Wyeth-Ayerst, Anxiolytic; sedation; status epilepticus
Paclitaxel/ Taxol		Solution 6 mg/mL **Cremophor EL 51%; Ethyl alcohol 49% (v/v)**	Dilute with saline, dextrose 5% or lactated Ringer's to 0.3-1.2 mg/mL.	IV infusion	Bristol-Myers Squibb, Antineoplastic
Tacrolimus (FK 506)/ Prograf		5 mg/mL **Cremophor EL 20%, Ethyl alcohol 80%**	Dilute 250 or 1000-fold into saline or dextrose 5% to 0.004-0.02 mg/mL	IV infusion	Fujisawa, Immuno-suppresent (transplant rejection)
Teniposide (VM-26)/ Vumon		50 mg/mL **Cremophor EL 50%, Ethyl alcohol 42%, Dimethylacetamide 6%,** Benzyl alcohol 30 mg/mL pH 5 (Maleic acid)	Dilute with saline or dextrose 5% to 0.1-1 mg/mL	IV infusion over 30-60 minutes	Bristol-Myers Squibb, Antineoplastic
Testosterone Enanthate/ Delatestryl		200 mg/mL **Sesame oil,** Chlorobutanol 5 mg/mL	None	IM	BTG

Table VIII. List of Prodrugs for Parenteral Administration.

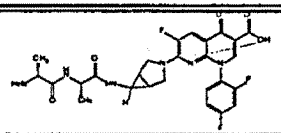
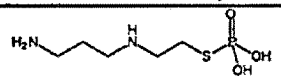
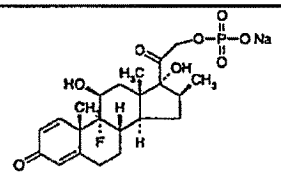
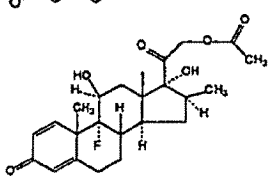
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Ala-trofloxacin mesylate/ Trovan		Solution 5 mg/mL pH 3.4-4.3	Amide	Dilute to 1-2 mg/mL with 5% dextrose	IV infusion over 60 minutes
Amifostine/ Ethyol		Lyophilized powder 500 mg	Phosphor-ylated thiol	Reconstitute with saline to 50 mg/mL (stable at room temperature for 5 hours). May be further diluted to 5 mg/mL with saline.	IV infusion over 15-30 minutes
Betametha-sone Phosphate sodium and Betametha-sone Acetate/ Celestone soluspan	 	**Suspension** Betamethasone sodium phosphate 3 mg/mL, Betamethasone acetate 3 mg/mL, Sodium phosphate dibasic 7.1 mg/mL, Sodium phosphate monobasic 3.4 mg/mL, EDTA 0.1 mg/mL, Benzalkonium chloride 0.2 mg/mL, pH 6.8-7.2	Water soluble phosphate ester and Water insoluble acetate ester	None	IM

Table VIII (cont.). List of Prodrugs for Parenteral Administration.

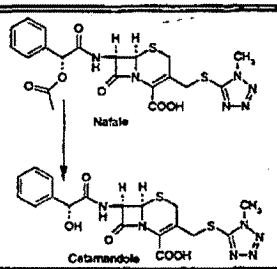
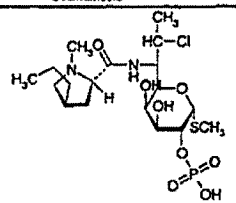
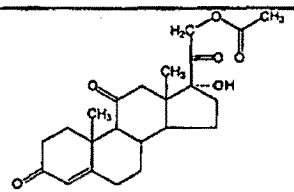
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Cefamandole /Mandol		Solid 1-10 g Sodium carbonate 63 mg/gram cefamandole, pH 6-8.5	Formate ester - rapid hydrolysis after dissolution	Reconstitute to 100-285 mg/mL with WFI, saline or dextrose 5%.	IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes
Clindamycin Phosphate/ Cleocin phosphate		**1)** Solution 150 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9.4 mg/mL pH = 5-6. 2) Ready to use solution 0.5-18 mg/mL Dextrose 5%, EDTA 0.04 mg/mL.	Water soluble phosphate ester	Dilute concentrated solution with saline or lactated Ringer's to ≤ 18 mg/mL.	IV infusion at 30 mg/hour
Cortisone Acetate/ Cortone		**Suspension** 50 mg/mL, Sodium carboxymethylcellulose 5 mg/mL, TWEEN 80 at 4 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	Water insoluble acetate ester	None	IM only

Table VIII (cont.). List of Prodrugs for Parenteral Administration.

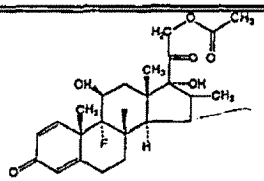
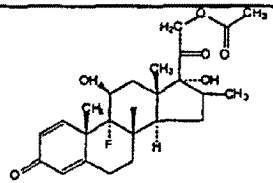
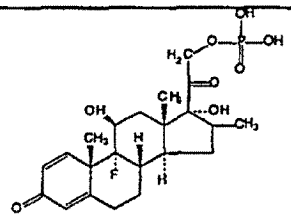
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Dexamethasone Acetate/ Decadron-LA		**Suspension** 8 mg/mL TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Water insoluble acetate ester	Gentle swirl contents to resuspend settled particles.	IM/ Intralesional/ Intra-articular/ Soft tissue
Dexamethasone Acetate/ Dalalone D.P.		**Suspension** 16 mg/mL Sodium carboxymethylcellulose 5 mg/mL, TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Water insoluble acetate ester	Gentle swirl contents to resuspend settled particles.	IM/ Intra-articular/ Soft tissue (Not intralesional)
Dexamethasone Phosphate sodium/ Decadron		**Solution** 4 and 24 mg/mL w/wo Lidocaine 10 mg/mL, Creatinine 8 mg/mL, Sodium citrate 10 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5 under nitrogen	Water soluble phosphate ester	For IV infusion dilute with saline or dextrose 5%.	IV bolus/ IV infusion/ IM/ Intralesional/ Intra-articular/ Soft tissue

Table VIII (cont.). List of Prodrugs for Parenteral Administration.

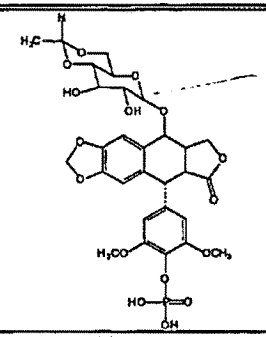
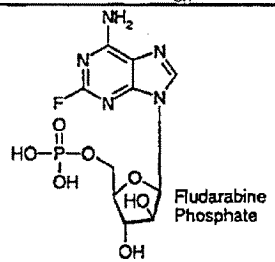
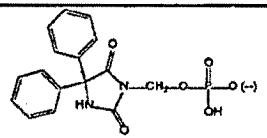
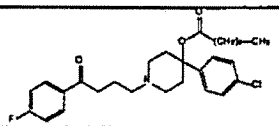
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Etoposide Phosphate/ Etopophos		Lyophilized powder 100-1000 mg, Sodium citrate 32-327 mg/mL, Dextran 40 at 300-3000 mg	Water soluble phosphate ester	Reconstitute with WFI, saline or dextrose 5% to 10-20 mg/mL which is further diluted with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes
Fludarabine Phosphate		Lyophilized powder 50 mg, Mannitol 50 mg pH 7-8	Water soluble phosphate ester	Reconstitute with 2 mL WFI to 25 mg/mL then further diluted with 100-125 mL saline or dextrose 5% to ~ 0.5 mg/mL.	IV infusion over 30 minutes
Fos-phenytoin/ Cerebyx		Solution 75 mg/mL Tromethamine, pH = 8.6-9.0	Water soluble hydroxy-methyl phosphate ester	None for IM. For IV infusion dilute with saline or dextrose 5% to 1.5-25 mg PE/mL.	IM/ IV infusion at ≤ 150 PE/minute
Haloperidol Decanoate/ Haldol decanoate		**Non-aqueous solution** 50-100 mg/mL in **Sesame Oil** Benzyl alcohol 1.2%	Water insoluble deconate ester	None	IM

Table VIII (cont.). List of Prodrugs for Parenteral Administration.

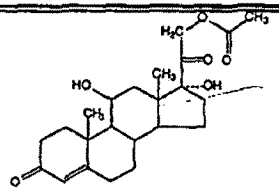
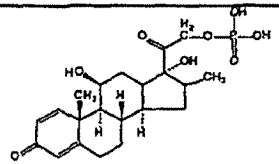
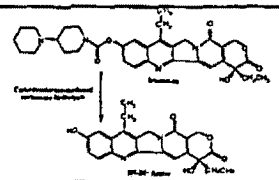
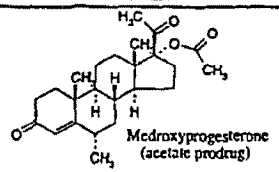
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Hydro-cortisone Acetate/ Hydro-cortone Acetate		**Suspension** 50 mg/mL TWEEN 80 at 4 mg/mL, Sodium carboxymethylcellulose 5 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL/	Water insoluble acetate ester	None	IM/ Intralesional/ Intra-articular
Hydro-cortisone Phosphate sodium/ Hydro-cortone Phosphate		Solution / 50 mg/mL Creatinine 8 mg/mL, Sodium citrate 10 mg/mL, Sodium bisulfite 3.2 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, pH 7.5-8.5	Water soluble phosphate ester	None or dilute with saline or dextrose 5%.	SC/ IM/ IV bolus/ IV infusion
Irinotecan HCl/ Camptosar		Solution 20 mg/mL, Sorbitol 45 mg/mL, Lactic acid 0.9 mg/mL pH 3.0-3.8	Water soluble carbamate	Dilute with dextrose 5% or saline to 0.12-1.1 mg/mL.	IV infusion over 90 minutes
Medroxypro gesterone Acetate/ Depo-Provera	 Medroxyprogesterone (acetate prodrug)	**Suspension** 150-400 mg/mL, PEG 3350: 20-29 mg/mL, TWEEN 80 at 2.4 mg/mL, Sodium chloride: 8.7 mg/mL, Methylparaben: 1.4 mg/mL, Propylparaben: 0.15 mg/mL		None	IM once every 3 months

Table VIII (cont.). List of Prodrugs for Parenteral Administration.

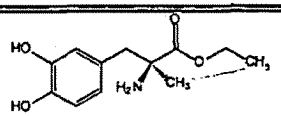
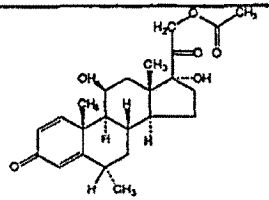
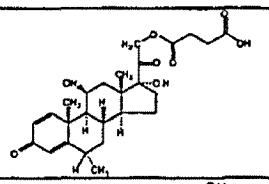
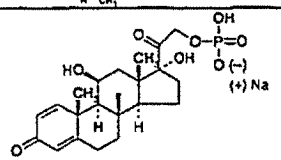
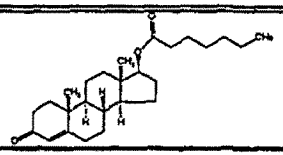
Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Methyl-dopate HCl/ Aldomet Ester HCl		Solution 50 mg/mL Citric acid 5 mg/mL, Sodium bisulfite 3.2 mg/mL, Monothioglycerol 2 mg/mL, EDTA 0.5 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL pH 3-4.2	Ethyl ester	Dilute with dextrose 5% to 10 mg/mL.	IV infusion over 30-60 minutes
Methyl-prednisolone Acetate/ Depo-Medrol		**Suspension** 20-80 mg/mL PEG 3350 3%, TWEEN 80 at 2 mg/mL, Sodium phosphates 2 mg/mL, Benzyl alcohol 9 mg/mL, Sodium chloride (isotonic), pH 3.5-7.0	Water insoluble acetate ester	None	IM/ Intrasynovial/ Soft tissue or Intralesional
Methy-prednisolone Succinate sodium / Solu-Medrol		Lyophilized powder 40-2000 mg Sodium phosphates 18 mg/mL w/wo Lactose 25 mg/mL, Benzyl alcohol 9 mg/mL pH 7-8	Water soluble succinate ester	Reconstitute with WFI to 40-65 mg/mL. For IV infusion further dilute with saline or dextrose 5%.	IM/ IV bolus/ IV infusion
Prednisolone Phosphate sodium/ Hydeltrasol (Not in 1999 PDR as injectable)		Solution 20 mg/mL **Niacinamide 25 mg/mL**, EDTA 0.5 mg/mL, Sodium bisulfite 1 mg/mL, Phenol 5 mg/mL pH 7-8	Water soluble phosphate ester	None or for IV infusion dilute with 50-1000 mL saline or dextrose 5%.	IM/ IV bolus/ IV infusion/ Soft tissue/ Intra-articular/ Intralesional

Table VIII (cont.). List of Prodrugs for Parenteral Administration.

Drug Name/ Marketed Name	Structure	Formulation	Type of prodrug	Preadministration preparation	Route of Administration
Testosterone Enanthate/ Delatestryl		**Non-aqueous solution** 200 mg/mL **Sesame oil,** Chlorobutanol 5 mg/mL	Water insoluble heptanate ester	None	IM

as sodium carboxymethylcellulose at ~5 mg/mL (i.e., dexamethasone acetate), PEG 3350 at 30 mg/mL (i.e., methylprednisolone acetate) or sorbitol at 50% (i.e., triamcinolone hexacetonide).

8. Depots

Sesame oil formulations of oil-soluble drugs provide a sustained-release depot at the injection site that releases drug by diffusion-like uptake of oil. For example, the prodrugs haloperidol deconate and testosterone enanthate are formulated in 100% sesame oil and administered intramuscularly once a month.

9. Liposomes

An exciting new era of the parenteral sciences began with the approval of liposomal products. A liposome is a lipid bilayer and an aqueous-based multilayered spherical drug delivery system where the drug is encapsulated inside the liposome, and is released as the liposome is eroded *in vivo*. A typical liposome formulation contains water with lipid at ~5 mg/mL, an isotonicifier, a pH 5–8 buffer, and with or without cholesterol. These liposomes are injected either by IV infusion or intrathecally. Table X lists the six currently available liposomal products of the four drugs amphotericin B (3 liposome formulations), cytarabine, daunorubicin and doxorubicin. The amphotericin B liposomal products are administered by IV infusion and have an *in vivo* elimination half-life of 40–150 hours. The daunorubicin liposomal formulation has an *in vivo* half-life of 4.4 hours compared to 0.8 hours for the conventional formulation (1, pg. 1970). The cytarabine liposomal formulation, Depocyt, is administered intrathecally once every 2 weeks, while the conventional formulation is given twice per week.

To further increase the *in vivo* circulating times, liposomes can be covalently derivatized with polyethyleneglycol to produce PEGylated or stealth liposomes. The only commercially available PEGylated liposome is doxorubicin in Doxil and is administered by IV infusion and has a half-life of 50–55 hours (1, pg. 2985). The proteins adenosine deaminase (Adagen) and asparginase (Oncaspar) are also available as a PEGylated derivative.

10. Polymeric Microspheres

The era of controlled release using polymeric microspheres began with the approval of the peptide leuprolide as lupron depot. The drug is incorporated into a biocompatible polymer and transformed into lyophilized microspheres during the manufacturing process. The reconstituted microspheres are injected intramuscularly and slowly erode *in vivo*, releasing the drug. In the marketed formulation, leuprolide is in lyophilized microspheres with DL-lactic/glycolic acid copolymer (PLGA), gelatin and mannitol, which is then reconstituted prior to administration to a suspension using an aqueous solution of sodium carboxymethylcellulose, TWEEN 80 and mannitol. The microspheres provide a depot of drug and are administered once every 1–4 months, depending on the dose (3.75 mg/1 month, 30 mg/4 months). One of the leuprolide formulations uses a dual chamber syringe for ease of reconstitution and administration.

A polymeric PLGA microsphere formulation of human growth hormone (Nutropin Depot) finished Phase III clinical trials in 1999 (13). In this formulation, human growth hormone is made into an insoluble complex with zinc, and encapsulated into PLGA microspheres in a non-aqueous cryogenic process (14). The resulting free-flowing powder is reconstituted to a suspension prior to subcutaneous or intramuscular administration.

11. Polymeric Gels

Polymeric gels provide a depot of drug that is released over 1–4 weeks. The era of controlled release using polymeric gels began with the approval of doxycycline hyclate which is available as a 7-day controlled-release system that is a solution upon subgingival administration, but solidifies upon contact with the crevicular fluid. This product is marketed as Atridox® in a Atrigel Delivery System which is a two-syringe set-up where syringe A contains the polymer poly(DL-lactide) dissolved in N-methyl-2-pyrrolidone, and syringe B contains solid doxycycline. Upon coupling the two syringes, the liquid in syringe A is injected into syringe B and repeatedly mixed to complete dissolution, and then the yellow viscous liquid is administered subgingivally.

Local delivery directly into tumors of the anti-tumor cancer drugs fluorouracil and cisplatin, as well a subcutaneous injection of leuprolide are in clinical trials using a polymeric gel formulation.

III. Containers/Vials

Most injectable products are still marketed in traditional vials, ampules and infusion bags. However, there is increased use of more convenient containers such as prefilled syringes, dual chamber syringes and pen-type injectors. Prefilled syringes are especially useful in emergency situations such as in the use of the antithrombotics dalteparin, danaparoid and enoxaparin; the analgesics morphine, hydromorphone, fentanyl, lidocaine and sumatripan; the sedatives lorazepam and propofol; and the antihypertensive labetalol. Dual chamber syringes are used to avoid the usual manipulations involved in reconstitution of a lyophilized powder, and one syringe contains the solid drug while the second syringe contains the liquid diluent, which are mixed prior to administration. Products that use a dual chamber set-up include diltiazem, doxycycline and leuprolide. Pen-type injectors such as NovoPen® with insulin involve a 1–3 mL cartridge that goes into the pen-like delivery device, and the epinephrine autoinjector for intramuscular self-administration.

IV. Future

The future is promising for the formulation sciences, in general, and also for the parenteral formulation sciences. New parenteral achievements will likely include targeted delivery, more sophisticated controlled delivery, novel formulations and new excipients, which may utilize new technologies and be marketed in new devices. Biotechnology proteins and antibodies will likely continue to be at the forefronts of the parenteral sciences. The new and exciting field of gene therapy will likely rely on injectable and

Table IX. List of Suspension Formulations for Parenteral Administration.

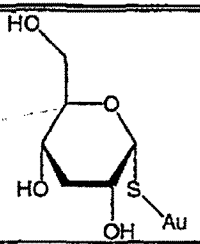
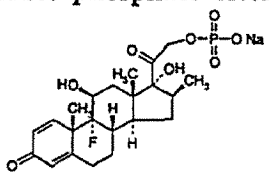
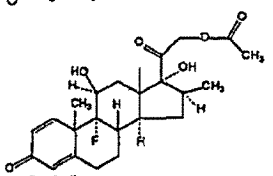
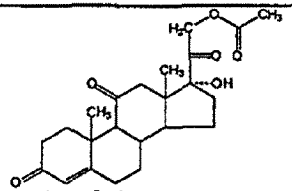
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Aurothio-glucose/ Solganal		50 mg/mL **in sesame oil** Aluminum monostearate 2%, Propylparaben 0.1%	None	**IM (oil)** Prolonged release due to slow absorption
Betametha-sone Phosphate sodium and Betametha-sone Acetate/ Celestone soluspan	**Water soluble phosphate ester prodrug**   **Water insoluble acetate ester prodrug**	Betamethasone phosphate 3 mg/mL, Betamethasone acetate 3 mg/mL, EDTA 0.1 mg/mL, Benzalkonium chloride 0.2 mg/mL, Sodium phosphates 10.5 mg/mL, pH 6.8-7.2	None	IM
Cortisone Acetate/ Cortone	 **Water insoluble ester prodrug**	50 mg/mL, TWEEN 80 at 4 mg/mL, Sodium CMC 5 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM only

Table IX (cont.). List of Suspension Formulations for Parenteral Administration.

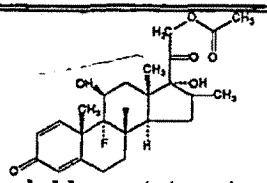
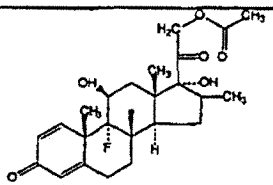
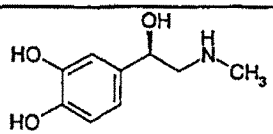
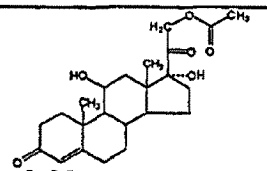
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Dexamethasone Acetate/ Decadron-LA	 **Water insoluble acetate ester prodrug**	8 mg/mL TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM/ Intralesional/ Intra-articular/ Soft tissue
Dexamethasone Acetate/ Dalalone D.P.	 **Water insoluble acetate ester prodrug**	16 mg/mL TWEEN 80 at 0.75 mg/mL, Sodium CMC 5 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM// Intra-articular/ Soft tissue (Not intralesional)
Epinephrine HCl/ Susphrine		5 mg/mL **Glycerin 325 mg/mL, Thioglycolic acid 6.6 mg/mL,** Ascorbic acid 10 mg/mL, Phenol 5 mg/mL,	Shake contents of vial to disperse particles to uniformity.	SC
Hydrocortisone Acetate/ Hydrocortone Acetate	 **Water insoluble acetate ester prodrug**	50 mg/mL TWEEN 80 at 4 mg/mL, Sodium CMC 5 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM/ Intralesional/ Intra-articular

Table IX (cont.). List of Suspension Formulations for Parenteral Administration.

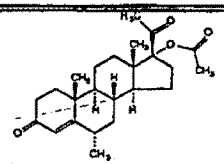
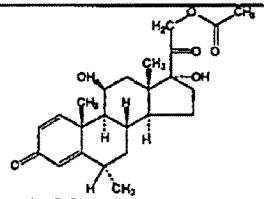
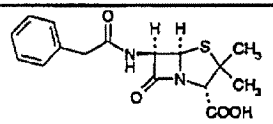
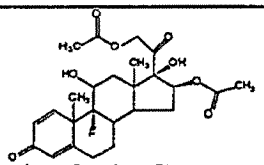
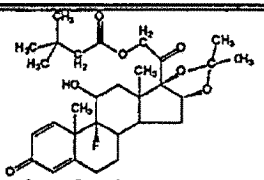
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Medroxyprogesterone Acetate/ Depo-Provera	 **Water insoluble acetate ester prodrug**	150-400 mg/mL, **PEG 3350: 2-3%** TWEEN 80 at 2.4 mg/mL, Sodium chloride 8.7 mg/mL, Methylparaben: 1.4 mg/mL, Propylparaben: 0.15 mg/mL	None	IM once every 3 months
Methyl-prednisolone Acetate/ Depo-Medrol	 **Water insoluble acetate ester prodrug**	20-80 mg/mL **PEG 3350 3%,** TWEEN 80 at 2 mg/mL, Sodium phosphates 2 mg/mL, Benzyl alcohol 9 mg/mL, Sodium chloride (isotonic), pH 3.5-7.0	None	IM/ Intrasynovial/ Soft tissue or Intralesional
Penicillin G benzathine and Penicillin G procaine / Bicillin		150,000-600,000 units each/mL CMC 0.55%, Lecithin 0.5% Povidone 0.1%, Methylparaben 0.1%, Propylparaben 0.01%, Sodium citrate pH 6-8.5	Shake vial before withdrawing the desired dose.	IM
Triamcinolone Diacetate/ Aristocorte	 **Water insoluble diacetate ester prodrug**	20-40 mg/mL PEG 3350 at 3%, TWEEN 80 at 0.2% Sodium chloride 8.5 mg/mL, Benzyl alcohol 9 mg/mL, pH ~ 6	None	IM/ Intra-articular/ Intrasynovial/ Intralesional

Table IX (cont.). List of Suspension Formulations for Parenteral Administration.

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration
Triamcinolone Hexacetonide/ Aristospan	 **Water insoluble ester prodrug**	5-20 mg/mL **Sorbitol 50%,** TWEEN 80 at 0.2-0.4% Benzyl alcohol 9 mg/mL, pH 4.5- 6.5	None	Intra-articular/ Intralesional

CMC = Carboxymethylcellulose

Table X. List of Liposomal Formulated Parenteral Products for Parenteral Administration.

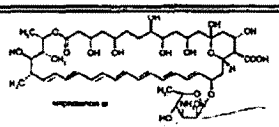
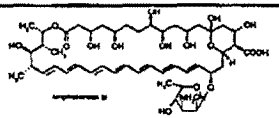
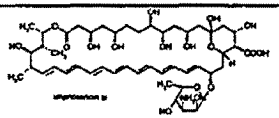
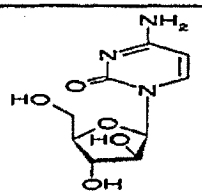
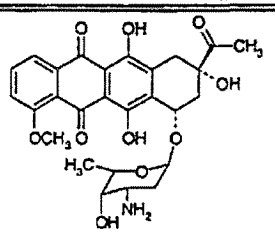
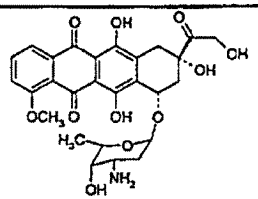
Drug Name/ Marketed Name	Structure	Formulation	Lipid-to-drug molar ratio	Preadministration preparation	Route of Administration
Amphoter-icin B/ Abelcet		**Opaque suspension** 5 mg/mL DMPC 3.4 mg/mL, DMPG 1.5 mg/mL, Sodium chloride 9 mg/mL pH = 5-7	1:1	Dilute to 1-2 mg/mL with 5% dextrose	IV infusion at 2.5 mg/kg/hr
Amphoter-icin B cholesteryl sulfate/ Amphotec		Lyophilized powder 50 -100 mg SCS 2.6 mg/mL, Lactose 95 mg/mL, TRIS 0.56 mg/mL, EDTA 0.037 mg/mL,	1:1	Reconstitute with WFI to a 5 mg/mL **colloidal dispersion,.** Dilute to 0.16 - 0.83 mg/mL with 5% dextrose.	IV infusion at 3-4 mg/kg/hr
Amphoter-icin B/ Ambisome		Lyophilized powder 50 mg HSPC 18 mg/mL, DSPG 7 mg/mL, Cholesterol 4 mg/mL, Alpha tocopherol 0.05 mg/mL, Sucrose 75 mg/mL, Disodium succinate 2 mg/mL pH 5.0-6.0	4:1	Reconstitute with WFI to a 4 mg/mL **translucent suspension,.** Dilute to 1-2 mg/mL with 5% dextrose.	IV infusion at 3-5 mg/kg/hr
Cytarabine (Ara-C)/ DepoCyte		**Suspension Multivesicular Lipid Particle** 5 mg/mL DOPC 5.7 mg/mL, DPPG 1 mg/mL, Cholesterol 4 mg/mL, Sodium chloride 9 mg/mL pH 5.5-8.5	1:1	None	Intrathecal

Table X (cont.). List of Liposomal Formulated Parenteral Products for Parenteral Administration.

Drug Name/ Marketed Name	Structure	Formulation	Lipid-to-drug molar ratio	Preadministration preparation	Route of Administration
Dauno-rubicin Citrate/ DaunoXome		Solution I 2 mg/mL, DSPC: Cholesterol in 2:1 molar ratio	18:1	Dilute 1:1 with dextrose 5% to 1 mg/mL.	IV infusion over 60 minutes
Doxorubicin HCl/ Doxil **(Pegylated stealth liposome)**		**Liposomal dispersion** 2 mg/mL, MPEG-DSPE 3.2 mg/mL, HSPC 9,6 mg/mL, Cholesterol 3.2 mg/mL, Ammonium sulfate 2 mg/mL, Histidine	1:1	Dilute the dose into 250 mL of dextrose 5%.	IV infusion over 30 minutes

DMPC = L-α-dimyristoylphosphatidylcholine

DMPG = L-α-dimyristoylphosphatidylglycerol
DOPC = Dioleoylphosphatidylcholine
DPPG = Dipalmitoylphosphatidylglycerol
DSPC = Distearoylphosphatidylcholine
DSPG = Distearoylphosphatidylglycerol
HSPC = Hydrogenated soy phosphatidylcholine
MPEG-DSPE = N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium
SCS = Sodium cholesteryl sulfate

Table XI. Abbreviations Used in the Compilation	
Abbreviation	Meaning
ACE	angiotensin-converting enzyme
C, G, T (Fomiversen)	C = cytosine G= guanine T= thymine
CHF	congestive heart failure
CMV	Cytomegalovirus
EDTA	ethylenediamine tetraacetic acid
HCl	hydrochloride salt
IM	intramuscular
IP	intraperitoneal
IV	intravenous
LH-RH	leutenizing hormone-releasing hormone
PCI	percutaneous cardiovascular intervention
PDR	Physician's Desk Reference
PEG	polyethyleneglycol
PG	propylene glycol
PSVT	paroxysmal supraventricular tachycardia
SC	subcutaneous
TRIS	tris(hydroxymethyl)aminomethane
TWEEN	polysorbate
WFI	water for injection
w/wo	with or without

solution formulations for delivery of antisense oligonucleotides (15, 16), such as with the anti-sense ophthalmic product fomiversen (Vitravene). In general, formulation approaches along with drug design will be the means to achieve optimal drug delivery based upon therapeutic needs.

New approaches could include nanoparticles (17), submicron solid particles coated with either natural or semisynthetic phospholipids (18), mixed-micelles, microemulsions for injection (19), and soluble self-assembled block copolymers to either solubilize drug in a micelle-like structure [PEO-b-PAA-DOX, poly(ethylene oxide)-block-poly(aspartic acid)-doxorubicin] or covalently bind drug (20). "Smart" controlled-release systems that deliver drug when needed could be the next generation in controlled release, including pulsatile delivery to mimic human circadian rhythms or normal hormone production. The release of drug could be triggered by timed events or more sophisticated means, such as a chemical stimulus, photosensors, blood pressure sensors, or some type of biofeedback mechanism. New excipients will likely be approved, such as sulfobutyl ether β-cyclodextrin, tetraglycol, triglyme, transcutol, 2-pyrrolidone (Soluphor® P), glycerol formal, Solutol HS-15, and poloxamers which will expand the number of formulation additives available to the formulation scientist.

Devices such as needle-free injectors (already in use with vaccines) for both solutions and solids (21) could revolutionize the manner in which injectable drugs are administered. The increased emphasis on home health care will likely result in home infusion devices and set-ups such as battery operated and/or pocket-sized infusion pumps. We are likely to continue to see more applications of convenient injection devices, prefilled syringes, dual chamber devices and ready-to-use solutions.

Advanced technologies will likely be used in commercial production of future parenteral products; for example, the use of nanoparticles for injection of water-insoluble drugs. Supercritical fluid processing to form spherical microparticles (22) and perhaps a designed distribution of particle size has tremendous potential in future formulations and pharmaceutical manufacturing.

Combinations of novel formulations and novel delivery systems that are in active research (23) will certainly be developed. One can imagine the many combinations of needle-free injection of solutions or solids, controlled-release systems, "stealth" carriers, targeted delivery, vaccines, gene therapy, antibodies and specially designed small molecules. Yes, as the parenteral sciences continue to mature, future products will be science fiction come true!

Notes on the Compilation

A few comments on the compilation are in order to help the reader understand the table format, chemical structures, some occasional additional information, highlighted portions, and abbreviations.

1) The order of lines within the formulation box is:
   a) Solution or lyophilized powder
   b) Drug concentration or amount (i.e., mg/mL, mg, units/mL, etc.)
   c) Excipients and concentration or amount (i.e., mg/mL, %, mg, etc.)
      —organic solvent(s)
      —suspending agent(s)
      —bulking agent(s)
      —isotonicifier(s)

—preservative(s)
—buffer
d) pH

2) Some drugs have the pKa listed, but this is not comprehensive and is added for informative purposes.
3) The chemical structures are drawn in most instances as the neutral species even though the market product may be a salt form.
4) In the drug name, the counter ion is in lower case, but a covalently bound prodrug moiety is capitalized.
5) Some entries were not found in the 1999 PDR at all or not as injectables, but were found in other references. In these cases "(Not in 1999 PDR)" is added under the marketed name.
6) Various portions of some entries are highlighted in **bold** typeface, in order to help the reader clearly notice key formulation aspect(s).
7) Some drugs are marketed in multiple formulations, and in these cases the formulations are numbered.
8) There are some peptide entries to highlight new formulation approaches.
9) Abbreviations used herein (Table XI).

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19. C. V. Corswant, P. Thorén, and S. Engström, "Triglyceride-based microemulsion for intravenous administration of sparingly soluble substances," *Journal of Pharmaceutical Sciences*, **87**, 200 (1998).
20. G. S. Kwon and T. Okano, "Soluble self-assembled block copolymers for drug delivery," *Pharmaceutical Research*, **16**, 597 (1999).
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22. R. Ghaderi, P. Artursson, and J. Calfors, "Preparation of biodegradable microparticles using solution-enhanced dispersion by supercritical fluids (SEDS)," *Pharmaceutical Research*, **16**, 676 (1999).
23. R. D. Sinisterra, V. P. Shastri, R. Najjar, and R. Langer, "Encapsulation and release of rhodium(II) citrate and its association complex with hydroxypropyl-b-cyclodextrin from biodegradable polymer microspheres," *Journal of Pharmaceutical Sciences.*, **88**, 574 (1999).

ATTACHMENT F - COMPILATION

TAB 13

REVIEW ARTICLE

Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999) Part II

ROBERT G. STRICKLEY

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[Editor's Note: This review article on Injectable Products is being published in three parts. The introduction and summary appeared in the November/December 1999 issue. The final Part will appear in the March/April 2000 issue of the *Journal*.]

Injectable Products

Sources of Information:

1. Physician's Desk Reference, 53rd ed., Medical Economics Company, Inc., Montvale, NJ, 1999.
2. Lawrence A. Trissel, Handbook on Injectable Drugs, 10th ed., American Society of Health-System Pharmacists, Inc., Bethesda, MD, 1998.
3. Lynn D. Phillips and Merrily A. Kuhn, Manual of IV Medications, 2nd ed., Lippincott-Raven Publishers, Philadelphia, PA, 1999.
4. D. A. Hussar, "New drugs of 1998," *Journal of the American Pharmaceutical Association*, **39**, 151 (1999).
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6. Food and Drug Administration internet website, http://www.fda.gov/, See human drugs, what's new, new and generics approvals.

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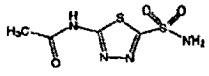
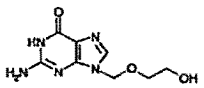
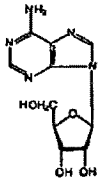
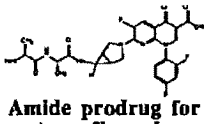
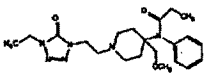
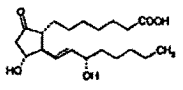
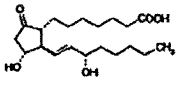
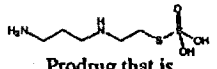
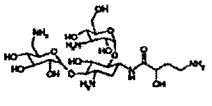
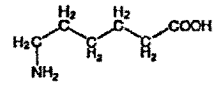
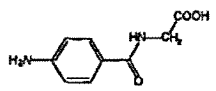
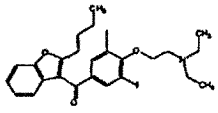
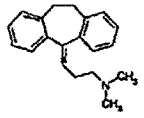
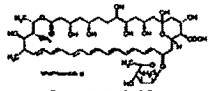
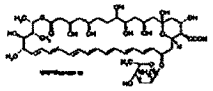
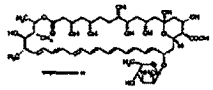
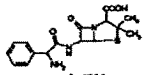
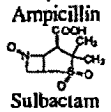
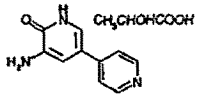
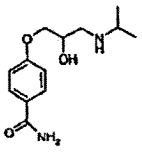
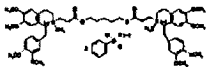
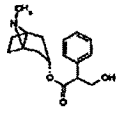
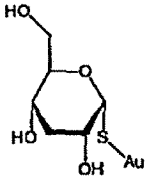
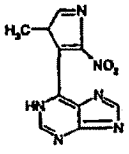
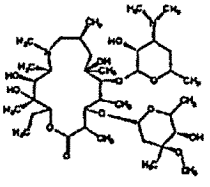
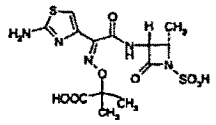
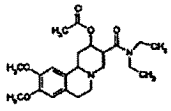
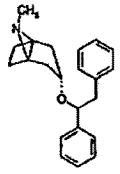
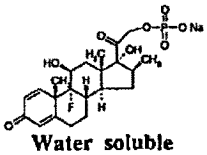
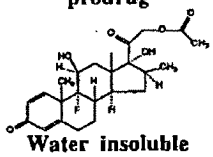
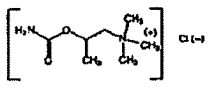
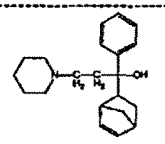
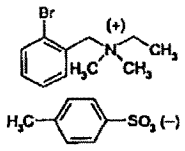
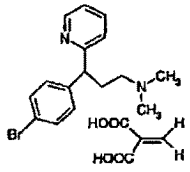
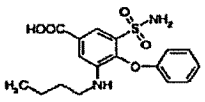
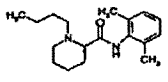
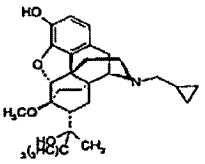
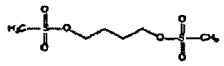
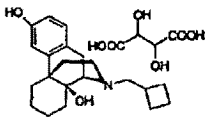
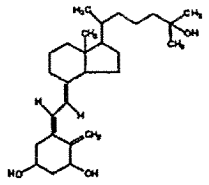
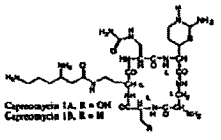
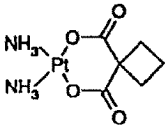
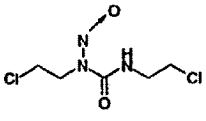
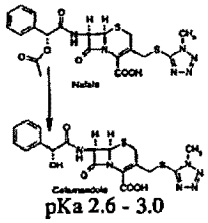
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Acetazolamide sodium/ Diamox	 pKa = 7.2	Solution 500 mg pH 9.2	Constitute with 5 mL WFI to ≤ 100 mg/mL.	IV bolus/ IV infusion; IM but may be painful due to alkaline pH	Lederle, Antiglaucoma; diuretic in treatment of mountain sickness
Acyclovir sodium/ Zovirax	 pKa ~ 10	Lyophilized powder 500 - 1000 mg **pH 10.5 - 11.6**	Reconstitute with WFI to 50 mg/mL; Dilute with dextrose 5% or saline to < 7 mg/mL.	IV infusion over 1 hour	Glaxo Wellcome, Antiviral
Adenosine/ Adenocard IV (bolus), Adenoscan (IV infusion)		Solution 3 mg/mL, Sodium chloride 9 mg/mL, pH 4.5-7.5	None	IV bolus/ IV infusion at 0.14 mg/kg/min for 6 minutes	Fujisawa, Conversion to sinus rhythm of PSVT (bolus). Adjunct for thallium-201 myocardial perfusion scintigraphy (infusion)
Alatrofloxacin mesylate/ Trovan	 **Amide prodrug for trovafloxacin**	Solution 5 mg/mL pH 3.4-4.3	Dilute with dextrose 5% to 1-2 mg/mL. (potentially incompatible with saline and lactated Ringer's)	IV Infusion over 60 minutes	Pfizer, Antibiotic
Alfentanil HCl/ Alfenta		Solution 0.5 mg/mL, Sodium chloride (isotonic) pH 4-6	None for bolus. For IV infusion dilute with saline, dextrose 5%, or lactated Ringer's to 0.025-0.080 mg/mL.	IV bolus/ IV infusion at 0.5-3.0 ug/kg/min	Taylor, Analgesic
Alprostadil (prostaglandinE1/ Caverject		Lyophilized powder 6-46 ug Lactose 172 mg, Sodium citrate 47 mg, Benzyl alcohol 8.4 mg	Reconstitute with 1.2 mL water preserved with benzyl alcohol 0.95% w/v. (~ 0.5-1.1 ug is lost due to adsorption to the vial and syringe.)	Intra-cavernosal	Pharmacia & Upjohn, Erectile dysfunction
Alprostadil **alfadex** (prostaglandinE1/ Edex	 complexed with **α-cyclodextrin**	Lyophilized powder 6-50 ug complexed with 200-1610 ug of **α-cyclodextrin** Lactose 56 mg pH 4-8	Reconstitute with 1.2 mL saline.	Intra-cavernosal	Schwarz Pharma, Erectile dysfunction
Amifostine/ Ethyol	 Prodrug that is dephosphorylated by alkaline phosphatase to active free thiol	Lyophilized powder 500 mg	Reconstitute with saline to 50 mg/mL (stable at room temperature for 5 hours). May be further diluted with saline to 5 mg/mL.	IV infusion over 15-30 minutes	Alza, Antineoplastic adjuvant [cytoprotective and radioprotective (reduces toxic effect of cisplatin)]
Amikacin sulfate		Solution 250 mg/mL, Sodium metabisulfite 0.66% Sodium citrate 2.8 % pH 3.5 - 5.5	For IV infusion dilute with saline or dextrose 5% to 2.5-5 mg/mL.	IM/ IV Infusion over 30 - 60 minutes	Elkins-Sinn, Antibiotic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Aminocaproic acid/ Amicar		Solution 250 mg/mL, Benzyl alcohol 0.9% pH 6.8	Dilute with saline or dextrose 5% to ~ 15-20 mg/mL.	IV infusion at 4 grams/hour	Immunex, Enhancing hemostasis when fibrinolysis contributes to bleeding
Amino-hippurate sodium "PAH"		Solution 200 mg/mL	None	IV infusion at 6-10 mg/kg and 10-24 mg/min	Merck, Measures effective renal plasma flow
Amiodarone HCL/ Cordarone		Solution 50 mg/mL, **TWEEN 80 at 10%,** Benzyl alcohol 2% pH 4.1	Dilute with dextrose 5% to < 2 mg/mL.	IV infusion at 5-15 mg/min dextrose	Wyeth-Ayerst, Antiarrhythmic, Antianginal
Amitriptyline HCl/ Elavil		Solution 10 mg/mL, Dextrose 44 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL pH 4-6	None	IM	Zeneca, Antidepressant
Amphoter-icin B/ Abelcet	 complexed 1:1 (drug-to-lipid molar ratio) with [L-α-dimyristoylphosphati-dylcholine (DMPC) and L-α-dimyristoylphosphati-dylglycerol (DMPG) in a 7:3 mole ratio]	**Liposome opaque suspension** 5 mg/mL DMPC 3.4 mg/mL, DMPG 1.5 mg/mL, Sodium chloride 9 mg/mL pH = 5-7	Dilute with dextrose 5% to 1-2 mg/mL.	IV infusion at 2.5 mg/kg/hr	The Liposome Company, Antifungal
Amphoter-icin B cholesteryl sulfate/ Amphotec	 complexed 1:1 molar with cholesteryl sulfate	Lyophilized powder 50 -100 mg After reconstitution with WFI to a 5 mg/mL **colloidal liposomal dispersion,** Sodium cholesteryl sulfate 2.6 mg/mL, EDTA 0.037 mg/mL, Lactose 95 mg/mL, TRIS 0.56 mg/mL	Reconstitute with WFI to 5 mg/mL. Dilute with dextrose 5% to 0.16 - 0.83 mg/mL.	IV infusion at 3-4 mg/kg/hr	Sequus (Purchased by AlzA), Antifungal
Amphoter-icin B/ Ambisome		Lyophilized powder 50 mg After reconstitution with WFI to a 4 mg/mL **translucent liposomal suspension,** Hydrogenated soy phosphatidylcholine 18 mg/mL, Distearoylphosphatidylglycerol 7 mg/mL, Cholesterol 4 mg/mL, Alpha tocopherol 0.05 mg/mL, Sucrose 75 mg/mL, Disodium succinate 2 mg/mL pH 5.0-6.0	Reconstitute with WFI to 4 mg/mL. Dilute with dextrose 5% to 1-2 mg/mL.	IV infusion at 3-5 mg/kg/hr	Fugisawa (developed by NeXstar, now Gilead), Antifungal

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Ampicillin and Sulbactam sodium/ Unasyn	 Ampicillin  Sulbactam	Powder 1-2 grams (ampicillin), 0.5-1.0 grams (sulbactam) pH = 8-10	Reconstitute with WFI to 250 mg/mL ampicillin and 125 mg/mL sulbactam. For IV dilute with saline or dextrose 5% to 3-45 mg/mL.	IM/ IV infusion over 10-30 minutes	Pfizer, Antibacterial (ampicillin)
Amrinone lactate/ Inocor (not in 1999 PDR)		Solution 5 mg/mL, Sodium metabisulfite 0.25 mg/mL, pH = 3-4	None or dilute with saline or half-saline to 1-3 mg/mL.	Slow IV bolus over 2-3 minutes IV infusion at 5-10 ug/kg/min	Sanofi Winthrop, Inotropic and vasodilator (short term management of CHF)
Atenolol/ Tenormin		Solution 0.5 mg/mL, Sodium chloride (to isotonic), Citric acid to pH = 5.5 - 6.2	None, or dilution with saline or dextrose 5%.	IV infusion at 1 mg/min	Zeneca, Antihypertensive and treatment of acute myocardial infarction
Atracurium besylate/ Tracrium		Solution 10 mg/mL w/wo Benzyl alcohol 0.9% pH = 3.2-3.6 (benzene sulfonic acid)	None for IV bolus For IV infusion dilute with saline or dextrose 5% to 0.2-0.5 mg/mL.	IV bolus/ IV infusion at 5-13 ug/kg/min	Glaxo Wellcome, General anesthesia (Skeletal muscle relaxant)
Atrophine sulfate		Solution 0.1-1.0 mg/mL, Sodium chloride 9 mg/mL, w/wo Benzyl alcohol 1.5% pH 3-6	None	SC/ IM/ IV bolus	Elkins-Sinn, Astra, and Baxter, Anticholinergic, Antispasmodic
Aurothio-glucose/ Solganal		**Suspension** 50 mg/mL **in sesame oil** Aluminum monostearate 2%, Propylparaben 0.1%	None	**IM (oil)** Prolonged release due to slow absorption	Schering Corp., Antirheumatic
Azathioprine sodium/ Imuran		Lyophilized power 100 mg **pH = 9.8-11**	Reconstitute with 10 mL WFI. For IV infusion dilute with saline or dextrose 5%.	IV bolus/ IV Infusion	Glaxo Wellcome, Immuno-suppressive anti-metabolite; management of severe rheumatoid arthritis
Azithromy-cin/ Zithromax		Lyophilized powder, 500 mg, Citric acid 414 mg	Reconstitute with 5 mL WFI, and dilute to 1-2 mg/mL with saline, dextrose 5%, or lactated Ringer's.	IV infusion of 500 mg at 1 mg/mL over 3 hours, or 2 mg/mL over 1 hour	Pfizer, Antibiotic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Aztreonam/ Azactam		1) Lyophilized powder 0.5-2 g, L-arginine 780mg/gram aztreonam pH = 4.5-7.5 2) Frozen Solution 20-40 mg/mL Lactose 14-34 mg/mL, Arginine 16-32 mg/mL pH 4.5-7.5	For IM reconstitute with at least 3 mL WFI or saline to ~ 100-500 mg/mL. For IV bolus reconstitute with WFI to 50-200 mg/mL. For IV infusion reconstitute with 3 mL WFI, then dilute with saline, dextrose 5%, lactated Ringer's to ≤ 20 mg/mL.	IM/ IV bolus/ IV Infusion/	BMS, Antibiotic
Benzquinamide (Not in 1999 PDR)		Powder 50 mg pH = 3-4	Reconstitute with WFI to 25 mg/mL.	IM/ IV infusion	Pfizer, Prevent nausea with surgery anesthesia
Benztropine mesylate/ Cogentin		Solution 1 mg/mL, Sodium chloride 9 mg/mL pH = 5-8	None	IM/ (IV bolus is alright, but has no advantage over IM)	Merck, Anticholinergic used in psychotic patients with acute dystonic reactions, and in Parkinson's disease
Betamethasone Phosphate sodium and Betamethasone Acetate/ Celestone soluspan	 **Water soluble phosphate ester prodrug**  **Water insoluble acetate ester prodrug**	**Suspension** Betamethasone sodium phosphate 3 mg/mL, Betamethasone acetate 3 mg/mL, Sodium phosphate dibasic 7.1 mg/mL, Sodium phosphate monobasic 3.4 mg/mL, EDTA 0.1 mg/mL, Benzalkonium chloride 0.2 mg/mL, pH 6.8-7.2	None	IM	Schering, Anti-inflammatory and for allergies
Bethanechol chloride/ Urecholine		Solution 5.1 mg/mL, pH neutral	None	SC	Merck, Cholinergic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Biperidan Lactate/ Akineton		Solution 5 mg/mL Sodium lactate 1.4%	None	IV/ IM	Knoll, Parkinson's Disease
Bretylium tosylate/ Bretylol		Solution 50 mg/mL pH 4.5-7	None for IV bolus or IM. For IV infusion dilute with saline, dextrose 5%, or lactated Ringer's to 10 mg/mL.	IM/ IV bolus/ IV infusion at 1-2 mg/min	Astra, Antidysrhythmic
Brom-pheniramine maleate (Liquid formulation not in 1999 PDR)		Solution 10 mg/mL, Methylparaben 0.18%, Propylparaben 0.02%, pH = 6.7-7.1	None for IM/SC/IV bolus. For IV infusion dilute with saline to 1 mg/mL.	SC/ IM/ IV bolus/ IV infusion/	Muro, Antihistamine
Bumetanide/ Bumex		Solution 0.25 mg/mL, Sodium chloride 8.5 mg/mL, Benzyl alcohol 10 mg/mL, EDTA 0.1 mg/mL, Ammonium acetate 4 mg/mL, pH 6.8-7.8	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus over 1-2 minutes/ IV infusion at 1 mg/hr	Baxter, Diuretic
Bupivacaine HCl/ Sensorcaine	 pKa = 8.1	Solution 2.5-7.5 mg/mL Sodium chloride to isotonic, w/wo Epinephrine 9 ug/mL, Sodium metabisulfite 0.5 mg/mL, Methylparaben 1 mg/mL, Citric acid 0.2 mg/mL, pH 4-6.5	None	Epidural/ Spinal/ Sympathetic nerve/ Catheter into the area being anesthetized,~ 175-225 mg/ (not IV)	Astra, Local anesthesia
Buprenor-phine HCl (30-times more potent than morphine)/ Buprenex		Solution 0.3 mg/mL, Dextrose 50 mg/mL pH 3.5-5.5	None or dilute with saline, dextrose 5%, lactated Ringer's	Deep IM/ IV bolus over 2 minutes.	Reckitt-Coleman, Analgesic
Busulfan/ Busulfex		Solution 6 mg/mL **PEG 400 at 67% N, N-dimethylacetamide (DMA) 33%,**	Dilute with saline or dextrose 5% to 0.6 mg/mL.	IV infusion	Orphan Medical, Neoplastic
Butorphanol tartrate/ Stadol (Injectable not in 1999 PDR, the only product is a nasal formulation.)		**Injectable solution:** 1-2 mg/mL Sodium chloride 6.4 mg/mL Citrate buffer 0.045M pH 3-5.5. **Nasal spray solution:** 10 mg/mL, Sodium chloride, Citric acid, Benzethonium chloride, pH 5.0.	None	Nasal Spray (1 spray is ~ 1 mg in 0.1 mL)/ IM/ IV bolus (1-4 mg)	BMS, Analgesic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Calcitonin - Salmon, Miacalcin	Polypeptide hormone 32 amino-acids (H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2)	Solution 200 I.U./mL, Phenol 5 mg/mL, Sodium chloride 7.5 mg/mL, Acetate buffer pH ~ 4	None	IM/ SC/ also Nasal spray of 2000 I.U./mL, and one spray contains 0.1 mL or 200 I.U.	Novartis, Treatment of postmenopausal osteoporosis; Paget's disease, and hypercalcemia
Calcitriol/ Calcijex		Solution 1-2 ug/mL, **TWEEN 20 at 4 mg/mL, Sodium ascorbate 10 mg/mL,** Sodium chloride 1.5 mg/mL, EDTA 1.1 mg/mL, Sodium phosphates 9.2 mg/mL, pH 6.5-8.0	None	IV bolus	Abbott, Management of hypocalcemia in patients undergoing chronic renal dialysis
Capreomycin sulfate/ Capastat		Powder 1000 mg	Reconstitute with 2 mL WFI or saline to 500 mg/mL (~ 3 minutes to dissolve). For IM no dilution, but may reconstitute with less water to 200-350 mg/mL For IV infusion dilute into 100 mL saline.	IM/ IV infusion over 60 minutes	Dura, Antibiotic
Carboplatin/ Paraplatin		Powder 50-450 mg, Mannitol equal mass as carboplatin. pH 5-7	Reconstitute with WFI, saline or dextrose 5% to 10 mg/mL. May be further diluted to 0.5 mg/mL with saline or dextrose 5%.	IV infusion of at least 15 minutes using 0.5-10 mg/mL.	BMS, Antineoplastic
Carmustine/ BiCNU		Lyophilized solid 100 mg pH 5-6	**Reconstitute with supplied 3 mL of ethanol,** then further dilute with 27 mL WFI to a final **10% ethanol.**	IV infusion over 1-2 hours, 150-200 mg/m^2	BMS, Antineoplastic
Cefamandole /Mandol (Formate ester **prodrug** - rapid hydrolysis after dissolution)	 pKa 2.6 - 3.0	Solid 1-10 g Sodium carbonate 63 mg/gram cefamandole, pH 6-8.5	Reconstitute with WFI, saline or dextrose 5% to 100-285 mg/mL.	IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes	Lilly, Antibacterial

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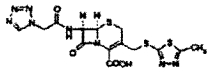
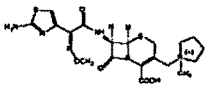
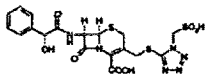
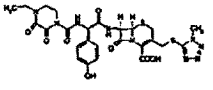
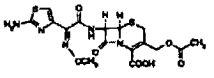
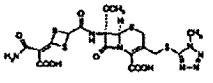
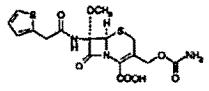
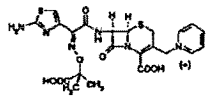
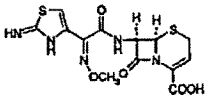
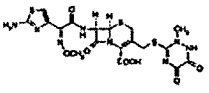
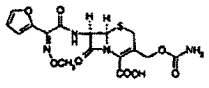
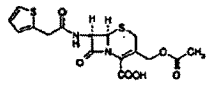
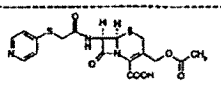
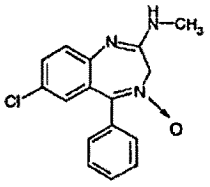
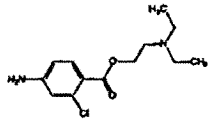
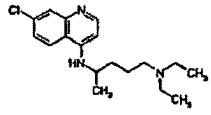
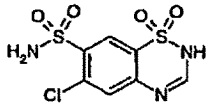
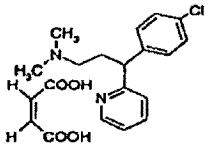
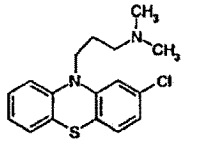
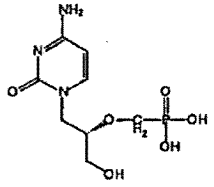
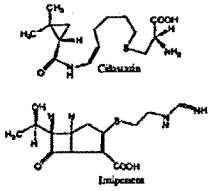
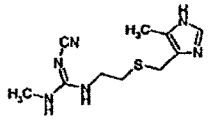
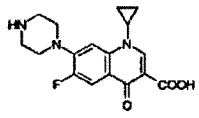
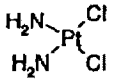
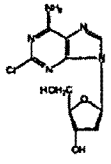
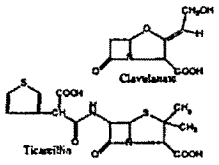
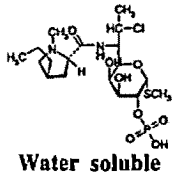
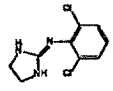
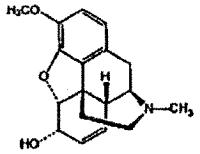
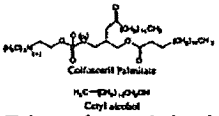
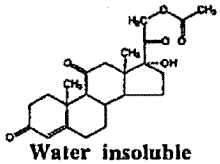
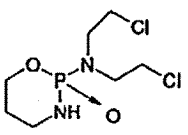
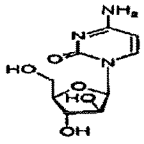
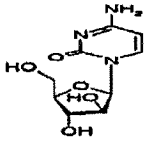
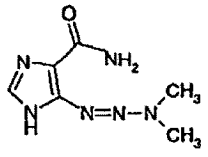
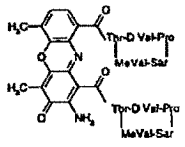
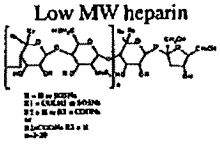
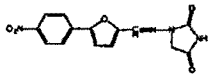
Cefazolin sodium/ Ancef, Kefzol		1) Lyophilized powder 0.5-10 g pH 4.5 - 6. 2) Frozen solution 10-20 mg/mL, Dextrose ~ 40-48 mg/mL pH 4.5-7.	Reconstitute with WFI, or saline to 225-330 mg/mL for IM, and dilute with WFI. to ~ 100 mg/mL for IV bolus, and dilute with saline, dextrose or lactated Ringer's to 10 mg/mL for IV infusion	IM/ IV bolus over 3-5 minutes/ IV infusion	Smith-Kline Beecham and, Lilly, Antibiotic
Cefepime HCl/ Maxipime		Solid mixture 0.5-2 g, L-Arginine 725 mg/g cefepime pH 4.0-6.0	Reconstitute with saline, dextrose 5% or lactated Ringer's to 280 mg/mL for IM, 100-160 mg/mL for IV bolus, 20-40 mg/mL for IV infusion.	IM/ IV bolus over 3-5 minutes/ IV infusion over 30 minutes	BMS, Antibiotic
Cefonicid sodium/ Monocid		Lyophilized powder 0.5-1 g, pH 3.5 - 6.5	Reconstitute with WFI to 225-325 mg/mL for IM and IV bolus, and dilute with saline, dextrose 5% or lactated Ringer's to 10 mg/mL for IV infusion.	IM/ IV bolus over 3-5 minutes/ IV infusion	Smith-Kline Beecham, Antibiotic
Cefopera-zone sodium/ Cefobid		1) Crystalline powder 0.5-1 g, pH 4.5 - 6. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 36-46 mg/mL pH 4.5-7.	Reconstitute with saline or dextrose 5% to 280 mg/mL for IV bolus. Dilute with lidocaine 2% to ~ 200 mg/mL for IM. Dilute with saline, dextrose 5% or lactated Ringer's to 2-25 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes	Pfizer, Antibiotic
Cefotaxime sodium/ Claforan		1) Powder 0.5-2 g, pH 4.5 - 6. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 14-34 mg/mL, Sodium citrate pH 5-7.5	Reconstitute with WFI to 230-330 mg/mL for IM, 50-180 mg/mL for IV bolus, and dilute with saline or dextrose to 10 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over 15-30 minutes	Hoechst Marion Roussel, Antibiotic
Cefotetan disodium/ Cefotan		1) Powder 1-10 g pH 4.5-6.5. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 22-38 mg/mL, Sodium bicarbonate pH 4-6.5	For IM, reconstitute with WFI, saline, 0.5% or 1% lidocaine to 400-500 mg/mL. For IV, reconstitute with WFI to 95-180 mg/mL, and dilute with saline or dextrose 5% to 10 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over 20-60 minutes	Zeneca, Antibiotic

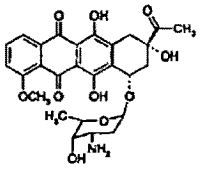
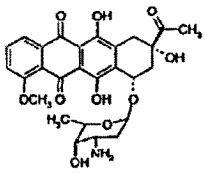
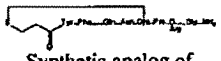
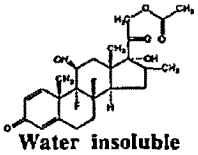
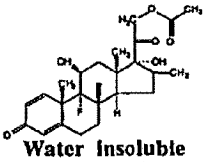
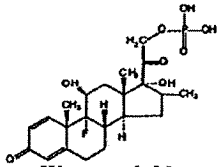
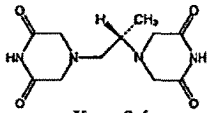
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cefoxitin sodium/ Mefoxin		1) Powder 1-10 g pH 4.2-7.0. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 22-40 mg/mL, Sodium bicarbonate pH 6.5	Reconstitute with WFI to 100-200 mg/mL for IV bolus. For IV infusion reconstitute with saline or dextrose 5% to 100 mg/mL, then dilute to 10 mg/mL	IV bolus over 3-5 minutes/ IV infusion over ~ 30 minutes	Merck, Antibiotic
Ceftazidime/ (Ceptaz, Fortaz, Tazidime, Tazicef)		1) Powder w/wo Sodium carbonate at 118 mg/g ceftazidime, w/wo L-Arginine at 349 mg/gram ceftazidime pH 5-7. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 50 mg/mL, Sodium bicarbonate pH 4-6.5	For IM, reconstitute with WFI, saline, 0.5% or 1% lidocaine to 250 mg/mL. For IV, reconstitute with WFI to 90-170 mg/mL, and dilute with saline or dextrose 5%. to 10-40 mg/mL for IV infusion.	Deep IM/ IV bolus over 3-5 minutes/ IV infusion over ~ 30-60 minutes	Glaxo Wellcome, Lilly and, SmithKline Beecham, Antibiotic
Ceftizoxime sodium/ Cefizox		Crystalline powder 0.5-2 g pH = 6-8	Reconstitute with WFI to 270 mg/mL for IM, 95 mg/mL for IV bolus, and dilute with IV fluids to 10-40 mg/mL for IV infusion.	Deep IM/ IV over 3-5 minutes/ IV Infusion	Fujisawa, Antibiotic
Ceftriaxone sodium/ Rocephin		1) Crystalline powder 0.25-10 g, pH = 6-8. 2) Frozen solution 20-40 mg/mL, Dextrose ~ 24-38 mg/mL, pH 6.7	For IM, reconstitute with WFI, saline, dextrose 5% or lidocaine 1% to 250 mg/mL. For IV infusion, reconstitute with WFI to 100 mg/mL, then dilute with saline or dextrose 5% to 10-40 mg/mL.	Deep IM/ IV Infusion over 30 minutes	Roche, Antibiotic
Cefuroxime, sodium/ Zinacef		1) Crystalline powder 0.75-7.5 g, pH = 6-8.5. 2) Frozen solution 15-30 mg/mL, Dextrose ~ 28 mg/mL, Sodium citrate 60-120 mg/mL pH 5-7.5	Reconstitute with WFI to 220 mg/mL for IM, and 90 mg/mL for IV bolus. For IV infusion, reconstitute with saline or dextrose 5% to 7.5-15 mg/mL.	Deep IM/ IV over 3-5 minutes/ IV Infusion over 15-60 minutes	Glaxo Wellcome, Antibiotic
Cephalothin sodium/ Keflin Neutral (Not in 1999 PDR)		1) Powder 1-20 g, Sodium carbonate 30 mg/gram cephalothin pH = 6-8.5 2) Frozen solution 20-40 mg/mL, Dextrose ~ 50 mg/mL, Sodium bicarbonate pH = 6-8.5	Reconstitute with saline or dextrose 5% to 250 mg/mL for IM, 100 mg/mL for IV, and 20-40 mg/mL for IV infusion.	Deep IM/ IV over 3-5 minutes/ IV infusion	Lilly, Antibiotic

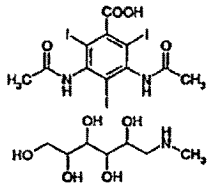
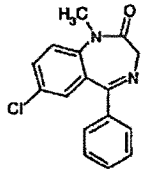
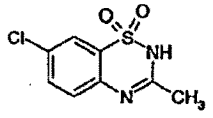
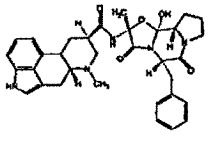
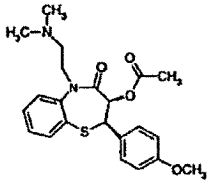
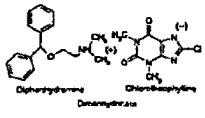
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cephapirin sodium/ Cefadyl (Not in 1999 PDR)		Powder 0.5-20 g, pH = 6-8.	Reconstitute with saline or dextrose 5% to 500 mg/mL for IM, 50-200 mg/mL for IV, and 100 mg/mL for IV infusion.	Deep IM/ IV over 3-5 minutes/ IV infusion	Apothecon, Antibiotic
Chlordiaz-epoxide HCL/ Librium		Powder 100 mg, Supplied diluent: PG 20% TWEEN 80 at 4%, Benzyl alcohol 1.5%, Maleic acid 1.6% pH = 3	Reconstitute with supplied diluent to 50 mg/mL for IM. Reconstitute with saline or WFI to 20 mg/mL for IV bolus.	IM/ Slow IV bolus over 1 minute	ICN, Tranquilizer
Chloro-procaine HCl/ Nesacaine		Solution 10-30 mg/mL Sodium chloride 3.3-6.7 mg/mL, w/wo EDTA 0.1 mg/mL, w/wo Methylparaben 1 mg/mL, pH 2.7-4.0	None	Single injection or continuously through an indwelling catheter.	Astra, Local anesthetic
Chloroquine HCl/ Aralen		Solution, 50 mg/mL pH 5.5-6.5	None	IM	Sanofi Winthrop, Antimalaria and antiamebic
Chloro-thiazide sodium/ Diuril		Lyophilized powder 500 mg, Mannitol 250 mg, Thimerasol 0.4 mg, pH 9.2-10	Reconstitute with 18 mL WFI to 28 mg/mL.	IV/ IV Infusion	Merck, Diuretic and hypertensive
Chlorphenir-amine maleate/ Chlor-trimeton (Not in 1999 PDR as injectable)		Solution, 10-100 mg/mL pH 4-5.2	None	IV (not the 100 mg/mL)/ SC/ IM	Schering, Antihistamine
Chlorproma-zine HCl/ Thorazine		Solution 25 mg/mL, Sodium chloride 6 mg/mL, Sodium bisulfite 1 mg/mL, Sodium sulfite 1 mg/mL, w/wo benzyl alcohol 2%, Ascorbic acid 2 mg/mL, pH 3-5	None for IM. Dilute with saline to 1 mg/mL for IV.	Deep IM in buttock/ IV bolus at 0.5-1 mg/minute	Smith-Kline Beecham, Antipsychotic, antiemetic (nausea), tranquilizer

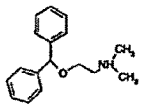
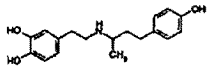
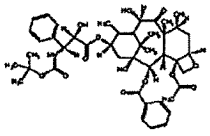
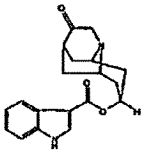
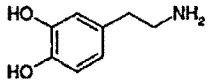
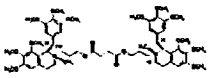
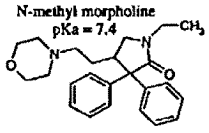
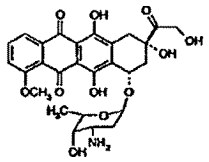
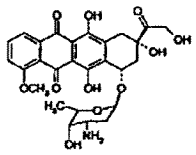
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cidofovir/ Vistide		Solution 75 mg/mL, pH 7.4	Dilute into 100 mL saline to ~ 3-5 mg/mL.	IV infusion at 5 mg/kg over 1 hour. Required predose of 2 grams probenecid orally (reduces renal clearance by blocking active renal tubular secretion).	Gilead, Antiviral treatment of cytomegalovirus in AIDS patients
Cilastatin (inhibitor of renal dipeptidase, dehydro-peptidase I) and Imipenam/ Primaxin		Powder 500-750 mg each, Sodium carbonate 10-20 mg (IV), pH 6.5-7.5	IM: Reconstitute with lidocaine 1% to 250 mg/mL suspension. IV: Reconstitute with 100 mL saline or dextrose then diluted with 100 mL saline or dextrose to 2.5-4 mg/mL solution	IM/ IV infusion	Merck, Antibiotic treatment of serious infections
Cimetidine HCl/ Tagamet		1) Solution 150 mg/mL Phenol 5 mg/mL pH 4-6. 2) Infusion solution 6 mg/mL Sodium chloride 9 mg/mL.	None for IM. Dilute with saline, dextrose 5% or lactated Ringer's to 15 mg/mL for IV bolus and 6 mg/mL for IV infusion.	IM/ Slow IV bolus at least 5 minutes/ IV Infusion over 15-20 minutes	Smith-Kline Beecham, Antiulcerative (histamine H2-receptor antagonist
Ciprofloxacin/ Cipro		1) Solution 10 mg/mL, Lactic acid, pH 3.3-3.9. 2) Infusion solution 2 mg/mL, Dextrose 5%, Lactic acid, pH 3.5-4.6.	Dilute with saline, dextrose 5% or lactated Ringer's to 1-2 mg/mL.	IV infusion over 60 minutes, 200-400 mg every 12 hours	Bayer, Antibacterial
Cisplatin/ Platinol		1) Lyophilized powder, after reconstitution contains 1 mg/mL, Mannitol 10 mg/mL, Sodium chloride 9 mg/mL, pH = 3.5-5.5. 2) Solution 1 mg/mL Sodium chloride 9 mg/mL.	Reconstitute with WFI to 1 mg/mL	IV infusion	Bristol-Meyers Oncology, Antineoplastic
Cladribine/ Leustatin		Solution 1 mg/mL, Sodium chloride 9 mg/mL, Sodium phophates, pH 5.5-8.0	Dilute with 500 mL saline to 0.09 mg/kg/day (not recommended to use dextrose 5% due to increased drug degradation)	IV infusion over 24 hours after	Ortho, Antineoplastic

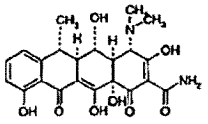
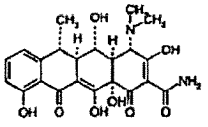
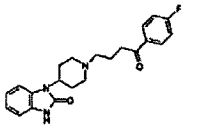
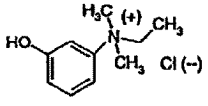
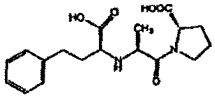
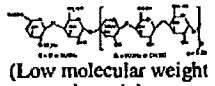
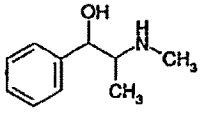
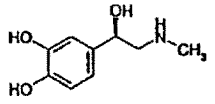
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Clavulanate potassium and ticarcillin disodium/ Timentin		1) Powder Clavulanate 0.1g, Ticarcillin 3 g. 2) Frozen solution Clavulanate 1 mg/mL, Ticarcillin 30 mg/mL	Reconstitute with WFI or saline to 8 mg/mL clavulanate and 200 mg/mL ticarcillin, further dilute with saline or lactated Ringer's to 10-100 mg/mL	IV infusion over 30 minutes	SmithKline Beecham, Antibiotic
Clindamycin Phosphate/ Cleocin phosphate	 **Water soluble phosphate ester prodrug**	1) Solution 150 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9.4 mg/mL pH = 5-6. 2) Ready to use solution 0.5-18 mg/mL Dextrose 5%, EDTA 0.04 mg/mL.	Dilute concentrated solution with saline or lactated Ringer's to ≤ 18 mg/mL.	IV infusion at 30 mg/hour	Pharmacia & Upjohn, Antibiotic
Clonidine/ Duraclon		Solution 0.1 mg/mL, Sodium chloride 9 mg/mL pH 5-7	None	IV infusion	Roxane, Analgesic
Codeine phosphate (Not in 1999 PDR as an injectable)		Solution, 15-60 mg/mL, w/wo Chlorobutanol 5 mg/mL, EDTA 1 mg/mL, Sodium metabisulfite 1-2 mg/mL, Acetate buffer pH 3-6.	None	SC/ IM/ IV occasionally	Elkins-Sinn and Wyeth, Analgesic, anticough
Colfosceril palmitrate (DPPC), Cetyl alcohol and Tyloxapol/ Exosurf neonatal	 Tyloxapol: oxyethylated tertiary octylphenol formaldehyde polymer	Lyophilized powder DPPC 108 mg Cetyl alcohol 12 mg Tyloxapol 8 mg, Sodium chloride 47 mg pH 5-7 (A synthetic lung surfactant)	Reconstitute with 8 mL WFI.	Intratracheal Suspension	Glaxo Wellcome, Prevention and treatment of Respiratory Disease Syndrome in low birth weight infants
Cortisone Acetate/ Cortone	 **Water insoluble ester prodrug**	**Suspension** 50 mg/mL, **Sodium carboxy-methylcellulose** 5 mg/mL, TWEEN 80 at 4 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM only	Merck, Endocrine disorders, rheumatoid arthritis, allergies
Cyanocobal-amin (Vitamin B12)	MW = 1355, porphoryn like with Co (+) at the center, synthesized by bacteria	Solution 0.03-1 mg/mL Sodium chloride Benzyl alcohol, pH 4.5-7	None	SC/ IM	Elkins-Sinn, Nutrient
Cyclophos-phamide/ Cytoxan		Lyophilized powder 100-2000 mg Mannitol 75 mg/100 mg cyclophosphamide pH 3-9	Reconstitute with WFI to 20 mg/mL. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus/ IV infusion/ IP/ intrapleural	Bristol-Myers Squibb, Antineoplastic

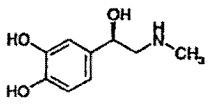
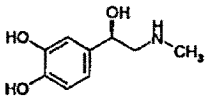
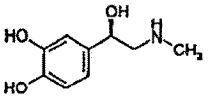
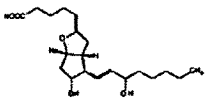
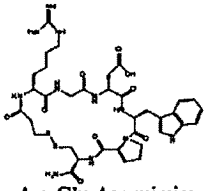
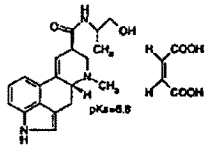
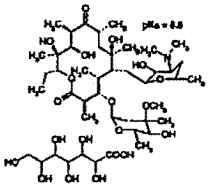
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Cyclosporin/ Sandimmune	Cyclic peptide (11 amino acids), MW ~ 1200	Solution, 50 mg/mL **Cremophor EL 65%, Ethanol 35%,** blanketed with nitrogen	Dilute with saline or dextrose 5% to 1-2.5 mg/mL (1 mL into 20-100 mL).	IV infusion over 2-6 hours	Novartis, Immuno-suppresent
Cytarabine (Ara-C)/ Cytosar-U		Lyophilized powder 500-2000 mg pH 5	Reconstitute with saline or WFI with benzyl alcohol 0.9% to 20-100 mg/mL.	Intrathecal/ SC/ IV bolus/ IV Infusion/	Pharmacia & Upjohn, Antineoplastic, Antiviral
Cytarabine (Ara-C)/ DepoCyte		**Suspension Multivesicular Lipid Particle** 5 mg/mL Cholesterol 4 mg/mL Dioleoylphosphatidylcholine (DOPC) 5.7 mg/mL, Dipalmitoylphosphatidylglycerol (DPPG) 1 mg/mL Sodium chloride 9 mg/mL pH 5.5-8.5	None	Intrathecal	Chiron (Developed by DepoTech) Antineoplastic, Antiviral
Dacarbazine/ DTIC-Dome		Solid 100-200 mg Mannitol and Citric acid, pH 3-4	Reconstitute with WFI to 10 mg/mL. For IV infusion may be further diluted with saline or dextrose 5% to 0.4 mg/mL	IV over 1 minute/ IV Infusion over 15-30 minutes	Bayer, Antineoplastic
Dactino-mycin/ Cosmegen		Lyophilized powder 0.5 mg, Mannitol 20 mg, pH 5.5-7	Reconstitute with 1.1 mL WFI. For IV infusion further dilute with saline or dextrose 5%.	IV bolus/ IV Infusion/	Merck, Antibiotic
Dalteparin/ Fragmin	Low MW heparin 	Solution (prefilled syringe and multi-use vial) 64-160 mg/mL Sodium chloride, w/wo Benzyl alcohol 0.15% pH 5.0-7.5	None	SC	Pharmacia & Upjohn, Antithrombotic
Danaparoid/ Orgaran	84% heparin sulfate, 12% dermatan sulfate, 4% chondroitin sulfate (isolated from porcine intestinal mucosa)	Solution (prefilled syringe or ampule) 1250 anti-Xa units/mL, Sodium chloride, Sodium sulfite 0.15% pH 7	None	SC	Organon, Antithrombotic
Dantrolene sodium/ Dantrium		Lyophilized powder 20 mg, Mannitol 3000 mg, pH 9.5	Reconstitute with 60 mL WFI to 0.3 mg/mL. For IV infusion further dilute with IV fluids.	IV bolus/ IV infusion over 1 hour.	Procter & Gamble Pharm., (Muscle relaxant) Treatment of hypermetabolism and hyperthermia

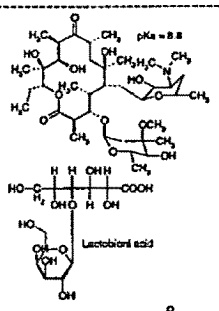
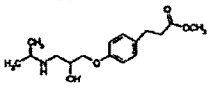
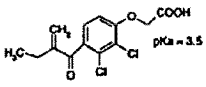
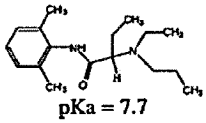
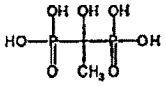
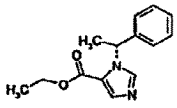
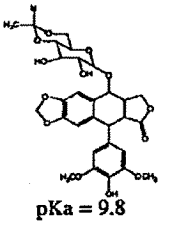
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Daunorubicin HCl/ Cerubidine		Lyophilized powder 21.4 mg, Mannitol 100 mg pH 4.5-6.2	Reconstitute with 4 mL WFI to 5 mg/mL, then further dilute with 10-15 mL saline and then inject into rapidly flowing IV infusion of saline or dextrose 5%.	IV infusion	Bedford, Antibiotic
Daunorubicin Citrate/ DaunoXome		Solution liposome 2 mg/mL, Distearoylphosphatidylcholine: Cholesterol in 2:1 molar ratio, lipid to drug ratio of 18.7:1 diameter of 45 nm	Dilute 1:1 with dextrose 5% to 1 mg/mL.	IV infusion over 60 minutes	NeXstar (now Gilead), Antibiotic
Desmopressin acetate/ DDAVP	 Synthetic analog of natural hormone 8-arginine vasopressin (ADH)	Solution 4 ug/mL, Sodium chloride 9 mg/mL, w/wo Chlorobutanol pH 4	None for SC or IV bolus. For IV infusion dilute with saline to (0.3 ug/kg) in 50 mL.	SC/ IV bolus/ IV infusion over 15-30 minutes	Rhone-Poulenc, Rorer, Hemophilia (maintain homeostasis)
Dexamethasone Acetate/ Decadron-LA	 **Water insoluble acetate ester prodrug**	**Suspension** 8 mg/mL Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, TWEEN 80 at 0.75 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM/ Intralesional/ Intra-articular/ Soft tissue	Merck, Anti-inflammatory
Dexamethasone Acetate/ Dalalone D.P.	 **Water insoluble acetate ester prodrug**	**Suspension** 16 mg/mL **Sodium carboxymethylcellulose** 5 mg/mL, TWEEN 80 at 0.75 mg/mL, Sodium chloride 6.7 mg/mL, Creatinine 5 mg/mL, EDTA 0.5 mg/mL, Benzyl alcohol 9 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5	Gentle swirl contents to resuspend settled particles.	IM/ Intra-articular/ Soft tissue (Not intralesional)	Forest, Anti-inflammatory
Dexamethasone Phosphate sodium/ Decadron	 **Water soluble phosphate ester prodrug**	**Solution** 4 and 24 mg/mL w/wo Lidocaine 10 mg/mL, Creatinine 8 mg/mL, Sodium citrate 10 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Sodium bisulfite 1 mg/mL pH 5.0-7.5 under nitrogen	For IV infusion dilute with saline or dextrose 5%.	IV bolus/ IV infusion/ IM/ Intralesional/ Intra-articular/ Soft tissue	Merck, Anti-inflammatory
Dexrazoxan/ Zinecard	 pKa = 2.1	Powder 250-500 mg, Provided diluent: 25 and 50 mL of Sodium lactate 0.167 Molar, pH 3.5-5.5	Reconstitute with provided diluent to 10 mg/mL. For IV infusion dilute with saline or dextrose 5% to 1.3-5.0 mg/mL.	IV bolus/ IV infusion	Pharmacia & Upjohn, Cardioprotective agent used in conjunction with doxorubicin

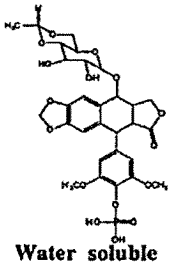
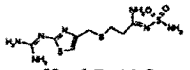
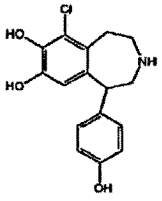
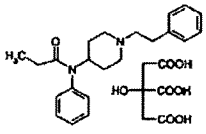
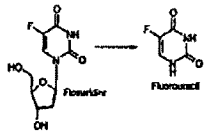
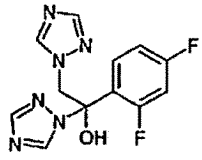
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Diatrizoate meglumine (Not in 1999 PDR)		Solution 300-600 mg/mL Sodium citrate, EDTA pH 6-7	None	IV/ IM/ Intra-arterial/ Intra-articular or selected area for visualization	Nycomed and Bracco, Radiopaque medium for "visualizing" *in vivo*
Diazepam/ Valium		Solution 5 mg/mL **Propylene glycol 40%, Ethyl alcohol 10%,** Benzyl alcohol 1.5%, Sodium benzoate 5%, Benzoic acid pH 6-7	None	IM/ IV through running IV tube at 1 minute per 5 mg diazepam	Roche, Management of anxiety disorders, Skeletal muscle relaxant
Diazoxide/ Hyperstat		Solution 15 mg/mL **pH 11.6**	None	IV bolus/ "IV Minibolus" (1-3 mg/kg every 5-15 minutes up to 150 mg)	Schering, Antihypertensive (prompt reduction of blood pressure)
Digoxin/ Lanoxin	Secondary glycoside extracted from the leaves of *Digitalis lanata*, (insoluble in water)	Solution 0.25 mg/mL **Propylene glycol 40%, Ethyl alcohol 10%,** Sodium phosphate and 0.08%, Citric acid. pH of 6.8 to 7.2	None or can be diluted 4-fold with WFI, saline or dextrose 5%, but must be used immediately due to precipitation	IV over 1-5 minutes/ rarely IM due to pain with IM injection.	Glaxo Wellcome, Cardiotonic
Dihydro-ergotamine mesylate/ D.H.E 45		Solution 1 mg/mL, **Glycerin 15%, Ethyl alcohol 6.1%,** pH 3.6	None	IV bolus/ IM/ SC	Novartis, Migraine headaches
Diltiazem/ Cardizem		1) Solution 5 mg/mL, **Sorbitol 71 mg/mL** Citric acid 0.75 mg/mL, Sodium citrate 0.65 mg/mL, pH 3.7-4.1. 2) Lyophilized powder in a dual chamber syringe **Syringe A:** Diltiazem 25 mg, Mannitol 37.5 mg, **Syringe B:** 5 mL WFI with Sodium chloride 0.6% and Benzyl alcohol 0.5% pH 4.0-7.0. 3) Lyophilized powder, 100 mg, Mannitol 75 mg	Reconstitute the contents within the Lyo-ject syringe. For IV infusion dilution a solution with saline to 0.5-1.2 mg/mL, or reconstitute the 100 mg lyophilized powder with saline to 1 mg/mL.	IV bolus over 2 minutes/ IV Infusion.	Hoechst Marion Roussel, Antianginal; Antihypertensive; Arrhythmia; Atrial Fibrillation; Calcium Channel Blocker
Dimenhy-drinate (Not in 1999 PDR as an injectable)		Solution 50 mg/mL **Propylene glycol 50%,** Benzyl alcohol 5%, pH 6-7	None for IM. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 5 mg/mL	IM/ IV	Steris, Antiemetic

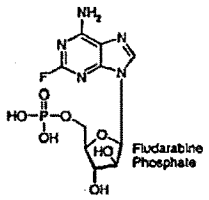
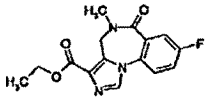
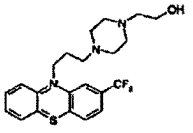
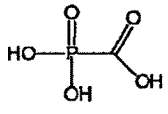
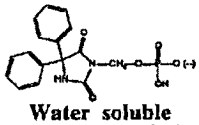
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Diphenhydramine HCl/ Benadryl		Solution 50 mg/mL Benzethonium chloride 0.1% pH 5-6	None for IM or IV bolus. For IV infusion may be diluted with saline, dextrose 5% or lactated Ringer's	Deep IM/ Slow IV bolus/ IV Infusion/ (Not SC)	Parke-Davis, Antihistamine, also motion sickness
Dobutamine HCl		Solution 12.5 mg/mL, Sodium bisulfite 0.24 mg/mL, pH 2.5-5.5	Dilute with saline, dextrose 5%, lactated Ringer's to 0.5-5.0 mg/mL.	IV infusion	Lilly, Cardiotonic (inotropic agent)
Docetaxel/ Taxotere		Solution 40 mg/mL in **TWEEN 80** Provided **diluent of Ethyl alcohol 13%** in water	Dilute with provided diluent (13% ethyl alcohol) to 10 mg/mL.	IV infusion over 1 hour	Rhone-Poulenc Rorer, Antineoplastic
Dolasetron mesylate/ Anzemet		Solution 20 mg/mL Mannitol 38 mg/mL, Acetate buffer pH 3.2-3.8	None for IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 0.25 mg/mL.	IV bolus at 100 mg per 30 seconds/ IV infusion at 0.35-1.8 mg/kg over 15 minutes	Hoechst Marion Roussel, Antinaseant, Antiemetic
Dopamine		Solution 40-160 mg/mL, Sodium metabisulfite 0.9%, Sodium citrate buffer, pH 3.3	Dilute with saline, dextrose 5% or lactated Ringer's to ~ 0.4-3.0 mg/mL	IV infusion	Astra, Cardiotonic and antihypotensive
Doxacurium chloride/ Noromax		Solution 1 mg/mL Benzyl alcohol 0.9% pH 3.9-5	None or dilute with saline or dextrose 5% to as low as 0.1 mg/mL.	IV bolus	Glaxo Wellcome, Skeletal muscle relaxant
Doxapram HCl/ Dopram		Solution 20 mg/mL Benzyl alcohol 0.9% pH 3.5-5	None for IV bolus. For IV infusion dilute with saline or dextrose 5% to 1 mg/mL	IV bolus/ IV infusion	Robbins, Respiratory stimulant
Doxorubicin HCl/ Adriamycin PFS and RDF; Rubex		1) Lyophilized powder 10-150 mg, Lactose 5 mg/mg doxorubicin, Methylparaben 0.1 mg/mg doxorubicin pH 3.8-6.5. 2) Solution 2 mg/mL Sodium chloride 9 mg/mL pH 3.0	Reconstitute with saline to 2 mg/mL	IV in not less than 3-5 minutes through a Y-site or a 3-way stopcock of a free-flowing infusion of saline or dextrose 5%.	Pharmacia & Upjohn and Astra and BMS (powder only), Antineoplastic
Doxorubicin HCl/ Doxil **(Pegylated stealth liposome formulation)**		**Liposomal dispersion** 2 mg/mL, N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium (MPEG-DSPE) 3.2 mg/mL, Hydrogenated soy phosphatidylcholine (HSPC) 9.6 mg/mL, Cholesterol 3.2 mg/mL, Ammonium sulfate 2 mg/mL, Histidine	Dilute the dose into 250 mL of dextrose 5%.	IV infusion over 30 minutes	Sequus, Antineoplastic, AIDS-related Kaposi's sarcoma

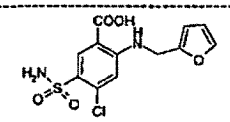
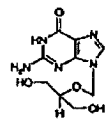
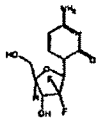
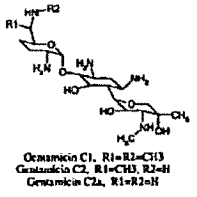
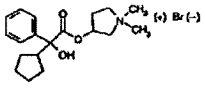
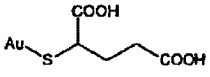
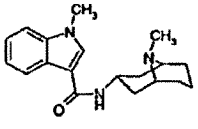
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Doxycycline hyclate (HCl hemihydrate)/ Atridox		Powder **Two syringe mixing system.** **Syringe A:** Poly(DL-lactide) ~ 33 mg/mL dissolved in 5 mL of N-methyl-2-pyrrolidone (NMP), **Syringe B:** Doxycycline hyclate 42.5 mg	Couple syringe A to syringe B and inject liquid contents into the powder, then mix 100 time in the syringe.	Subgingival (solution that solidifies upon contact with the crevicular fluid providing 7-day controlled release	Block, Antibiotic
Doxycycline hyclate (HCl hemihydrate)/ Vibramycin		Powder, 100-200 mg, Ascorbic acid 480-960 mg pH 1.8-3.3	Reconstitute with WFI to 10 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 0.1-1.0 mg/mL	IV infusion over 1-4 hours	Pfizer, Antibiotic
Droperidol citrate/ Fentanyl Droperidol		Solution 2.5 mg/mL, Fentanyl citrate 0.05 mg/mL, Lactic acid pH 3-4	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 0.01-0.05 mg/mL.	IM/ IV bolus/ IV infusion	Astra, Tranquilizer, Antipsychotic
Edrophonium chloride/ Tensilon		Solution 10 mg/mL, Sodium sulfite 0.2%, w/wo Phenol 0.45%, Citric acid pH 5.4	None	IV bolus/ IM/ SC	ICN, Choleringeric (inhibition of acetyl-cholinesterase)
Enalaprilat/ Vasotec		Solution 1.25 mg/mL Sodium chloride (isotonic) Benzyl alcohol 0.9% pH 6.5-7.5	None or dilution of 0.6-1.2 mg with 50 mL saline, dextrose 5% or lactated Ringer's.	IV infusion over 5 minutes	Merck, Antihypertensive (ACE Inhibitor)
Enoxaparin sodium/ Lovenox	 (Low molecular weight heparin)	Solution (Prefilled syringes available) 100 mg/mL pH 5.5-7.5	None	SC	Rhone-Poulenc Rorer, Antithrombolytic
Ephedrine sulfate (Not in 1999 PDR as an injectable)		Solution 25-50 mg/mL pH 4.5-7	None	Slow IV/ IM/ SC	Abbott, Sympathomimetic (nasal decongestant), mydriatic, allergy in emergency
Epinephrine HCl/ Epipen Epinephrine autoinjector (Adrenalin)		Solution 0.5-1.0 mg/mL Sodium chloride 1.8 mg/mL Sodium metabisulfite 0.5%, pH 2.2-5	None	IM	Dista, Emergency treatment of allergies

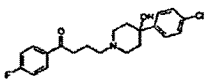
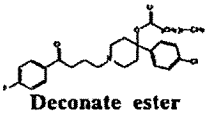
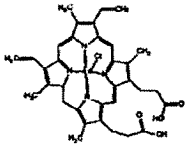
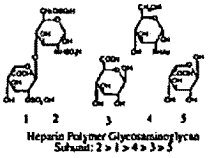
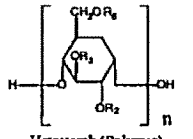
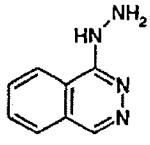
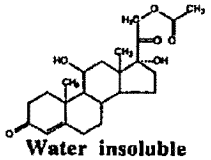
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Epinephrine HCl/ Susphrine		**Suspension** 5 mg/mL **Glycerin 325 mg/mL. Thioglycolic acid 6.6 mg/mL,** Phenol 5 mg/mL, Ascorbic acid 10 mg/mL,	Shake contents of vial to disperse particles to uniformity.	SC	Fores, Asthma
Epinephrine HCl and Bupivacaine HCl/ Sensorcaine		Solution 0.005 mg/mL Bupivacaine 2.5-7.5 mg/mL, Sodium metabisulfife 0.5%, Citric acid pH 3.3-5.5	None	Local infiltration	Astra, Local anesthesia (Bupivacaine)
Epinephrine HCl and Lidocaine HCl/ Xylocaine		Solution 0.005 mg/mL Lidocaine 10-15 mg/mL, Sodium chloride Sodium metabisulfife 0.5%, w/wo Methylparaben 1 mg/mL Citric acid pH 5-7	Dilute 20-200-fold with saline	IV infusion	Astra, Anesthesia (Lidocaine)
Epoprostenol sodium/ Flolan		Lyophilized powder 0.5-1.5 mg Mannitol 50 mg, Sodium chloride 2.9 mg Glycine 3.8 mg, **pH 10.2-10.8.** Provided diluent: Water with Glycine 1.9 mg/mL, Sodium chloride 1.5 mg/mL.	Reconstitute with provided diluent to 0.003-0.015 mg/mL.	IV infusion	Glaxo Wellcome, Antihypertensive
Eptifibatide/ Integrillin	 Arg-Gly-Asp mimic: [binds to (GP) IIb/IIIa ($\alpha_{IIb}\beta_3$)]	Solution 0.75-2 mg/mL Citric acid 5.25 mg/mL pH 5.25	None for IV bolus. For IV infusion dilute with saline or dextrose 5% to 0.75 mg/mL.	IV bolus/ IV infusion	Cor and Key, Treatment of acute coronary syndrome: In patients undergoing PCI (Inhibits platelet aggregation)
Ergonovine maleate/ Ergotrate maleate (Not in 1999 PDR)		Solution 0.2 mg/mL, Phenol 0.25%, Ethyl lactate 0.1%, Lactic acid 0.1%, pH 2.7-3.4	Dilute with 5 mL saline.	IV/ IM over 1 minute	Lilly, Oxytocic
Erythro-mycin gluceptate/ Ilotycin gluceptate (Not in 1999 PDR)		Powder 1000 mg pH 7.7	Reconstitute with WFI to 50 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 1.0 mg/mL	IV infusion	Dista, Antibiotic

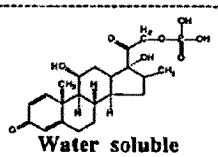
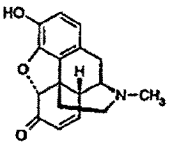
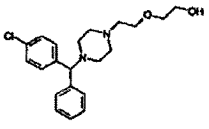
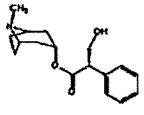
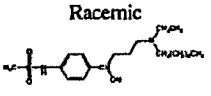
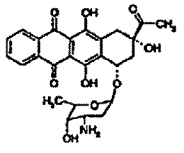
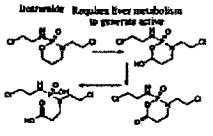
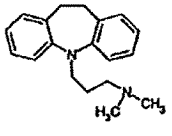
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Erythro-mycin lactobionate		Powder 500-1000 mg pH 7.7	Reconstitute with WFI to 50 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 1.0 mg/mL	IV infusion	Lederle, Antibiotic
Esmolol HCl/ Brevibloc		Solution 250 mg/mL **Propylene glycol 25%,** **Ethyl alcohol 25%,** Sodium acetate pH 3.3-5.5	Dilute with saline, dextrose 5% or lactated Ringer's to 10 mg/mL.	IV infusion	Ohmeda (Baxter), Antiarrhythmic
Ethacrynate sodium/ Sodium edecrin		Lyophilized powder 50 mg, Mannitol 62.5 mg pH = 6.3-7	Reconstitute with 50 mL saline or dextrose 5% to 1 mg/mL	Slow IV bolus/ IV infusion	Merck, Diuretic
Etidocaine HCl/ Duranest	 pKa = 7.7	Solution 10-15 mg/mL Epinephrine 0.005 mg/mL, Sodium chloride 6-7 mg/mL, w/wo Sodium metabisulfite 0.5 mg/mL, w/wo Citric acid, pH 3.0-5.0	None	Local infiltration	Astra, Local anesthetic
Etidronate disodium/ Didronel		Solution 50 mg/mL	Dilute with saline to 0.6-1.2 mg/mL	IV infusion over 2 hours	MGI, Treatment of hypercalcemia
Etomidate/ Amidate (Not in 1999 PDR)		Solution 2 mg/mL **Propylene glycol 35%**	None	IV bolus over 30-60 seconds	Abbott, Hypnotic
Etoposide/ Etoposide injection and VePesid	 pKa = 9.8	**Non-aqueous Solution** 20 mg/mL **PEG 300 60%,** **Ethyl alcohol 30%,** **TWEEN 80 at 8.0%,** Benzyl alcohol 3.0 %, Citric acid 2 mg/mL pH = 3-4	Dilute with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes	Astra and Bristol-Myers-Squibb, Antineoplastic

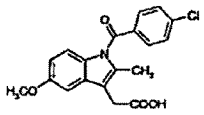
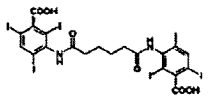
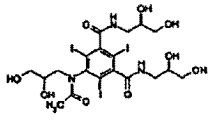
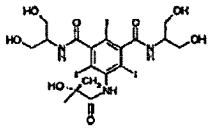
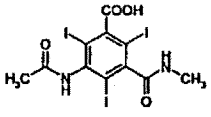
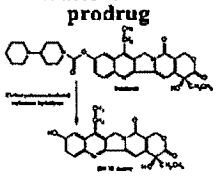
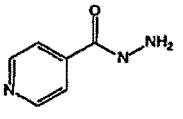
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Etoposide Phosphate/ Etopophos	 **Water soluble phosphate ester prodrug**	Lyophilized powder 100-1000 mg, Dextran 40 at 300-3000 mg Sodium citrate 32-327 mg/mL,	Reconstitute with WFI, saline or dextrose 5% to 10-20 mg/mL which is further diluted with saline or dextrose 5% to 0.2-0.4 mg/mL.	IV infusion over 30-60 minutes	Bristol-Myers-Squibb, Antineoplastic
Famotidine/ Pepcid	 pKa 6.7, 11.2	Solution 10 mg/mL L-aspartic acid 4 mg/mL, Mannitol 20 mg/mL, Benzyl alcohol 0.9%, pH 5-6	For IV bolus dilute with saline, dextrose 5% or lactated Ringer's to 2-4 mg/mL, and for IV infusion dilute to 0.2 mg/mL.	IV bolus over > 2 minutes/ IV infusion over 15-30 minutes	Merck, Antiulcerative (inhibition of gastric secretion)
Fenoldopam mesylate/ Corlopam		Solution 10 mg/mL, **Propylene glycol 50%**, Sodium metabisulfite 1 mg/mL, Citric acid 3.4 mg/mL, Sodium citrate 0.61 mg/mL	Dilute with saline or dextrose 5% to 0.04 mg/mL.	IV infusion	Neurex, Antihypertensive
Fentanyl citrate Sublimaze (See Droperidol)		Solution 0.050 mg/mL pH 4-7.5	None for IM and IV bolus. For IV infusion dilute with saline or dextrose 5% to 0.0025-0.020 mg/mL	IM/ IV bolus over 1-2 minutes/ IV infusion	Asra, Baxter and Elkins- Sinn, Analgesic
Floxuridine/ FUDR		Powder 500 mg pH 4-5	Reconstitute with 5 mL WFI to 100 mg/mL then further diluted with saline or dextrose 5% to 0.1-0.6 mg/kg/day.	Intra-arterial infusion	Roche, Antineoplastic
Fluconazole/ Diflucan (selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha-demethylation)		Solution 2 mg/mL Sodium chloride 9 mg/mL, or Dextrose 56 mg/mL, pH 4-8	None	IV infusion at ≤ 200 mg/hour	Pfizer, Antifungal

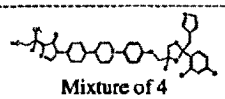
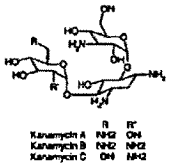
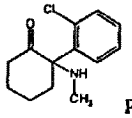
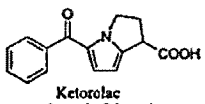
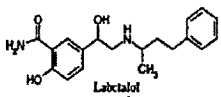
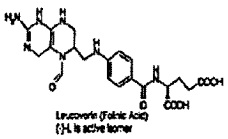
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Fludarabine Phosphate	 **Water soluble phosphate ester prodrug**	Lyophilized powder 50 mg, Mannitol 50 mg pH 7-8	Reconstitute with 2 mL WFI to 25 mg/mL then further diluted with 100-125 mL saline or dextrose 5% to ~ 0.5 mg/mL.	IV infusion over 30 minutes	Berlex, Antineoplastic
Flumazenil/ Romazicon		Solution 0.1 mg/mL, Sodium chloride 9 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, EDTA 0.01%, Acetic acid 0.01%, pH 4	None or dilute with saline, dextrose 5% or lactated Ringer's.	IV bolus over 15 seconds through a freely running IV infusion line	Roche, Treatment of benzodiazepine overdose (benzo-diazepine antagonist)
Fluorouracil (Not in 1999 PDR as an injectable)		Solution 50 mg/mL pH 9.2	None for IV bolus. For IV infusion dilute with dextrose 5% to 1-10 mg/mL.	IV bolus/ IV infusion	Roche, Antineoplastic
Fluphenazine HCl/ Prolixin (Not in 1999 PDR as an injectable)		Solution, 2.5 mg/mL Sodium chloride (isotonic), Methylparaben 0.1%, Propylparaben 0.01% pH 5	None	IM	Apothecon Antipsychotic
Fomiversen sodium/ Vitravene	**ANTI-Sense oligonucleotide** 5'-GCG TTT GCT CTT CTT CTT GCG-3'	Solution 6.6 mg/mL Sodium chloride, Sodium carbonate, Sodium bicarbonate pH 8.7	None	Intravitreal (0.5 mL/eye)	Ciba Vision, Antiviral
Foscarnet sodium/ Foscavir		Solution 24 mg/mL pH 7.4	None for central line infusion, but infusion in peripheral line must be diluted with saline or dextrose 5% to 12 mg/mL.	IV infusion	Astra, Antiviral
Fosphenytoin/ Cerebyx	 **Water soluble hydroxy-methyl phosphate ester prodrug**	Solution 75 mg/mL (50 mg/mL phenytoin equivalents, PE) Tromethamine, pH = 8.6-9.0	None for IM. For IV infusion dilute with saline or dextrose 5% to 1.5- 25 mg PE/mL.	IM/ IV infusion at ≤ 150 PE/minute	Parke-Davis, Anticonvulsant

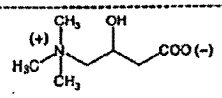
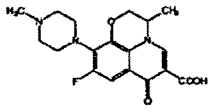
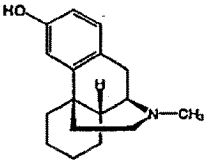
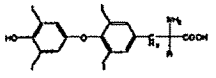
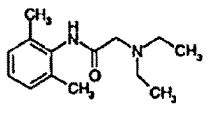
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Furosemide (Frusemide)/ Formerly Lasix		Solution 10 mg/mL Sodium chloride (isotonic) pH 8-9	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus over 1-2 minutes/ IV infusion at ≤ 4 mg/minute	Astra and Baxter and Elkins-Sinn, Antihypertensive; Diuretic
Ganciclovir sodium (DHPG)/ Cytovene		Lyophilized powder 500 mg pH 11 (Solubility at pH 7 = 6 mg/mL, pKa 2.2, 9.4, active drug is triphosphate)	Reconstitute with 10 mL WFI to 50 mg/mL then further dilute with 100 mL saline, dextrose 5% or lactated Ringer's to ~ 5 mg/mL.	IV infusion at 5 mg/kg over 1 hour	Syntex (Roche), Treatment of CMV retinitis in immune-compromised patients
Gemcitabine HCl/ Gemzar		Lyophilized powder 200-1000 mg, pH 2.7-3.3	Reconstitute with saline to 40 mg/mL which may be further diluted with saline to 0.1 mg/mL.	IV infusion over 30 minutes	Lilly , Antineoplastic
Gentamicin sulfate/ Garamycin	 Gentamicin C1, R1=R2=CH3 Gentamicin C2, R1=CH3, R2=H Gentamicin C2a, R1=R2=H	Solution 10-40 mg/mL Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, Sodium bisulfite 3.2 mg/mL, EDTA 0.1 mg/mL pH 3-5.5	None for IM. For IV infusion dilute with 50-200 mL saline or dextrose 5%.	IM/ IV Infusion over 0.5-2 hours	Schering, Antibiotic
Glucagon	His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr	Lyophilized powder 1 mg Lactose 49 mg. Provided diluent: Water with Glycerin 1.2% pH < 3	Reconstitute with provided diluent to 1 mg/mL. If the dose is > 2 mg, then reconstitute with WFI.	IV at ≤ 1 mg/min	Lilly, Treatment of hypoglycemia
Glyco-pyrrolate/ Robinul		Solution 0.2 mg/mL Benzyl alcohol 0.9% pH 2-3	None	IM/ IV bolus	Robbins, Anticholinergic
Gold thiomaleate sodium / Aurolate, Myochrysine		Solution 50 mg/mL Benzyl alcohol 0.5% pH 5.8-6.5	None	IM (Intragluteally)	Merck & Co., Antirheumatic
Granisetron HCl/ Kytril		Solution 1 mg/mL Sodium chloride 9 mg/mL w/wo Benzyl alcohol 10 mg/mL w/wo Citric acid 9 mg/mL, pH 4.7-7	None for IV bolus. For IV infusion dilute with 20-50 mL saline or dextrose 5% (10-40 ug/kg).	IV bolus over 30 seconds/ IV infusion over 5 minutes	Smith-Kline Beecham, Antinauseant, Antiemetic

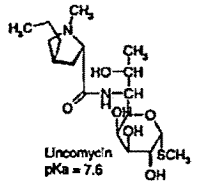
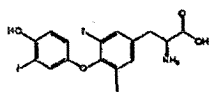
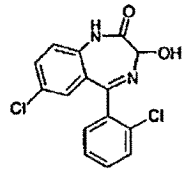
Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Haloperidol lactate/ Haldol		Solution 5 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, Lactic acid pH 3-4	None	IM/ Seldom via IV bolus or IV infusion	Ortho-McNeil, Psychotic disorders, Tourette's Disorder
Haloperidol Decanoate/ Haldol decanoate	 **Deconate ester prodrug for prolonged effect**	**Non-aqueous solution** 50-100 mg/mL in **Sesame Oil** Benzyl alcohol 1.2%	None	IM	Ortho-McNeil, psychotic disorders, Tourette's Disorder
Hemin/ Panhematin (a.k.a Hematin)		Lyophilized powder 313 mg, **Sorbitol 300 mg** Sodium carbonate 215 mg,	Reconstitute with 43 mL WFI to 7 mg/mL.	IV infusion using a 0.45 um filter	Abbott, Treatment of acute intermittent porphyria related to menstration
Heparin sodium	 Heparin Polymer Glycosaminoglycan Subunit: 2 > 1 > 4 > 3 > 5	Solution 10-20,000 units/mL, Benzyl alcohol ≤ 10 mg/mL w/wo Sodium chloride 1 mg/mL pH 5-7.5	None or dilute with saline or lactated Ringer's to 10-100 units/mL.	IV infusion	Wyeth-Ayerst and Lilly, Anticoagulant
Hetastarch/ Hespan	 Hetastarch (Polymer) R_2, R_3, R_6 = H or CH_2CH_2OH R_6 = branching point	Solution 60 mg/mL, Sodium chloride 9 mg/mL pH 3.5-7.0	None	IV infusion	DuPont, Plasma volume expansion
Hydralazine HCl/ Apresoline (Not in 1999 PDR as an injectable)		Solution 20 mg/mL **Propylene glycol 10%,** Parabens 1 mg/mL pH 3-4	None	IM/ IV	SoloPak and CibaGeneva, Antihypertensive, Vasodilating Agent
Hydro-cortisone Acetate/ Hydrocortone Acetate (Slow onset of action, but long duration)	 **Water insoluble acetate ester prodrug**	Suspension 50 mg/mL **Sodium carboxy-methylcellulose 5 mg/mL,** TWEEN 80 at 4 mg/mL, Sodium chloride 9 mg/mL, Benzyl alcohol 9 mg/mL	None	IM/ Intralesional/ Intra-articular	Merck, Replacement therapy in adrenocortical deficiency, Anti-inflammatory

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Hydro-cortisone Phosphate sodium / Hydrocortone Phosphate	 **Water soluble phosphate ester prodrug**	Solution 50 mg/mL Creatinine 8 mg/mL, Sodium bisulfite 3.2 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Sodium citrate 10 mg/mL pH 7.5-8.5	None or dilute with saline or dextrose 5%.	SC/ IM/ IV bolus/ IV infusion	Merck, Replacement therapy in adrenocortical deficiency, Anti-inflammatory
Hydromor-phone/ Dilaudid HCl		1) Solution 10 mg/mL Sodium citrate 2 mg/mL, Citric acid 2 mg/mL pH 4-5.5. 2) Lyophilized powder 250 mg	Dilute solution with saline to 2 mg/mL. Reconstitute powder with 25 mL WFI to 10 mg/mL and dilution with saline to 2 mg/mL.	SC/ IM/ IV (over 2-3 minutes)	Knoll, Analgesic
Hydroxyzine HCl/ Vistaril		Solution 25-50 mg/mL, Benzyl alcohol 0.9%, pH 3.5-6	None	IM	Pfizer, Tranquilizer
Hyoscyamine sulfate/ Levsin		Solution 0.5 mg/mL	None	SC/ IM/ IV bolus	Schwarz, Peptic ulcers
Ibutilide fumarate/ Corvert	Racemic 	Solution 0.1 mg/mL Sodium chloride 8.9 mg/mL pH 4.6	None or dilute with 50 mL saline or dextrose 5% to 0.017 mg/mL.	IV infusion	Pharmacia & Upjohn, Antiarrhythmic
Idarubicin HCl/ Idamycin		Solution 1 mg/mL **Glycerin 25 mg/mL**, pH 3.5	None	IV infusion over 10-15 minutes in running line of saline or dextrose 5%	Pharmacia & Upjohn, Antineoplastic
Ifosfamide/ Ifex		Powder 1000-3000 mg pH 6	Reconstitute with WFI to 50 mg/mL then further dilute with saline, dextrose 5% or lactated Ringer's to 0.6-20 mg/mL.	IV infusion over at least 30 minutes with Mesna	Bristol-Myers-Squibb, Antineoplastic
Imipenem (See Cilastatin)					
Imipramine HCl/ Tofranil (Not in 1999 PDR as an injectable)		Solution 12.5 mg/mL Sodium bisulfite 0.5 mg/mL, Sodium sulfite 0.5 mg/mL, Ascorbic acid 1 mg/mL pH 4-5	None	IM	Geigy, The original tricyclic antidepressant

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Indomethacin sodium/ Indocin I.V.		Lyophilized powder, 1 mg pH 6-7.5	Reconstitute with saline to 0.5-1 mg/mL.	IV bolus	Merck, Nonsteroidal antiinflammatory
Iodipamide meglumine/ Cholografin Meglumine (Not in 1999 PDR)		Solution 520 mg/mL, Sodium citrate 3 mg/mL, EDTA 0.04% pH 6.5-7.7	Warm to body temperature.	IV infusion over 10-45 minutes	Squibb, Diagnostic aid (Radiopaque medium)
Iohexol/ Omnipaque (Not in 1999 PDR)		Solution 140-350 mg/mL, EDTA TRIS 1.2 mg/mL pH 6.8-7.7	Warm to body temperature.	IV/ Intra-arterial/ Intrathecal/	Nycomed, Diagnostic aid (Radiopaque medium)
Iopamidol/ Isovue (Not in 1999 PDR)		Solution 200-370 mg/mL EDTA, TRIS 1 mg/mL pH 6.5-7.5	Warm to body temperature.	IV/ Intra-arterial/ Intrathecal	Braco, Diagnostic aid (Radiopaque medium)
Iothalamate meglumine (or sodium)/ Conray (Not in 1999 PDR)		Solution 170-600 mg/mL	Warm to body temperature.	IV/ Intra-arterial	Mallinckrodt, Diagnostic aid (Radiopaque medium)
Irinotecan HCl/ Camptosar	**Water soluble prodrug** 	Solution 20 mg/mL, **Sorbitol 45 mg/mL**, Lactic acid 0.9 mg/mL pH 3.0-3.8	Dilute with dextrose 5% or saline to 0.12-1.1 mg/mL.	IV infusion over 90 minutes	Pharmacia & Upjohn, Metastastic carcinoma
Isoniazid/ Nydrazid		Solution 10 mg/mL, Chlorobutanol 0.25%, pH 6.0-7.0	None	IM	Apothecon, Tuberculosis
Isoproterenol HCl/ Isuprel HCl		Solution 0.2 mg/mL Sodium chloride 7 mg/mL, Sodium metabisulfite 1 mg/mL, Lactic acid 0.12 mg/mL, Sodium lactate 1.8 mg/mL pH 3.5-5.5	None for SC or IM. For IV bolus dilute with saline or dextrose 5% to 0.02 mg/mL, for IV infusion dilute to 0.0004-0.004 mg/mL.	SC/ IM IV bolus/ IV infusion/ [Intracardiac (extreme emergency)]	Sanofi Winthrop (Elkins-Sinn), Smooth muscle relaxant

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Itraconazole/ Sporanox	 Mixture of 4 diastereoisomers (two enantiomeric pairs)	Solution 10 mg/mL **Hydroxypropyl-β-cyclodextrin 40 %,** Propylene glycol 2.5%, pH 4.5	Dilute with saline to 5 mg/mL.	IV infusion	Janssen, Antifungal
Kanamycin sulfate/ Kantrex (Not in 1999 PDR)		Solution 37-333 mg/mL Sodium bisulfite 0.5%, Sodium citrate 2%, pH 4.5	None for IM. For IV infusion dilute with dextrose 5% or saline to 2.5-5 mg/mL.	IM/ IV infusion over 30-60 minutes/ Intraperitoneal instillation.	Apothecon, Antibiotic
Ketamine HCl/ Ketalar (Not in 1999 PDR)	 pKa = 7.5	Solution 10-100 mg/mL Sodium chloride (isotonic) Benzethonium chloride 0.1%, pH 3.5-5.5	None or dilute the 100 mg/mL with WFI, saline or dextrose 5% to 50 mg/mL	IM/ IV bolus over 60 seconds	Parke-Davis, Anesthetic
Ketorolac tromethamine/ Toradol	 Ketorolac racemic, only S is active pKa = 3.5	Solution (vials or cartridge-needle units) 15-30 mg/mL **Ethyl alcohol 10%,** Sodium chloride 6.7-8.7 mg/mL, w/wo citric acid 0.1%, pH 7-8	None	IM/ IV	Syntex (Roche), Analgesic, Nonsteroidal antiinflammatory
Labetalol HCl/ Normodyne and Trandate	 Labetalol racemic R,R = Dilevalol	Solution (vials and prefilled syringes) 5 mg/mL Dextrose 45 mg/mL, Methylparaben 0.8 mg/mL. Propylparaben 0.1 mg/mL, EDTA 0.1 mg/mL, Citric acid pH 3-4	None for IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 1 mg/mL.	IV bolus over 2 minutes/ IV infusion	Schering and Glaxo Wellcome, Antihypertensive
Leucovorin calcium/ Wellcovorin		Lyophilized powder 50-350 mg Sodium chloride 40-140 mg pH = 8.1	Reconstitute with WFI to 10-20 mg/mL.	IM/ IV bolus/ IV infusion (at < 160 mg/min)	Immunex, Glaxo Wellcome and Elkins Sinn. Antidote for folic acid antagonist; (Reduce toxic effect of high-dose methotrexate therapy in osteosarcoma
Leuprolide/ Lupron and Lupron Depot	5-Oxo-L-prolyl-L-histidyl- L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)	1) Solution for SC: 5 mg/mL Sodium chloride (isotonic) Benzyl alcohol 9 mg/mL **2) Lyophilized microspheres for IM.** (Depot dual-chamber syringe or single-dose vial) **Syringe A or in vial:** Solid 3.75-15 mg leuprolide, Purified gelatin 0.65-2.6 mg, **DL-lactic/glycolic acids copolymer 33-132 mg** D-mannitol 6.6-26 mg. **Syringe B or supplied diluent:** Aqueous solution of **Sodium carboxy-methylcellulose 5 mg,** TWEEN 80 at 1.0 mg, D-mannitol 50 mg, Acetic acid	None for SC solution. For IM reconstitute the microspheres with 1.5 mL of provided diluent to a suspension of 3-25 mg/mL.	IM/ SC	TAP, LH-RH agonist, Prostate cancer; Endometriosis; In children with central precocious puberty, Inhibition of the growth of certain hormone dependent tumors

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Levocarnitine/ Carnitor		Solution 200 mg/mL pH 6.0-6.5	None	IV over 2-3 minutes (50 mg/kg)	Sigma-Tau, Treatment in patients lacking endogenous levocarnitine
Levofloxacin/ Levaquin		1) Solution 25 mg/mL, Sodium chloride (isotonic) pH 3.8-5.8 2) Ready-to-use solution 5 mg/mL, Dextrose 5% pH 3.8-5.8	Dilute with saline, dextrose 5% or lactated Ringer's to 5 mg/mL.	IV infusion over ≥ 60 minutes.	Ortho-McNeil, Antibacterial
Levorphanol tartrate/ Levo-Dromoran		Solution 2 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL or, Phenol 4.5 mg/mL pH 4.3	None or dilute with 5 mL saline.	SC/ IM/ IV bolus/ IV infusion	ICN, Analgesic
Levo-thyroxine sodium/ Synthrod		Lyophilized powder 0.2-0.5 mg Mannitol 10 mg, Sodium phosphate tribasic 0.7-1.7 mg pH 7.5	Reconstitute with 5 mL saline.	IM/ IV at 0.1 mg over < 1 minute	Knoll, Hormone replacement; Hypothyroidism
Lidocaine HCl/ Xylocaine	 Lidocaine pKa = 7.9	1) Solution (vials and prefilled syringes) 5-40 mg/mL, Sodium chloride 6-7 mg/mL, Methylparaben 1 mg/mL pH 5-7 2) Solution 5-20 mg/mL Sodium chloride, Epinephrine 0.005 mg/mL, Sodium metabisulfite 0.5 mg/mL, Methylparaben 1 mg/mL Citric acid pH 3.3-5.5. 3) Solution 15 mg/mL Dextrose 7.5%	None for IM but for IV bolus only < 20 mg/mL, and for IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 1-4 mg/mL.	IM/ IV bolus/ IV infusion/ Local infiltration	Astra, Analgesic; Antidysrhythmic (class IB)

Drug Name/ Marketed Name	Structure	Formulation	Preadministration preparation	Route of Administration	Company and Indication
Lincomycin HCl/ Lincocin HCl (Not in 1999 PDR)	 Lincomycin pKa = 7.6	Solution 300 mg/mL Benzyl alcohol 9.5 mg/mL pH 3-5.5	None or for IV infusion dilute with saline or dextrose 5% to ≤ 10 mg/mL.	IM/ IV infusion at < 10 mg/mL/ Sub-conjunctival	Upjohn, Antibacterial
Liothyronine sodium/ Triostat		Solution 0.01 mg/mL pH 10.5	None	IV bolus	Jones, Thyroid hormone
Lorazepam/ Ativan	 Lorazepam Sol. water = 0.08 mg/mL pKa = 11.5, 13	Solution 2-4 mg/mL **PEG 400 at 0.18 mL/mL, in Propylene glycol** Benzyl alcohol 2%	None for IM. For IV dilute with equal volume of saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus at ≤ 2 mg/min	Wyeth-Ayerst, Anxiolytic; sedation; status epilepticus

ATTACHMENT F - COMPILATION

TAB 14

Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999) Part III

ROBERT G. STRICKLEY

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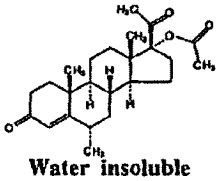
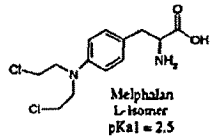
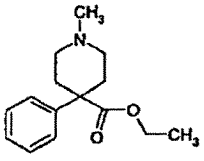
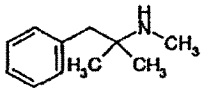
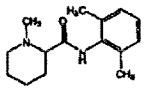
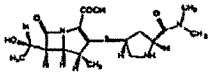
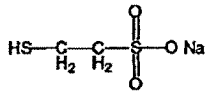
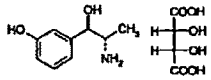
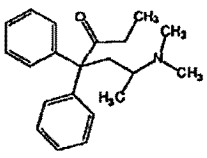
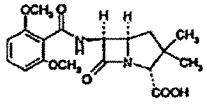
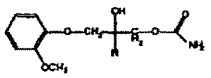
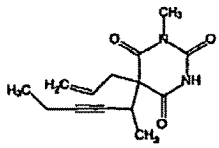
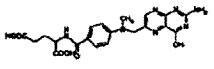
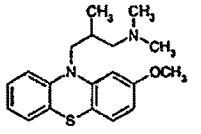
[Editor's Note: This Review Article on Injectable Products is being published in three parts. The introduction and summary appeared in the November/December 1999 issue of the *Journal*. Part II appeared in the January/February 2000 issue. This is Part III.]

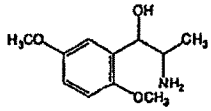
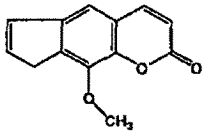
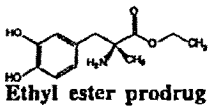
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Medroxyprogesterone Acetate/ Depo-Provera	 **Water insoluble acetate ester prodrug**	**Suspension** 150-400 mg/mL, **PEG 3350: 20-29 mg/mL,** TWEEN 80 at 2.4 mg/mL, Sodium chloride: 8.7 mg/mL, Methylparaben: 1.4 mg/mL, Propylparaben: 0.15 mg/mL	None	IM once every 3 months	Pharmacia & Upjohn, Contraceptive
Melphalan HCl/ Alkeran	 Melphalan L-isomer pKa1 = 2.5	Lyophilized powder 50 mg, Povidone 20 mg. Provided 10 mL diluent of Water 35%, **Propylene glycol 60%, Ethyl alcohol 5%,** Sodium citrate 0.2 g with pH 6.5-7.0	Reconstitute vigorously with provided diluent to 5.0 mg/mL, then further dilute with saline to ≤ 0.45 mg/mL.	IV infusion over 15-20 minutes	Glaxo-Wellcome, Antineoplastic, Alkylating agent.

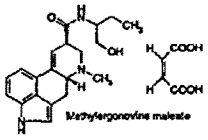
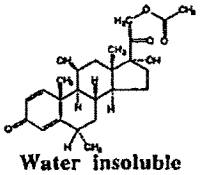
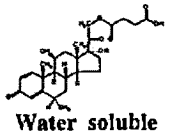
Correspondence address: 180 Kimball Way, South San Francisco, CA 94080

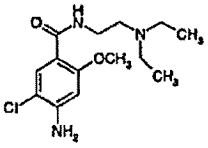
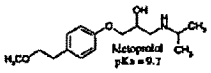
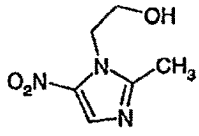
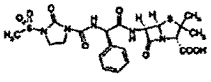
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Meperidine HCl/ Mepergan (a.k.a. Demerol)		Solution 25 mg/mL Promethazine 25 mg/mL, EDTA 0.1 mg/mL, Calcium chloride 0.04 mg/mL, Sodium formaldehyde sulfoxylate 0.75 mg/mL, Sodium metabisulfite 0.25 mg/mL, Sodium acetate, pH 3.5-6	None for SC or IM. For IV infusion dilute with at least 5 mL saline to 10 mg/mL.	SC/ IM/ IV infusion at 25 mg/min	Wyeth-Ayerst, Analgesic, Sedative, Anesthetic
Mephentermine sulfate/ Wyamine sulfate (Not in 1999 PDR)		Solution 15-30 mg/mL Parabens 2 mg/mL, Acetate buffer pH 4-6.5	None for IM or IV bolus. For IV infusion dilute with saline or dextrose 5% to 1 mg/mL.	IM/ IV bolus/ IV infusion	Wyeth-Ayerst, Antihypnotic
Mepivacaine HCl/ Polocaine		Solution 10-20 mg/mL	None	Local	Astra, Anesthetic
Meropenam/ Merrem		Powder 500-1000 mg, Sodium carbonate pH 7.3-8.3	For IV bolus reconstitute with WFI to 50 mg/mL. For IV infusion reconstitute with saline or dextrose 5% to 5 mg/mL.	IV bolus over 3-5 minutes / IV infusion over 15-30 minutes	Zeneca, Antibiotic

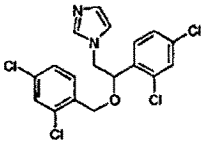
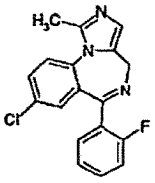
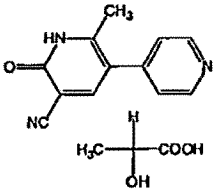
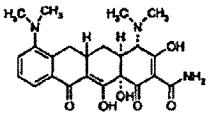
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Mesna/ Mesnex		Solution 100 mg/mL, w/wo Benzyl alcohol 10 mg/mL, EDTA 0.25 mg/mL, pH 6.5-8.5	Dilute with saline, dextrose 5% or lactated Ringer's to 20 mg/mL.	IV bolus over ≤ 1 minute	Bristol-Myers Squibb, Detoxifying agent (antineoplastic adjunct in conjunction with Ifosfamide administration)
Metaraminol bitartrate/ Aramine		Solution 10 mg/mL Sodium chloride 4.4 mg/mL, Methylparaben 0.15%, Propylparaben 0.02%, Sodium bisulfite 0.2%, pH 3.2-4.5	None for SC, IM or IV bolus. For IV infusion dilute with 500 mL saline or dextrose 5% to 0.03 - 0.2 mg/mL.	SC/ IM/ IV bolus/ IV infusion	Merck, Adrenergic (increases blood pressure in treatment of hypotension)
Methadone HCL/ Dolophine HCL		Solution 10 mg/mL Sodium chloride 9 mg/mL pH = 3-6.5	None	SC/ IM	Roxane, Analgesic, Sedation, Detoxification for heroin addiction
Methicillin sodium/ Staphcillin (Not in 1999 PDR)		Powder 1000-6000 mg, Sodium citrate 50 mg/gram methicillin, pH 6-8.5	Reconstitute with WFI to 500 mg/mL. No dilution for IM. For IV dilute with saline to 20 mg/mL, and for IV infusion to 2-20 mg/mL.	IM/ IV bolus/ IV infusion over 20-30 minutes	Apothecon, Antimicrobial

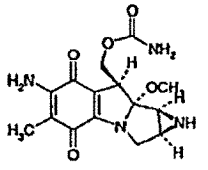
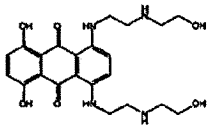
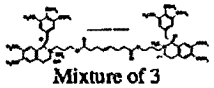
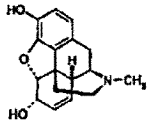
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Metho-carbamil/ Robaxin		Solution 100 mg/mL, **PEG 300 at 50%,** pH = 4-5	None for IM or IV bolus. For IV infusion dilute with ≤ 250 mL saline or dextrose 5%.	IM/ IV bolus at ≤ 30 mg/min/ IV infusion over 10-15 minutes	A.H. Robbins, Skeletal muscle relaxant in the treatment of painful musculoskeletal condition
Methohexital sodium		Powder 500-5000 mg, Sodium carbonate 30-300 mg, **pH 9-11**	Reconstitute with WFI to 166 mg/mL then further dilute with saline or dextrose 5% to 10 mg/mL.	IV bolus/ IV infusion	Jones Medical Industries, Ultra short acting anesthetic
Methotrexate sodium		1) Solution 25 mg/mL Sodium chloride 2.6-4.9 mg/mL, w/wo Benzyl alcohol 9 mg/mL, pH ~ 8.5. 2) Lyophilized powder 20-1000 mg, **pH 9-11**	Reconstitute the powder with saline or dextrose 5% to 1-50 mg/mL	IM/ IV/ Infusion/ Intra-arterial/ Intrathecal	Immunex, Antineoplastic, Immuno-suppressant, Antirheumetic
Metho-trimeprazine/ Levoprine (Not in 1999 PDR)		Solution 20 mg/mL Benzyl alcohol 0.9%, EDTA 0.065% (w/v), Sodium metabisulfite 0.3%, pH 4.5	None	IM	Immunex, Analgesic

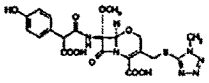
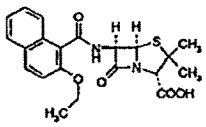
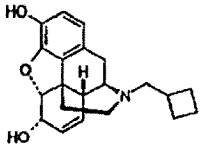
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Methoxamine HCl/ Vasoxyl		Solution 20 mg/mL Sodium chloride (isotonic) Citric acid 3 mg/mL, Sodium citrate 3 mg/mL, Potassium metabisulfite 1 mg/mL, pH 3-5	None for IM or IV bolus. For IV infusion dilute with dextrose 5% to 0.15 mg/mL.	IM/ IV bolus slowly (emergency)/ IV infusion	Glaxo Wellcome, Antihypotensive (increases blood pressure)
Methoxsalen/ Uvadex		Solution 0.02 mg/mL Sodium chloride 8 mg/mL, **Propylene glycol 5%, Ethyl alcohol 5%** Sodium acetate 1.7 mg/mL, Acetic acid 1.5 mg/mL pH not reported	Injected into photoactivation bag, then add 240 mL buffy coat, 300 mL plasma, and 200 mL saline, then reinfused.	IV infusion	Therakos, Photoactive substance used in extracorporeal treatment of leukocyte enriched buffy coat.
Methyldopate HCl/ Aldomet Ester HCl	 **Ethyl ester prodrug**	Solution 50 mg/mL **Monothioglycerol 2 mg/mL,** Sodium bisulfite 3.2 mg/mL, EDTA 0.5 mg/mL, Methylparaben 1.5 mg/mL, Propylparaben 0.2 mg/mL, Citric acid 5 mg/mL, pH 3-4.2	Dilute with dextrose 5% to 10 mg/mL.	IV infusion over 30-60 minutes	Merck, Antihypertensive

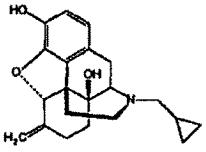
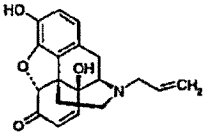
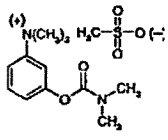
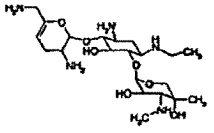
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Methyl-ergonovine maleate/ Methergine (Not in 1999 PDR)		Solution 0.2 mg/mL Sodium chloride 3 mg/mL, Tartaric acid 0.25 mg/mL, pH 2.7-3.5	None	IM/ IV in life threatening situation	Sandoz, Oxytocic, used to control postpartum hemorrhage
Methyl-prednisolone Acetate/ Depo-Medrol	 **Water insoluble acetate ester prodrug**	**Suspension** 20-80 mg/mL **PEG 3350 3%,** TWEEN 80 at 2 mg/mL, Sodium chloride (isotonic), Benzyl alcohol 9 mg/mL, Sodium phosphates 2 mg/mL, pH 3.5-7.0	None	IM/ Intrasynovial/ Soft tissue or Intralesional	Pharmacia & Upjohn, Anti-inflammatory glucocorticoid
Methyl-prednisolone Succinate sodium / Solu-Medrol	 **Water soluble succinate ester prodrug**	Lyophilized powder 40-2000 mg w/wo Lactose 25 mg/mL, Benzyl alcohol 9 mg/mL Sodium phosphates 18 mg/mL pH 7-8	Reconstitute with WFI to 40-65 mg/mL. For IV infusion further dilute with saline or dextrose 5%.	IM/ IV bolus/ IV infusion	Pharmacia & Upjohn, Anti-inflammatory glucocorticoid

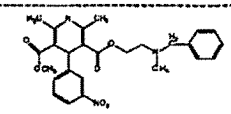
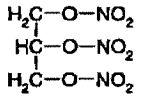
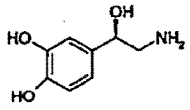
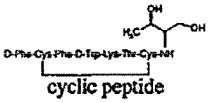
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Metoclo-pramide HCL/ Reglan		Solution 5 mg/mL Sodium chloride 8.5 mg/mL, pH 4.5.6.5	None for IM or IV bolus. For IV infusion dilute with 50 mL saline, dextrose 5% or lactated Ringer's to ~ 0.2 mg/mL.	IM/ IV bolus/ IV infusion	A.H. Robbins, Antiemetic, Anticholinergic
Metoprolol tartrate/ Lopressor		Solution 1 mg/mL Sodium chloride 9 mg/mL, pH 7.5	None	IV bolus over 2 minutes	Novartis, Antihypertensive, Antianginal, Antiarrhythmic
Metronidazole/ Flagyl		**1)** Solution 5 mg/mL, Sodium chloride 7.9 mg/mL, Sodium phosphate 0.5 mg/mL, Citric acid 0.22 mg/mL, pH 5-7, **2)** Lyophilized powder 500 mg (HCl salt) Mannitol 415 mg **pH 0.5-2.0**	Reconstitute with 4.4 mL WFI or saline to 100 mg/mL then further dilute with saline, dextrose 5% or lactated Ringer's to ≤ 8 mg/mL then **neutralize with Sodium carbonate to pH 6-7**	IV bolus/ IV infusion	SCS, Antibacterial
Mezlocillin sodium Mezlin		Crystalline powder 1-20 grams pH 4.5-8	Reconstitute with WFI, saline, dextrose 5% or lidocaine 0.5% (IM only) to 100-300 mg/mL, and for IV infusion further dilute with saline or dextrose 5%	IM/ IV bolus/ IV infusion	Bayer, Antibiotic

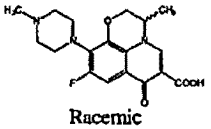
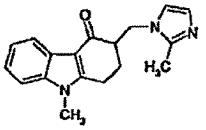
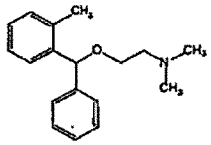
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Miconazole Monistat i.v. (Not in 1999 PDR as injectable, only as a cream)		Solution 10 mg/mL Cremophor 11.5%, Lactic acid 1 mg/mL, Methylparaben 0.5 mg/mL, Propylparaben 0.05 mg/mL, pH 3.7-5.7	Dilute with saline or dextrose 5% to 1 mg/mL	IV infusion over 30-60 minutes/ Intrathecal/ Bladder instillation	Janssen, Antifungal
Midazolam HCL/ Versed		Solution 1-5 mg/mL Sodium chloride 8 mg/mL, Benzyl alcohol 10 mg/mL, EDTA 0.01%, pH 3	None or dilute with saline or dextrose 5%	IM/ Slow IV bolus of 1 mg/mL	Roche, Anesthetic
Milrinone lactate/ Primacor		Solution 0.2-1.0 mg/mL Dextrose 47 mg/mL, Lactic acid 0.3-1.3 mg/mL pH 3-4	None or dilute with saline or dextrose 5% to 0.2 mg/mL.	IV infusion	Sanofi Winthrop, Cardiotonic, Inotropic/ Vasodilator
Minocycline HCL/ Minocin		Lyophilized powder 100 mg pH 2-3	Reconstitute with WFI to 20 mg/mL then diluted with 500-1000 mL saline or dextrose 5% to 0.1-0.2 mg/mL.	IV infusion	Lederle, Antibacterial

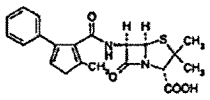
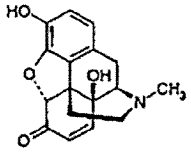
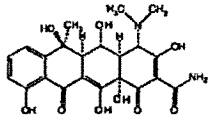
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Mitomycin/ Mutamycin		Lyophilized powder 5-40 mg Lactose 10-80 mg pH 6-8	Reconstitute with WFI to 0.5 mg/mL, may be further diluted with saline, dextrose 5% or lactated Ringer's to 0.02-0.04 mg/mL.	IV infusion	Bristol-Myers Squibb, Antineoplastic
Mitoxantrone HCL/ Novantrone		Solution 2 mg/mL, Sodium chloride 8 mg/mL, Acetate buffer 0.5 mg/mL, pH 3-4.5	Dilute with ≥ 50 mL saline or dextrose 5%.	IV infusion	Immunex, Antineoplastic
Mivacurium chloride/ Mivacron	 Mixture of 3 diastereoisomers	1) Solution 2 mg/mL Benzyl alcohol 0.9%, pH 3.5-5. 2) Solution 0.5 mg/mL Dextrose 5% pH 3.5-5	None	IV bolus (2 mg/mL)/ IV infusion (0.5 mg/mL)	Glaxo Wellcome, Short-acting muscle relaxant
Morphine sulfate/ Astramorph and Duramorph		Solution 0.5-25 mg/mL, Sodium chloride 9 mg/mL pH 2.5-6	For IV bolus dilute with 5 mL saline. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's to 0.1-1 mg/mL.	SC/ IM/ Slow IV bolus/ IV infusion/ Intrathecal/ Epidural	Astra, and Elkins-Sinn, Analgesic

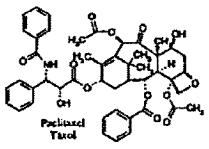
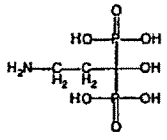
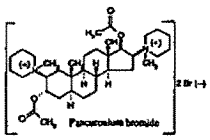
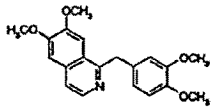
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Moxalactam disodium/ Moxam (Not in 1999 PDR)		Powder 1000-2000 mg Mannitol 150 mg/g moxalactam pH 5.5-6.5	For IM reconstitute with WFI, saline or lidocaine 0.5% to 333 mg/mL. For IV bolus reconstitute with WFI, saline dextrose 5% to 100 mg/mL, and for infusion further dilute with saline or dextrose 5%.	IM/ IV bolus/ IV infusion	Lilly, Antibacterial
Nafcillin sodium/ Unipen (Not in 1999 PDR)		Powder 1000-2000 mg Sodium citrate 35-70 mg pH 6-8.5	Reconstitute with WFI or saline to 250 mg/mL then for IV infusion further dilute with saline or dextrose 5% to 2-40 mg/mL.	IM/ IV bolus/ IV infusion	Wyeth-Ayerst and Apothecon, Antibacterial
Nalbuphine HCL/ Nubain		Solution 10-20 mg/mL w/wo Sodium chloride 2 mg/mL, Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL, Citrates 20 mg/mL, pH 3.5	None	SC/ IM/ IV bolus at 10 mg over 3-5 minutes	Endo, Analgesic

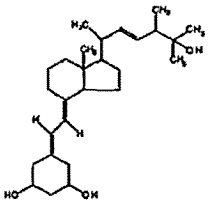
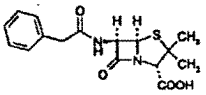
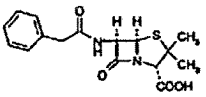
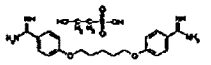
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Nalmefene HCl/ Revex		Solution 0.1-1.0 mg/mL Sodium chloride 9 mg/mL, pH 3.9	None or for IV bolus may be diluted 1:1 with saline.	SC/ IM/ IV bolus	Baxter, Narcotic antidote
Naloxone HCl/ Narcan		Solution 0.02-1 mg/mL Sodium chloride 8.3-8.6 mg/mL, (w/wo Methylparaben 0.18 mg/mL, Propylparaben 0.02 mg/mL) pH 3-4	None or for IV infusion dilute with saline or dextrose 5% to 0.004 mg/mL.	SC/ IM/ IV bolus/ IV infusion	Endo, Baxter, Elkins Sinn, Narcotic antagonist
Neostigmine methylsulfate/ Prostigmin		Solution 0.25-1 mg/mL w/wo Parabens 2 mg/mL, w/wo Phenol 4.5 mg/mL, Acetate pH 5.9	None	SC/ IM/ IV bolus	ICN, Cholinergic (acetylcholine esterase inhibitor)
Netilmicin sulfate/ Netromycin		Solution 100 mg/mL Benzyl alcohol 10 mg/mL, Sodium metabisulfite 2.4 mg/mL, Sodium sulfite 0.8 mg/mL, EDTA 0.1 mg/mL, pH 3.5-6	None for IM. For IV infusion dilute with 50-200 mL saline, dextrose 5% or lactated Ringer's to 2-3 mg/mL.	IM/ IV infusion	Schering, Antibacterial

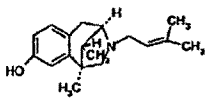
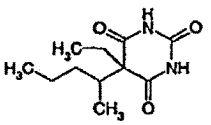
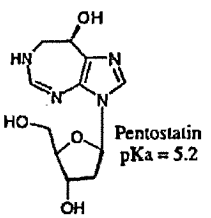
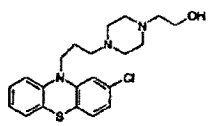
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Nicardipine/ Cardene		Solution 2.5 mg/mL **Sorbitol 48 mg/mL,** Citrates pH 3.5	Dilute with saline or dextrose 5% to 0.1 mg/mL.	IV infusion	Wyeth-Ayerst, Hypertension (Calcium influx inhibitor)
Nitroglycerin/ Nitro-Bid		Solution 5 mg/mL **Propylene glycol 4.5%, Ethyl alcohol 70%** pH 3-6	Dilute with saline or dextrose 5% to 25-40 ug/mL.	IV infusion	Hoechst Marion Roussel, Angina, Vasodilator
Norepinephrine bitartrate (Noradrenaline acid tartrate)/ Levophed (Not in 1999 PDR)		Solution 1 mg/mL Sodium chloride 7.5 mg/mL, Sodium metabisulfite 2 mg/mL, pH 3-4.5	Dilute with 250-1000 mL saline or dextrose 5% to 0.004 mg/mL	IV infusion	Sanofi Winthrop, Adrenergic (vasopressor) Antihypotensive
Octreotide acetate/ Sandostatin	 cyclic peptide	Solution 0.05-1.0 mg/mL Mannitol 45 mg/mL, w/wo Phenol 5 mg/mL, Lactic acid 3.4 mg/mL, Sodium bicarbonate, pH 4.2	None for SC, IM or IV bolus. For IV infusion dilute with 50-200 mL saline or dextrose 5%.	SC/ IM/ IV bolus over 3 minutes/ IV infusion over 15-30 minutes	Novartis, Antidiarrhea, GI hormone, Treatment of acromegaly

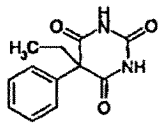
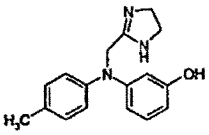
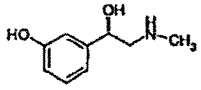
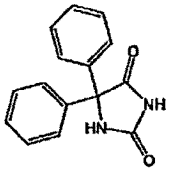
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Ofloxacin Floxin I.V.	 Racemic (S-isomer is Levofloxacin) pKa's ~ 4, 9	1) Solution 40 mg/mL, pH 3.5-5.5. 2) Ready-to-use solution 4 mg/mL, Dextrose 5% pH 3.8-5.8	Dilute with saline, dextrose 5% or lactated Ringer's to 4 mg/mL.	IV infusion over 60 minutes	Ortho-McNeil, Antibacterial
Ondansetron HCL/ Zofran	 Racemic	1) Solution 2 mg/mL, Sodium chloride 8.3-9.0 mg/mL, (w/wo Methylparaben 1.2 mg/mL, Propylparaben 0.15 mg/mL), Citric acid buffer pH 3.3-4. 2) Ready-to-use solution 0.64 mg/mL, Dextrose 5%, Citric acid buffer pH 3.0-4.0	For IV bolus inject 32 mg over 3 doses, and for IV infusion dilution with saline or dextrose 5% to 0.64 mg/mL.	IV bolus over 2-5 minutes/ IV infusion over 15 minutes	Glaxo Wellcome, Antiemetic (preventing nausea and vomiting induced chemotherapy)
Orphenadrine citrate/ Norflex		Solution 30 mg/mL Sodium chloride 2.9 mg/mL, Sodium bisulfite, pH < 7	None	IM/ IV bolus over 5 minutes	3M, Skeletal muscle relaxant

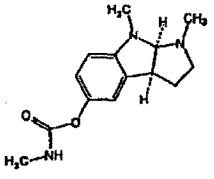
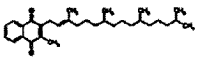
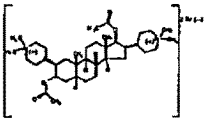
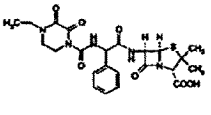
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Oxacillin sodium/ Prostaphilin (Not in 1999 PDR)		Powder 250-4000 mg Sodium phosphates 20 mg/1000 mg oxacillin, pH 6-8.5	Reconstitute with WFI or saline to 175 mg/mL for IM, to 100 mg/mL for IV bolus, and to 0.5-50 mg/mL for IV infusion.	IM/ IV bolus over 10 minutes/ IV infusion over 6 hours	Apothecon, Antibacterial
Oxymorphone HCL/ Numorphan	 pKa's = 8.2, 9.4	Solution 1-1.5 mg/mL, Sodium chloride 8 mg/mL, (w/wo Methylparaben 1.8 mg/mL, Propylparaben 0.2 mg/mL) pH 2.7-4.5	None for SC or IM. For IV dilute with 5 mL saline.	SC/ IM/ IV	ENDO, Analgesic
Oxytetracycline/ Terramycin		Solution 50-125 mg/mL, Lidocaine 20 mg/mL, **Propylene glycol 67-75%,** w/wo **Monothioglycerol 10 mg/mL,** Magnesium chloride 25-60 mg/mL, Sodium formaldehyde sulfoxylate 3-5 mg/mL, Ethanolamine 17-42 mg/mL, w/wo Citric acid 10 mg/mL, w/wo Propyl gallate 0.2 mg/mL	None	IM	Pfizer, Antibiotic

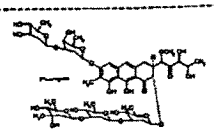
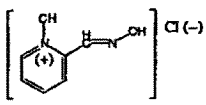
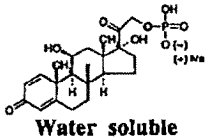
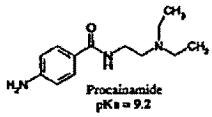
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Paclitaxel/ Taxol		Solution 6 mg/mL **Cremophor EL 51%, Ethyl alcohol 49% (v/v)**	Dilute with saline, dextrose 5% or lactated Ringer's to 0.3-1.2 mg/mL.	IV infusion	Bristol-Myers Squibb, Antineoplastic
Pamidronate disodium/ Aredia		Lyophilized powder, 30-90 mg Mannitol 375-470 mg, pH 6.5	Reconstitute with 10 mL WFI to 3-9 mg/mL then further dilute with 1000 mL saline or dextrose 5%.	IV infusion over 4-24 hours	Novartis, Inhibition of bone resorption
Pancuronium bromide/ Pavulon		Solution 1-2 mg/mL Benzyl alcohol 1%, Sodium chloride (isotonic), Sodium acetate 2 mg/mL pH 4	None for IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IV bolus/ IV infusion	Organon, Muscle relaxant
Papaverine HCL (Not in 1999 PDR)		Solution 30 mg/mL Chlorobutanol 0.5%, EDTA 0.005%, pH 3-4	None or dilute 1:1 with WFI.	IM/ IV bolus over 1-2 minutes	Lilly, Vasodilator (cerebral)

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Paricalcitol/ Zemplar		Solution 0.005 mg/mL **Propylene glycol 30%,** **Ethyl alcohol 20%**	None	IV bolus	Abbott, Treatment of secondary hyperpara-thyroidism associated with chronic failure.
Penicillin G benzathine and Penicillin G procaine / Bicillin		**Suspension** 150,000-600,000 units each/mL Lecithin 0.5% Povidone 0.1%, **Sodium carboxy-methylcellulose 0.55%,** Methylparaben 0.1%, Propylparaben 0.01%, Sodium citrate pH 6-8.5	Shake vial before withdrawing the desired dose.	IM	Wyeth-Ayerst, Antibacterial
Penicillin G potassium/ Pfizerpen		Powder 1,000,000-20,000,000 units Sodium citrate, pH 6-8.5	Reconstitute with WFI, saline or dextrose 5% to 30,000-1,000,000 units/mL.	IM/ IV infusion/ Intrapleural/ Intralesional/ Intrathecal	Pfizer, Antibacterial
Pentamidine isethionate/ Pentam 300 (Not in 1999 PDR)	 Pentamidine isethionate (hydroxy ethane sulfonic acid)	Powder 300 mg pH 4-5.5	Reconstitute with WFI or dextrose 5% to 60-100 mg/mL.	IM/ IV infusion	Fujisawa, Antiprotozoal

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Pentazocine lactate/ Talwin (Not in 1999 PDR as an injectable)		Solution 30 mg/mL Sodium chloride 1.5-2.8 mg/mL, Acetone sodium bisulfite 1-2 mg/mL, Methylparaben 1 mg/mL pH 4-5	None for SC or IM. For IV bolus dilute with saline to 5 mg/mL.	SC/ IM/ IV bolus	Sanofi Winthrop, Analgesic
Pentobarbital sodium/ Nembutal		Solution 50 mg/mL **Propylene glycol 40%,** **Ethyl alcohol 10%** **pH 9.5**	None or dilute with saline, dextrose 5% or lactated Ringer's.	IM/ Slow IV bolus (≤ 50 mg/min)	Abbott, Anticonvulsant, Sedative, Hypnotic, Anesthetic
Pentostatin/ Nipent	 Pentostatin pKa = 5.2	Lyophilized powder 10 mg Mannitol 50 mg pH 7.0-8.5	Reconstitute with 5 mL WFI to 2 mg/mL (IV bolus), which for IV infusion is further diluted with saline or dextrose 5% to 0.18-0.33 mg/mL.	Slow IV bolus/ IV infusion	Supergen, Antineoplastic (transition state inhibitor of adenosine deaminase)
Perphenazine/ Trilafon		Solution 5 mg/mL Sodium bisulfite, Citric acid, pH 4-5.5	None for IM. For IV dilute with saline to 0.5 mg/mL.	IM/ rarely IV or IV infusion at 1 mg/1-2 minutes	Schering, Antipsychotic, Antinausea

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Phenobarbital sodium/	 Phenobarbital pKa 1= 7.3, pKa2 = 11.8	Solution 30-130 mg/mL, **Propylene glycol 68%, Ethyl alcohol 10% pH 9.2-10.2**	None	IM/ Slow IV	Elkins-Sinn, Wyeth-Ayerst, Antipsychotic,
Phentolamine mesylate/ Regitine		Lyophilized powder 5 mg Mannitol 25 mg pH 4.5-6.5	Reconstitute with 1 mL WFI to 5 mg/mL which may be further diluted with saline to 0.1-1.0 mg/mL.	IM/ IV bolus/ IV infusion	Novartis, Antihypertensive
Phenyl-ephrine HCL/		Solution 10 mg/mL Sodium chloride 3.5 mg/mL, Citrate buffer 5 mg/mL, Sodium metabisulfite 2 mg/mL pH 3-6.5	None for SC or IM. For IV bolus dilute with saline to 1 mg/mL, and for IV infusion to 0.02-0.04 mg/mL.	SC/ IM/ IV bolus/ IV infusion	Baxter, Elkins-Sinn, Mydriatic, Decongestant
Phenytoin sodium/ (a.k.a. Dilantin)		Solution 50 mg/mL **Propylene glycol 40%, Ethyl alcohol 10% pH 10-12.3**	None	IM/ IV bolus at 50 mg/minute	Elkins-Sinn, Anticonvulsant

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Physo-stigmine salicylate		Solution 1 mg/mL Benzyl alcohol 2%, Sodium bisulfite 0.1%, pH 3.5-5.0	None	IM/ IV bolus at ≤ 1 mg/minute	Forrest, Cholinergic (Antidote for cholinesterase inhibitor)
Phytonadione (a.k.a Vitamin K1)/ Aqua-MEPHYTON		**Aqueous dispersion** 2-10 mg/mL **Polyoxyethylated fatty acid 70 mg/mL,** Dextrose 37 mg/mL, Benzyl alcohol 0.9%, pH 3.5-7	None for SC, IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's	SC/ IM/ IV bolus at ≤ 1 mg/minute/ IV infusion	Merck, Vitamin K deficiency
Pipe-curonium bromide/ Arduan		Lyophilized powder 10 mg pH 6	Reconstitute with 10 mL saline, dextrose 5% or lactated Ringer's to 1 mg/mL.	IV bolus	Organnon, Long acting neuromuscular blocking agent
Piperacillin sodium/ Piperacil		Lyophilized powder 2-40 grams pH 5.5-7.5	Reconstitute with WFI or saline to 400 mg/mL (IM) or 200 mg/mL (IV bolus), then further dilute with 50-100 mL saline, dextrose 5% or lactated Ringer's (IV infusion)	IM/ IV bolus over 3-5 minutes/ IV infusion over 30 minutes	Lederle, Antibacterial

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Plicamycin (Mithramycin) /Mithracin		Lyophilized powder 2.5 mg Mannitol 100 mg, Sodium phosphates pH 7	Reconstitute with 5 mL WFI to 0.5 mg/mL then further dilute with 1000 mL dextrose 5% or saline	IV infusion over 4-6 hours	Bayer, Antineoplastic
Pralidoxime chloride/ Protopam		Lyophilized powder 1000 mg pH 3.5-4.5	Reconstitute with 20 mL WFI to 50 mg/mL for IV bolus, and for IV infusion further dilute with 100 mL saline.	IV bolus over 2 minutes/ IV infusion over 15-30 minutes	Wyeth-Ayerst, Antidote for overdose or poisoning due to anticholinesterase
Prednisolone Phosphate sodium/ Hydeltrasol (Not in 1999 PDR as injectable)	 **Water soluble phosphate ester prodrug**	Solution 20 mg/mL **Niacinamide 25 mg/mL,** Phenol 5 mg/mL EDTA 0.5 mg/mL, Sodium bisulfite 1 mg/mL, pH 7-8	None or for IV infusion dilute with 50-1000 mL saline or dextrose 5%.	IM/ IV bolus/ IV infusion/ Soft tissue/ Intra-articular/ Intra-lesional	Merck, Anti-inflammatory, Adrenocortical steroid, Asthma, Glucocorticoid
Procainamide HCl	 Procainamide pKa = 9.2	Solution 100-500 mg/mL Benzyl alcohol 0.9%, Sodium bisulfite < 0.09%, pH 4-6	None for IM. For IV bolus dilute with dextrose 5% to 10-20 mg/mL, and for IV infusion dilute to 2-20 mg/mL.	IM/ IV bolus/ IV infusion (25-50 mg/minute)	Elkins-Sinn, Antiarrhythmic

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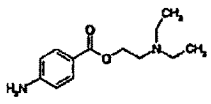
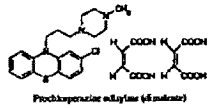
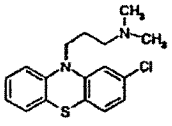
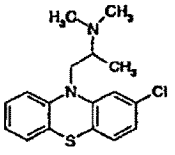
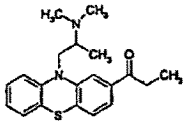
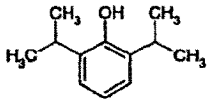
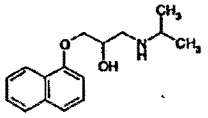
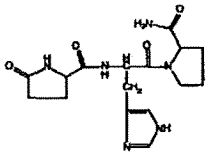
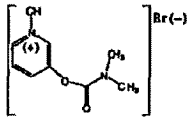
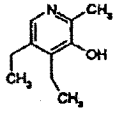
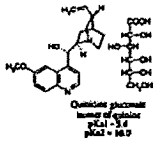
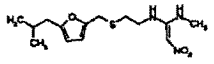
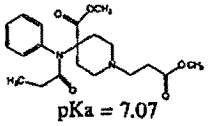
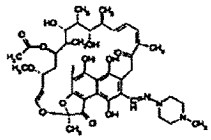
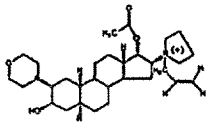
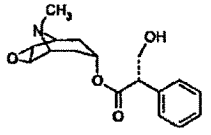
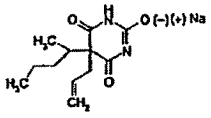
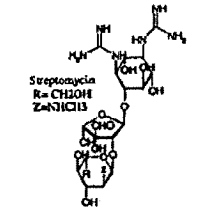
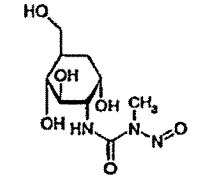
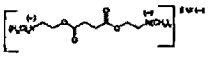
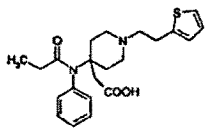
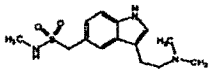
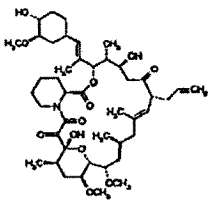
Procaine HCL/ Novocaine (Not in 1999 PDR)		Solution 10-100 mg/mL, Sodium chloride (isotonic), Acetone sodium bisulfite < 4 mg/mL, pH 3-5.5	None or dilute with dextrose 5%.	Infiltration/ Peripheral or sympathetic nerve block/ Subarachoid block	Sanofi Winthrop, Local anesthetic
Pro-chlorperzine edisylate/ Compazine		Solution 5 mg/mL Sodium saccharin 0.9 mg/mL, Benzyl alcohol 0.75%, Sodium biphosphate 5 mg/mL, Sodium tartrate 12 mg/mL, pH 4-6	None for IM. For IV bolus dilute with saline to 1 mg/mL, and for IV infusion dilute to 0.01-0.02 mg/mL.	IM/ IV bolus/ IV infusion/	SmithKline Beecham, Antiemetic, Antipsychotic
Promazine HCL/ Sparine (Not in 1999 PDR)		Solution 50 mg/mL Sodium formaldehyde sulfoxylate < 1 mg/mL, Sodium citrate pH 4-5.5	None for IM. For IV bolus dilute with saline to 2.5-25 mg/mL.	IM/ IV bolus	Wyeth-Ayerst, Antipsychotic, Tranquilizer
Promethazine HCL/ (Phenergan) (See also Meperdine/ Mepergan		Solution 25 mg/mL Meperidine 25 mg/mL, EDTA 0.1 mg/mL, Calcium chloride 0.04 mg/mL, Sodium formaldehyde sulfoxylate 0.75 mg/mL, Sodium metabisulfite 0.25 mg/mL, Sodium acetate, pH 3.5-6	None for SC or IM. For IV infusion dilute with at least 5 mL saline to 10 mg/mL.	SC/ IM/ IV infusion at 25 mg/min	Wyeth-Ayerst, Analgesic (narcotic), Sedative, Anesthetic

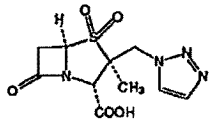
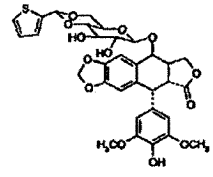
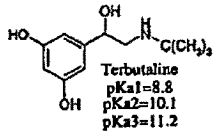
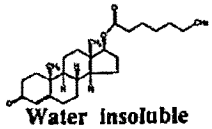
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Propiomazine HCL/ Largon (Not in 1999 PDR)		Solution 20 mg/mL Sodium formaldehyde sulfoxylate, Sodium acetate pH 4.7-5.3	None	IM/ IV bolus at 10 mg/min	Wyeth-Ayerst, Tranquilizer, Sedative, Hypnotic
Propofol/ Diprivan	 pKa =11	**Emulsion,** 10 mg/mL, Soybean oil 100 mg/mL, Glycerol 22.5 mg/mL, Egg lecithin 12 mg/mL, EDTA pH 7-8.5 (under nitrogen to prevent oxidation)	None (shake well)	IV bolus/ IV infusion	Zeneca, Anesthetic, Sedative
Propranolol/ Inderal		Solution 1 mg/mL Citric acid pH 2.8-3.5	None for IV bolus, but for IV infusion dilute with dextrose 5% to 0.02-0.1 mg/mL.	IV bolus/ IV infusion	Wyeth-Ayerst, Antiarrhythmic, Antihypertensive emergencies, Antianginal
Protirelin/ Thyrel		Solution 0.5 mg/mL Sodium chloride 9 mg/mL pH 6.5	None	IV bolus	Ferring, Diagnostic assessment of thyroid function

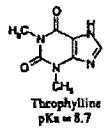
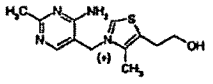
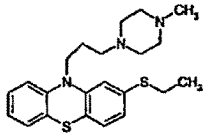
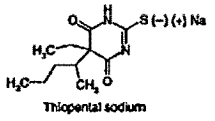
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Pyridostigmine bromide/ Mestinon		Solution 2 mg/mL Methylparaben 0.2%, Propylparaben 0.02%, Sodium citrate pH 5	None	IM/ IV bolus	ICN, Cholinesterase inhibitor
Pyridoxine/ (vitamin B6) (Not in 1999 PDR as an injectable)		Solution 100 mg/mL, Benzyl alcohol 1.5%, **pH 2-3.8**	None	SC/ IM/ IV	Steris
Quinidine gluconate (Not in 1999 PDR as an injectable)		Solution 80 mg/mL EDTA 0.005%, Phenol 0.25%, pH 5.5-7	None for IM. For IV dilute with 50 mL dextrose 5% to 16 mg/mL	IM/ IV infusion	Lilly, Antimalaria, Antiarrhythmic
Ranitidine HCL/ Zantac		1) Solution 25 mg/mL, Phenol 5 mg/mL, Sodium phosphates 3.5 mg/mL pH 6.7-7.3, 2) Solution 1 mg/mL, Sodium chloride 4.5 mg/mL, Citric acid 0.3 mg/mL, Sodium phosphates 1.8 mg/mL pH 6.7-7.3	None for IM (25 mg/mL). For IV bolus dilute with saline to 2.5 mg/mL. For IV infusion use the premixed 1 mg/mL formulation or dilute with dextrose 5% to 0.5 mg/mL.	IM/ IV bolus/ IV infusion	Glaxo Wellcome, Antiulcerative

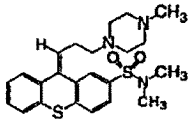
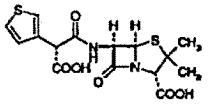
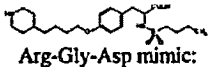
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Remifentanil HCl/ Ultiva	 pKa = 7.07	Lyophilized powder 1-5 mg Glycine 15 mg pH 3	Reconstitute with WFI to 1 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to 0.02-0.25 mg/mL.	IV infusion	Glaxo Wellcome, Analgesic
Rifampin/ Rifadin I.V.	 Rifampin pKa1 = 1.7 (4-phenoxy) pKa2 = 7.9 (3-piperazine)	Powder 600 mg Sodium formaldehyde sulfoxylate 10 mg, pH 7.8-8.8	Reconstitute with WFI to 60 mg/mL, then further dilute with 100-500 mL saline or dextrose 5%.	IV infusion	Hoechst Marion Roussel, Antibacterial
Rocuronium bromide/ Zemuron		Solution 10 mg/mL Sodium acetate 2 mg/mL pH 4	None for IV bolus. For IV infusion dilute with saline or dextrose 5% or lactated Ringer's to 0.5 mg/mL.	IV bolus/ IV infusion	Organnon, Nondepolarizing neuromuscular blocking agent
Scopolamine HBr (Hyoscine HBR)/ (Not in 1999 PDR as injectable)		Solution 0.4-1 mg/mL Methylparaben 1.8 mg/mL Propylparaben 0.2 mg/mL pH 3.5-6.5	None for SC or IM. For IV bolus and infusion dilute with WFI.	SC/ IM/ IV bolus/ IV infusion	Fujisawa, Anticholinergic

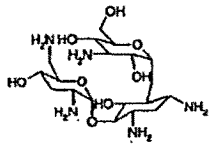
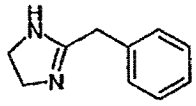
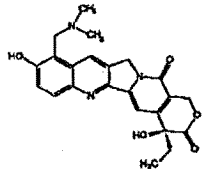
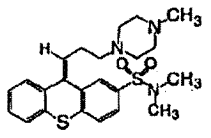
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Secobarbital sodium (in Tubex cartridge)		Solution 50 mg/mL **Propylene glycol 50%,** Phenol < 2.5 mg/mL **pH 9.5-10.5**	None for IM. For IV dilute with WFI, saline or lactated Ringer's to 5 mg/mL.	IM (< 5 mL)/ Slow IV bolus at < 50 mg/15 seconds	Wyeth-Ayerst, Sedative, Hypnotic, Preanesthetic
Streptomycin sulfate		Solution 400 mg/mL Sodium citrate 12 mg/mL, Phenol 0.25%, Sodium metabisulfite 2 mg/mL pH 4.5-7	None for IM. For IV infusion dilute with 100 mL dextrose 5%.	Deep IM/ IV infusion not recommended, but it may be performed	Pfizer, Antibacterial
Streptozocin/ Zanosar		Lyophilized powder 1000 mg Citric acid 220 mg, pH 3.5-4.5	Reconstitute with 9.5 mL saline or dextrose 5% to 100 mg/mL (IV bolus), then further dilute with 10-200 mL saline or dextrose 5% (IV infusion).	IV bolus/ IV infusion over 0.2-6 hours	Pharmacia & Upjohn, Antineoplastic, (inhibits DNA synthesis)
Succinylcholine chloride/ Anectine		Solution 20 mg/mL Sodium chloride (isotonic) Methylparaben 0.1%, pH 3.5	None for IM or IV bolus. For IV infusion dilute with saline or lactated Ringer's to 1-2 mg/mL.	IM/ IV bolus/ IV infusion	Glaxo Wellcome, Muscle relaxant - ultra short acting

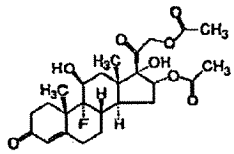
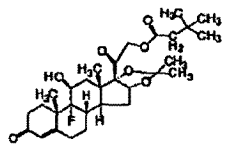
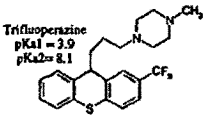
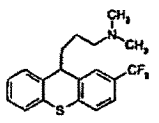
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Sufentanil citrate/ Sufenta		Solution 0.05 mg/mL pH 3.5-6	None	IM/ IV bolus/ IV infusion/ Epidural for labor or delivery	Taylor, Analgesic (narcotic)
Sulbactam (See ampicillin)					
Sulfa-methoxazole (See trimethoprim					
Sumatriptan succinate/ Imitrex		Solution 12 mg/mL Sodium chloride 7 mg/mL pH 4.2-5.3	None	SC	Glaxo Wellcome, Migraine headache
Tacrolimus (FK 506)/ Prograf		**Non-aqueous Solution** 5 mg/mL **Ethyl alcohol 80%, Cremophor EL 20%**	Dilute 250 or 1000-fold into saline or dextrose 5% to 0.004-0.02 mg/mL	IV infusion	Fujisawa, Immuno-suppresent (transplant rejection)

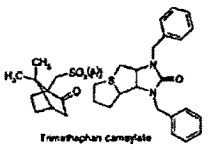
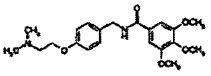
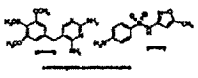
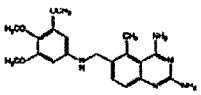
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Tazobactam sodium and Piperacillin sodium/ Zosyn		Lyophilized powder 250 - 500 mg (Tazobactam), 2000-4000 mg (Piperacillin) pH 4.5-5.5	Reconstitute with 20-40 mL WFI, saline or dextrose 5%, then further dilute with saline or dextrose 5% to 50-150 mL.	IV infusion	Lederle, Antibacterial combination
Teniposide (VM-26)/ Vumon		**Non-aqueous Solution** 50 mg/mL **Cremophor EL 500 mg/mL, Ethyl alcohol 42%, Dimethylacetamide 60 mg/mL,** Benzyl alcohol 30 mg/mL pH 5 (Maleic acid)	Dilute with saline or dextrose 5% to 0.1-1 mg/mL	IV infusion over 30-60 minutes	Bristol-Myers Squibb, Antineoplastic (causes breaks in DNA)
Terbutaline sulfate/ Brethine and, Bricanyl	 Terbutaline pKa1=8.8 pKa2=10.1 pKa3=11.2	Solution 1 mg/mL Sodium chloride 8.9 mg/mL pH 3-5	None	SC	Novartis and Hoechst Marion Roussel, Broncodilator
Testosterone Enanthate/ Delatestryl	 **Water insoluble hexanate ester prodrug**	**Non-aqueous solution** 200 mg/mL **Sesame oil,** Chlorobutanol 5 mg/mL	None	IM	BTG

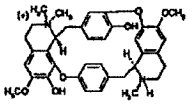
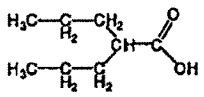
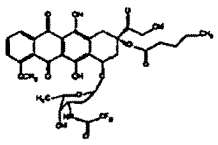
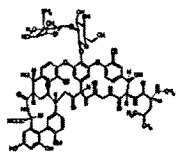
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Theophylline/ Aerolate (Not in 1999 PDR as injectable)	 Theophylline pKa = 8.7	Solution 0.4 - 4 mg/mL, pH 4.3	None	IV infusion	Abbott, Baxter, McGraw, Bronchodilator
Thiamine (Vitamin B1) HCL/		Solution 100 mg/mL Sodium formaldehyde sulfoxylate 1 mg/mL, Chlorobutanol 3.5 mg/mL pH 2.5-4.5	None for IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	IM/ IV bolus/ IV infusion	Elkins-Sinn, Vitamin
Thiethyl-perazine maleate/ Torecan		Solution 5 mg/mL **Sorbitol 20 mg/mL** Sodium metabisulfite 0.25 mg/mL, Ascorbic acid 1 mg/mL, pH 3-4	None	IM	Roxane, Antiemetic (nausea and vomiting
Thiopental sodium/ Pentothal sodium	 Thiopental sodium	Lyophilized powder 250-5000 mg Sodium carbonate 60 mg/1000 mg thiopental **pH 10-11**	Reconstitute. with WFI, saline or dextrose 5% to 2-50 mg/mL	IV infusion	Baxter, Short acting anesthetic
Thiotepa/ Thioplex		Lyophilized powder 15 mg pH 5.5-7.5	Reconstitute with 1.5 mL WFI to 10 mg/mL, then further dilute with saline to ~ 2 mg/mL.	IV bolus/ Intracavitary/ Intravesical	Immunex, Antineoplastic

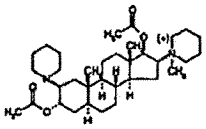
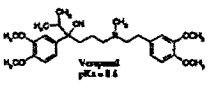
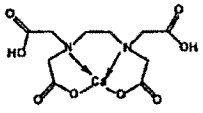
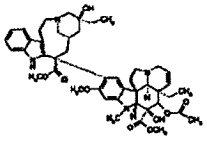
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Thiothixene HCL/ Navane		1) Lyophilized powder 10 mg Mannitol 100 mg pH 2.3-3.7 2) Solution 2 mg/mL, Dextrose 5%, Benzyl alcohol 0.9%, Propyl gallate 0.02% pH 2.5-3.5	Reconstitute the powder with 2.2 mL WFI to 5 mg/mL.	IM	Pfizer, Antipsychotic
Ticarcillin disodium/ Ticar		Lyophilized powder 1-30 grams pH 6-8	For IM reconstitute. with WFI, saline or lidocaine 1% (without epinephrine) to 385 mg/mL. For IV bolus reconstitute with saline, dextrose 5% or lactated Ringer's to 200 mg/mL, then for IV infusion further dilute with saline, dextrose or lactated Ringer's to 30-100 mg/mL.	IM/ IV bolus/ IV infusion	SmithKline Beecham, Antibacterial
Tirofiban HCL/ Aggrastat	 Arg-Gly-Asp mimic: [binds to (GP) IIb/IIIa ($\alpha_{IIb}\beta_3$)]	Solution 0.05-0.25 mg/mL, Sodium chloride 8-9 mg/mL, Citrates 0.6-3 mg/mL; pH 5.5-6.5	Dilute with saline or dextrose 5% to 0.05 mg/mL.	IV infusion	Merck, Antithrombolytic (nonpeptide antagonist of platelet receptor GPIIb/IIIa)

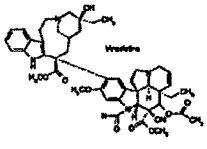
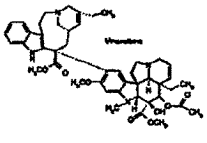
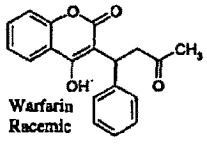
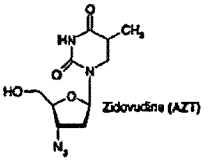
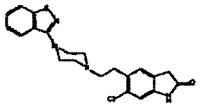
Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Tobramycin sulfate/ Nebcin		Solution 10-40 mg/mL Phenol 1.25-5 mg/mL, Sodium bisulfite 1.6-3.2 mg/mL, EDTA 0.1 mg/mL, pH 3-6.5	None for IM. For IV infusion dilute into 50-200 mL	IM/ IV infusion	Lilly and Lederle, Antibacterial
Tolazoline HCL/ Priscoline HCL (Not in 1999 PDR)		Solution 25 mg/mL Tartaric acid 6.5 mg/mL, Sodium citrate 6.5 mg/mL pH 3-4	None for SC, IM or IV bolus. For IV infusion dilute with saline, dextrose 5% or lactated Ringer's.	SC/ IM/ IV bolus/ IV infusion/ Intra-arterial	Ciba Geneva, Vasodilator)
Topotecan/ Hycamtin		Lyophilized powder 4 mg Mannitol 48 mg, Tartaric acid 20 mg, pH 2.5-3.5	Reconstitute with 4 mL WFI, then further dilute with saline or dextrose 5%.	IV infusion	SmithKline Beecham, Antineoplastic
Torsemide/ Demadex		Solution 10 mg/mL PEG 400 TRIS pH (no details reported)	Dilute with saline or dextrose 5% to 0.1-1 mg/mL.	IV infusion	Roche, Diuretic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Triamcinolone Diacetate/ Aristocorte		**Suspension** 20-40 mg/mL **PEG 3350 at 3%,** **TWEEN 80 at 0.2%** Sodium chloride 8.5 mg/mL, Benzyl alcohol 9 mg/mL, pH ~ 6	None	IM/ Intra-articular/ Intrasynovial/ Intralesional	Fujisawa, Glucocorticoid
Triamcinolone Hexacetonide/ Aristospan		**Suspension** 5-20 mg/mL **Sorbitol 50%,** TWEEN 80 at 0.2-0.4% Benzyl alcohol 9 mg/mL, pH 4.5- 6.5	None	Intra-articular/ Intralesional	Fujisawa, Glucocorticoid
Trifluoperazine HCL/ Stelazine		Solution 2 mg/mL Sodium saccharin 0.3 mg/mL, Benzyl alcohol 0.75%, Sodium tartrate 4.75 mg/mL, Sodium biphosphate 11.6 mg/mL, pH 4-5	None	IM	SmithKline Beecham, Antipsychotic
Triflupromazine (Not in 1999 PDR)		Solution 10-20 mg/mL, Benzyl alcohol 1.5%, Sodium chloride pH 3.5-5.2	None	IM/ IV bolus	Apotheeon, Antipsychotic, Tranquilizer

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Trimethaphan camsylate/ Arfonad (Not in 1999 PDR)		Solution 50 mg/mL Sodium acetate pH 5.2	Dilute with dextrose 5% to 1 mg/mL.	IV infusion	Roche, Antihypertensive
Trimetho-benzamide HCL/ Tigan		Solution 100 mg/mL, Methyl and propylparabens 0.1% (or phenol 0.45%), w/wo EDTA 0.1 mg/mL Sodium citrate 0.5 mg/mL, Citric acid 0.2 mg/mL pH 5	None	IM	Roberts, Antiemetic (control of nausea and vomiting)
Trimetho-prim & Sulfa-methoxazole/ Bactrim and Septra		Solution 16 mg/mL trimethoprim, 80 mg/mL sulfamethoxazole, **Propylene glycol 40%,** **Ethyl alcohol 10%,** **Diethanolamine 0.3%,** Benzyl alcohol 1%, Sodium metabisulfite 0.1% **pH 10**	Dilute 20-40 fold into dextrose 5%.	IV infusion	Roche and Monacrh, Antibacterial combination
Trimetrexate glucuronate/ Neutrexin		Lyophilized powder 25-200 mg pH 3.5-4.5	Reconstitute with WFI or dextrose 5% to 12.5 mg/mL then further dilute with dextrose 5% to 0.25-2 mg/mL.	IV infusion	U.S. Biosciences, In combination with leucovorin in treatment of pneumonia

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Tubocurarine chloride (Not in 1999 PDR)		Solution 3 mg/mL Sodium chloride (isotonic), Benzyl alcohol 0.9%, w/wo Chlorobutanol, w/wo Sodium metabisulfite 1 mg/mL, w/wo Sodium bisulfite 0.1%, Citric acid 1 mg/mL pH 2.5-5	None	IM/ IV bolus	Abbott, Lilly, Muscle relaxant
Valproate sodium/ Depacon		Solution 100 mg/mL EDTA 0.4 mg/mL pH 7.6	Dilute with 50 mL saline, dextrose 5% or lactated Ringer's.	IV infusion	Abbott, Antiepileptic
Valrubicin/ Valstar		**Nonaqueous solution** 40 mg/mL **Cremophor EL 50%,** **Ethyl alcohol 50%**	Dilute 20 mL with 55 mL saline to 10.6 mg/mL.	Intravesical instillation in the urinary bladder	Anthra, Antineoplastic
Vancomycin HCL/ Vancocin HCL		Lyophilized powder 500-1000 mg pH 2.5-4.5	Reconstitute with WFI to 50 mg/mL, then further dilute with saline, dextrose 5% or lactated Ringer's to ~ 5 mg/mL.	Intermittent or continuous IV infusion	Lilly, Antibiotic (tricyclic glycopeptide)

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Vecuronium bromide/ Norcuron		Lyophilized powder 10-20 mg Mannitol 97-194 mg, Citric acid 20-41 mg, Sodium phosphate dibasic 16-32 mg, pH 4	Reconstitute with WFI to 1 mg/mL (IV bolus), then further dilute with saline, dextrose 5% or lactated Ringer's to 0.1 mg/mL (IV infusion)	IV bolus/ IV infusion	Organon, Muscle relaxant
Verapamil HCL/ Isoptin (Not in 1999 PDR as an injectable)		Solution 2.5 mg/mL, Sodium chloride 8.5 mg/mL pH 4-6	None	IV bolus/ IV infusion	Knoll, Antianginal, Antiarrhythmic
Versenate disodium calcium (EDTA)		Solution 200 mg/mL	For IM to minimize pain add lidocaine or procaine 0.5%. For IV infusion dilute with 250-500 mL saline or dextrose 5%.	IM/ IV infusion	3M, Reduction of plasma levels of lead
Vinblastine sulfate/ Velban		Lyophilized powder 10 mg pH 3.5-5.5	Reconstitute with saline to 1 mg/mL.	IV bolus	Lilly, Antineoplastic

Drug Name/ Marketed Name	Structure	Formulation	Preadministration Preparation	Route of Administration	Company and Indication
Vincristine sulfate/ Oncovin		Solution 1 mg/mL, Mannitol 100 mg/mL, Methylparaben 1.3 mg/mL, Propylparaben 0.2 mg/mL, Acetic acid pH 3.5-5.5	None for IV bolus. For IV infusion dilute with saline or dextrose 5%	IV bolus/ IV infusion	Lilly, Antineoplastic
Vinorelbine tartrate/ Navelbine		Solution 10 mg/mL pH 3.5	Dilute with saline or dextrose 5% to 2-5 mg/mL (IV bolus), or to 0.5-2 mg/mL (IV infusion).	IV bolus/ IV infusion	Glaxo Wellcome, Antineoplastic
Warfarin sodium/ Coumadin		Lyophilized powder 5.5 mg Mannitol 100 mg, Sodium chloride 0.3 mg, Sodium phosphates 14 mg, pH 8.1-8.3	Reconstitute. with WFI to 2 mg/mL.	Slow IV over 2 minutes	Du Pont Pharma, Anticoagulant
Zidovudine/ Retrovir		Solution 10 mg/mL pH 5.5	Dilute with 5% dextrose to < 4 mg/mL.	IV infusion	Glaxo Wellcome, Antiviral
Ziprasidone mesylate/		Solution mg/mL Sulfobutylether-ß-cyclodextrin pH 7 (Details not reported)		IM SC	Pfizer, Antipsychotic (Phase III completed 1999)

ATTACHMENT F - COMPILATION

TAB 15

Review of Excipients and pH's for Parenteral Products Used in the United States

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ABSTRACT: Excipients used in U.S. parenteral products were categorized according to their function. The concentrations used in commercial products were also identified. The range of pH value in various products was tabulated with emphasis on products with extreme pH's. The uses of excipients in parenteral dosage form were discussed.

Introduction

The choice of excipients used in parenteral products is not as liberal as in other dosage forms because of two major concerns: safety in parenteral use and feasibility in sterilization. Acceptance of a substance to be used as an excipient in parenteral products often involves lengthy safety testing or production trials. To avoid uncertainty, most formulators tend to employ compounds used in existing parenteral products. This survey is intended to provide an overall view of excipients used in parenteral products available in the United States. For reason of stability or solubility the pH of a product could not always be adjusted to physiological pH (7.4). When problems arise formulators are often inquisitive about the pH of other products. This review, therefore, focuses on products with extreme pH's, and shows tabulation of pH range, acid or base used for adjustment, and product identity.

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Method

The *Physician's Desk Reference* (PDR), 1977–1980 editions (1), were the major source of information. For products not described in the PDR, manufacturers were contacted and the package inserts solicited.

Excipients were categorized according to their presumed function in the formulation. Concentrations were all calculated on % (w/v) base. For dry products, concentrations were calculated according to the commonly diluted volume. For each excipient, ascending concentrations were illustrated by the corresponding products and manufacturer. Examples of only three products were given if there were three or more products containing the same concentration of excipient. One exception is the category of buffer for which only the highest concentration was listed. All of this is shown in Table I.

Many products did not list pH in the PDR. Nevertheless, in these cases information was gathered from other references (2, 3), and Table II illustrates the variety of products employing extreme pH's. For conciseness only one example was given for each particular pH range.

Discussion

This survey brought to light the use of a few excipients uncommon for parenteral use such as phenylmercuric nitrate, dioctyl sodium sulfosuccinate, pectin, etc. Most of these excipients were found in old formulations not covered by the present FDA regulations. On the other hand, some excipients recommended

TABLE I.

I. Antimicr

1) Benz

2) Benz

3) Buty

4) Chlo

5) Met

6) Met

7) Myr

8) Phe

November-Dece

TABLE I. Excipients for Parenteral Products

I. Antimicrobial Preservatives		
1) Benzyl alcohol	0.5%	Cleocin Phosphate (Upjohn)
	0.75%	Stelazine (SKF)
		Compazine (SKF)
	0.83%	Solu-Medrol (Upjohn)
	0.88%	Cortisone Acetate (Upjohn)
	0.9%	Pronestyl (Squibb)
		Kenolog (Squibb)
		Vistaril (Pfizer)
	1.0%	Solu-Medrol (Upjohn)
	1.2%	Prolixin Decanoate (Squibb)
	1.5%	Vallum (Roche)
		Vesprin (Squibb)
	2.0%	Adrenosem (Beecham)
		Aminophyllin (Searle)
	4.0%	Kestrin (Hyrex)
	5.0%	Durabolin (Organon)
	10.0%	Deca-Durabolin (Organon)
2) Benzethonium chloride	0.01%	Ketaject (Bristol)
		Flexoject (Mayrand)
3) Butylparaben	0.015%	Duracillin A.S. (Lilly)
4) Chlorobutanol	0.25%	Nydrazid (Squibb)
		Novocain (Winthrop)
	0.5%	Hexa-Betalin (Lilly)
		Atropine Sulfate (Lilly)
5) Metacresol	0.16%	NPH Iletin (Lilly)
	0.1%	Demerol Hydrochloride (Winthrop)
	0.25%	Protamine, Zinc & Iletin (Lilly)
6) Methylparaben	0.01%	Lidoject-1 (Mayrand)
	0.045%	Celbenin (Beecham)
	0.065%	Apresoline Hydrochloride (Ciba)
	0.1%	Bicillin L-A (Wyeth)
		Prolixin (Squibb)
		Talwin (Winthrop)
	0.13%	Crysticillin (Squibb)
	0.15%	Neo-Betalin 12 (Lilly)
	0.18%	Garamycin (Schering)
		Bactocill (Beecham)
7) Myristylgamma picolinium chloride	0.17%	Depo-Provera (Upjohn)
8) Phenol	0.065%	NPH Iletin (Lilly)
	0.18%	Crysticillin (Squibb)
	0.25%	Ergotrate Maleate (Lilly)
	0.45%	Tensilon (Roche)
		Prostigmin (Roche)
	0.5%	Sus-Phrine (Berlex)
		Tagamet (SKF)

continued

TABLE I. *Continued*

9) Phenylmercuric nitrate	0.001%	Estradurin (Ayerst)
10) Propylparaben	0.005%	Bactocill (Beecham)
		Ceibenin (Beecham)
	0.01%	Prolixin (Squibb)
		Bicillin L-A (Wyeth)
		Bicillin C-R (Wyeth)
	0.02%	Crysticillin (Squibb)
		Garamycin (Schering)
	0.035%	Apresoline Hydrochloride (Ciba)
11) Thimerosal	0.001%	Wydase (Wyeth)
	0.01%	Test-Estrin (Marlyn)
		MICRhoGAM (Ortho)
	0.02%	Theelin R-P (Parke-Davis)
II. Solubilizers, Wetting Agents or Emulsifiers		
1) Dimethylacetamide	0.01%	Serpasil (Ciba)
2) Dioctyl sodium sulfosuccinate	0.015%	Testoject (Mayrand)
3) Egg yolk phospholipid	1.2%	Intralipid 10% (Cutter)
4) Ethyl alcohol	0.61%	Syntocinon (Sandoz)
	3.0%	Morrhuate Sodium (Lilly)
	6.0%	Kestrin (Hyrex)
	10.0%	Valium (Roche)
		Dilantin (Parke-Davis)
	49.0%	Crystodigin (Lilly)
5) Ethyl lactate	0.1%	Ergotrate Maleate (Lilly)
6) Glycerin	14.6%	Gynergen (Sandoz)
	15.0%	Cedilanid-D (Sandoz)
		DHE 45 (Sandoz)
	25.0%	Sus-Phrine (Berlex)
7) Lecithin	0.5%	Bicillin L-A (Wyeth)
		Wycillin (Wyeth)
	1.5%	Duracillin A.S. (Lilly)
	2.3%	Crysticillin (Squibb)
8) PEG-40 Castor oil[a]	7.0%	AquaMEPHYTON (MSD)
	11.5%	Monistat (Janssen)
9) Polyethylene glycol 300	0.01%	Apresoline Hydrochloride (Ciba)
	5.0%	Serpasil (Ciba)
	30.0%	Sandril (Lilly)
	50.0%	Seconal sodium (Lilly)
		Robaxin (Robins)
10) Polysorbate 20	0.01%	Test-Estrin (Marlyn)
11) Polysorbate 40	0.05%	Bicillin L-A (Wyeth)
12) Polysorbate 80	0.04%	Kenalog (Squibb)
	0.18%	Depo-Provera (Upjohn)
	0.20%	Aristospan (Lederle)
	0.39%	Cortisone Acetate (Upjohn)

continued

TABLE I. Co

13) Povl

14) Prop

15) Sodi
16) Sorb
17) Theo
III. Buffers
1) Ace
2) Adi
3) Ber
4) Cit
5) Ma
6) Pot
7) Sod
8) Sod
9) Lac
10) Sod
11) Sod
12) Sod
13) Sod
14) Sod
15) Tar
IV. Antioxid
1) Ace

2) Asc

TABLE I. *Continued*

	0.40%	Aristospan (Lederle)
		Duracillin A.S. (Lilly)
	4.0%	Librium (Roche)
13) Povidone	0.2%	Kestrin (Hyrex)
	0.3%	Crysticillin (Squibb)
		Wycillin (Wyeth)
	0.5%	Crysticillin (Squibb)
	0.55%	Bicillin C-R (Wyeth)
	0.6%	Bicillin L-A (Wyeth)
	1.0%	Duracillin A.S. (Lilly)
14) Propylene glycol	0.2%	Estradurin (Ayerst)
	20.0%	Librium (Roche)
	40.0%	Valium (Roche)
		Dilantin (Parke-Davis)
	50.0%	Dramamine (Searle)
		Dramoject (Mayrand)
15) Sodium desoxycholate	0.21%	Fungizone (Squibb)
16) Sorbitan monopalmitate	0.05%	Bicillin L-A (Wyeth)
17) Theophylline	5.0%	Dicurin Procaine (Lilly)
III. Buffers		
1) Acetic acid	0.22%	Neo-betalin 12 Crystalline (Lilly)
2) Adipic acid	1.0%	Serpasil (Ciba)
3) Benzoic acid and sodium benzoate	5.0%	Valium (Roche)
4) Citric acid	0.5%	Aldomet (MSD)
5) Maleic acid	1.6%	Librium (Roche)
6) Potassium phosphate	0.1%	Ouabain (Lilly)
7) Sodium phosphate monobasic	1.7%	Solu-Medrol (Upjohn)
8) Sodium phosphate dibasic	0.71%	Celestone (Schering)
9) Lactic acid	0.1%	Ergotrate Maleate (Lilly)
10) Sodium acetate	0.8%	Soluject (Mayrand)
11) Sodium bicarbonate	0.005%	Amipaque (Winthrop)
12) Sodium carbonate	0.06%	Brevital (Lilly)
13) Sodium citrate	4.0%	Duracillin A.S. (Lilly)
14) Sodium tartrate	1.2%	Compazine (SKF)
15) Tartaric acid	0.65%	Priscoline (Ciba)
IV. Antioxidants		
1) Acetone sodium bisulfite	0.2%	Taiwin (Winthrop)
		Bronkephrine (Breon)
	0.4%	Novocain (Winthrop)
	0.8%	Novocain (Breon)
2) Ascorbic acid	0.05%	Serpasil (Ciba)
	0.1%	Torecan (Boehringer)
	0.2%	Thorazine (SKF)
	1.0%	Sus-phrine (Cooper)
		Sandril (Lilly)
	3.0%	Tetracyn IV (Pfizer)

continued

TABLE I. *Continued*

3) Monothioglycerol	0.1%	Sandril (Lilly)
		Streptomycin Sulfate (Lilly)
	0.2%	Aldomet (MSD)
	0.5%	Phenergan (Wyeth)
4) Propyl gallate	0.02%	Navane (Roerig)
5) Sodium bisulfite	0.05%	Amigen (Travenol)
	0.08%	A-MethaPred (Abbott)
	0.09%	Pronestyl (Squibb)
	0.1%	Decadron (MSD)
		Tubocurarine (Lilly)
	0.16%	A-MethaPred (Abbott)
	0.2%	Levophed Bitartrate (Breon)
		Neo-Synephrine (Winthrop)
		Pronestyl (Squibb)
	0.32%	Nebcin (Lilly)
		Garamycin (Schering)
		Aldomet (MSD)
	0.45%	Kantrex (Bristol)
	0.66%	Kantrex (Bristol)
		Amikin (Bristol)
	1.0%	Intropin (Arnar-Stone)
6) Sodium metabisulfite	0.025%	Phenoject-50 (Mayrand)
		Torecan (Boehringer)
	0.148%	Reglan (Robins)
7) Sodium formaldehyde sulfoxylate	0.005%	Bejectal (Abbott)
	0.01%	Crysticillin (Squibb)
	0.03%	Crysticillin (Squibb)
8) Sodium sulfide	0.004%	Bejectal (Abbott)
		Bejex (Abbott)
9) Sodium sulfite	0.01%	Serpasil (Ciba)
	0.1%	Thorazine (SKF)
	0.2%	Tensilon (Roche)
10) Thioglycolic acid	0.5%	Sus-Phrine (Berlex)
V. Bulking Substances or Tonicity Modifiers		
1) Glycerine	1.6%	Regular Iletin (Lilly)
		Parathyroid (Lilly)
	2.25%	Intralipid (Cutter)
2) Lactose	0.14%	Wydase (Wyeth)
	1.0%	Adriamycin (Adria)
	2.5%	Solu-Medrol (Upjohn)
		A-MethaPred (Abbott)
	4.0%	Premarin (Ayerst)
	5.0%	Rabies Vaccine (Lilly)
3) Mannitol	0.4%	Aselacrin (Calbio)
	0.5%	Abbokinase (Abbott)
	1.0%	Profasi HP (Serono)

continued

TABLE I. C

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5) Sodi
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VI. Oleagi
1) Ben
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VII. Lubric
1) Sil
VIII. Susp
1) G
2) M
3) P
4) P
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5) S
IX. Chelati
1) Ed

TABLE I. *Continued*

	2.0%	Profasi HP (Serono)
		Cosmegen (MSD)
	2.5%	A-MethaPred (Abbott)
4) Dextrose	3.75%	AquaMEPHYTON (MSD)
	4.4%	Elavil (MSD)
	5.0%	Heavy Solution Nupercaine (Ciba)
5) Sodium chloride	q.s.	too numerous to list
6) Sodium sulfate	1.1%	Depo-Provera (Upjohn)
7) Sorbitol	2.0%	Torecan (Boehringer)
VI. Oleaginous Vehicles		
1) Benzyl benzoate	20.0%	BAL in Oil (Hynson, W. & D.)
	40.0%	Delalutin (Squibb)
2) Cottonseed oil	q.s.	Menoject-L A (Mayrand)
	87.4%	Depo-Testosterone (Upjohn)
3) Castor oil	q.s.	Delalutin (Squibb)
4) Peanut oil	80.0%	BAL in Oil (Hynson, W. & D.)
	q.s.	Pitressin Tannate in Oil (Parke-Davis)
5) Safflower oil[b]	10%	Liposyn (Abbott)
6) Sesame oil	q.s.	Delatestryl (Squibb)
		Drolban (Lilly)
		Prolixin Decanoate (Squibb)
7) Soybean oil[b]	10%	Intralipid 10% (Cutter)
VII. Lubricants		
1) Simethicone	0.004%	Premarin (Ayerst)
VIII. Suspending Agents		
1) Gelatin	2.0%	Rabies Vaccine (Lilly)
2) Methylcellulose	0.03%	Testoject-50 (Mayrand)
	1.05%	Percorten (Ciba)
3) Pectin	0.2%	Soluject (Mayrand)
4) Polyethylene glycol 4000	2.7%	Depo-Provera (Upjohn)
	2.9%	Depo-Medrol (Upjohn)
	3.0%	Aristocort (Lederle)
5) Sodium carboxymethylcellulose	0.05%	Crysticillin (Squibb)
	0.075%	Crysticillin (Squibb)
	0.2%	Steraject-50 (Mayrand)
		Kestrin (Hyrex)
	0.3%	Percoten (Ciba)
	0.49%	Cortisone Acetate (Upjohn)
	0.55%	Bicillin CR (Wyeth)
	0.60%	Bicillin LA (Wyeth)
	0.75%	Kenalog (Squibb)
5) Sorbitol solution	50.0%	Aristospan (Lederle)
IX. Chelating Agents		
1) Edetate disodium	0.00368%	Renovue-DIP (Squibb)

continued

TABLE I. *Continued*

	0.005%	Papaverine HCl (Lilly)
		Quinidine Gluconate (Lilly)
	0.01%	Garamycin (Schering)
		Nebcin (Lilly)
		Cholografin Meglumine (Squibb)
	0.04%	Renografin (Squibb)
	0.05%	Cleocin (Upjohn)
		Aldomet (MSD)
		Decaject-L.A. (Mayrand)
2) Edetate calcium disodium	0.04%	Amipaque (Winthrop)
3) Edetate tetrasodium	0.01%	Serpasil (Ciba)
X. Local Anesthetics		
1) Procaine HCl	1.0%	Glukor (Hyrex)
2) Benzyl alcohol	5%	Dramamine (Searle)
XI. Specific Stabilizers		
1) Creatinine	0.5%	Decadron-L.A. (MSD)
		Decaject-L.A. (Mayrand)
	0.8%	Decadron (MSD)
2) Glycine	1.5%	MICRhoGAM (Ortho)
	2.25%	Immu-G (Parke-Davis)
		Gamulin Rh (Parke-Davis)
3) Niacinamide	1.25%	Estraduria (Ayerst)
	2.5%	Soluject (Mayrand)
4) Sodium acetyltryptophanate	0.53%	Normal Serum Albumin (Parke-Davis)
		Plasbumin-5 (Cutter)
5) Sodium caprylate	0.4%	Normal Serum Albumin (Parke-Davis)
		Plasbumin-5 (Cutter)
6) Sodium saccharin	0.03%	Stelazine (SKF)
		Compazine (SKF)

[a] Synonym: Emulphor EL-620. [b] Nutrients in o/w emulsions.

by textbooks for parenteral preparations were not found in use by this survey, e.g., corn oil (4-6), thiourea (5), and potassium chloride (4). It is probable that these excipients may be used in foreign products or in U.S. products that are now no longer marketed. Under the current regulatory climate, the list of excipients is likely to become shorter because of deletion as a result of new toxicological findings. Some excipients, although employed in marketed products, may have difficulty in gaining approval if applications were made today. The following discussion is presented in the same order as shown in the tables.

Benzyl alcohol seemed to be the most commonly used preservative in both aqueous and nonaqueous vehicles. Although 1-2% is the range most often recommended, this survey shows many products employing less than 1% concentration. Higher concentrations, 5 or 10%, were used in one sesame oil preparation (Durabolin).

Although not found in this survey, benzalkonium chloride, chlorocresol, phenylethyl alcohol, phenylmercuric acetate could be considered useful preservatives (6).

The *p*-hydroxybenzoic esters (parabens) are often used in pairs for synergistic activity or for solubility reasons. The ratio of methylparaben to propylparaben varied, for example, 1.9 (Apresoline), 3.3 (Reno-M-30), 6.5 (Garamycin), 7.5 (Neo-Betaline), and 10 (Prolixin). Because of its greater water solubility, methylparaben is often used in aqueous preparations while butylparaben is used in oily formulations. Propylparaben is popular because it is intermediate to the aforementioned parabens as regards water and oil solubility and because it has the greatest activity for the least toxicity, compared with other parabens (7).

A variety of surfactants were found in the survey. Some reduce surface tension so that a hydrophobic surface on the suspended drug can be wetted rapidly; examples include polysorbate 80 in Aristospan and lecithin in Crystalcillin. Also, surfactants may completely solubilize the active agent, for instance, sodium desoxycholate for amphotericin B (Fungizone), and PEG-40 castor oil for miconazole (Monistat). In selecting surfactants other than those on the list, sorbitan monooleate (4) and Pluronics (6)[1] could be considered.

The purpose of labeling excipients on parenteral products is to inform medical professionals. This practice will be of little value, however, if the excipients cannot be properly identified. *The Merck Index* (8) is usually considered a most comprehensive and handy reference for medical professionals to identify chemicals, yet polysorbate 20 and PEG-40 castor oil are not mentioned. Still, it might be more informative if the label on Aqua MEPHYTON stated "PEG-40 Castor oil," rather than "polyethoxylated fatty acid derivative."

Other than using solvents or surfactants, molecular complexation is another way to solubilize drug substance for parenteral dosage form. One example is Dicurin Procaine which employs theophylline to solubilize merethoxylline. This complex renders the diuretic, merethoxylline, more potent and less irritating at the site of injection[2].

All the buffers used are acids or derived from acids, namely, phosphoric acid, carbonic acid, acetic acid, etc. Alkaline buffers such as tromethamine, glycine, etc., were not found in this survey. For high pH's, sodium hydroxide was used exclusively for pH adjustment. In most cases the active substances such as barbiturates or sulfonamides were themselves contributing buffer capacity. Since various amines had been the cations of organic salts in injectable products (tromethamine in Prostin, ethylenediamine in aminophyllin, and meglumine in Renografin), these amines conceivably could be used to buffer parenteral solutions. If the hydrolysis of an active substance is catalyzed by hydroxide ion, employment of basic amine buffers could minimize hydrolysis at autoclave temperatures (9).

The presence of certain counter-ions, either included in the salt form or added as buffer, could reduce pain on intramuscular injection. The former is exemplified by lysine or arginine in cephalosporin preparations (10) the latter by maleic acid in Librium Hydrochloride (11).

Selection of an antioxidant is the most difficult task for a formulator. Not only is preformulation screening of antioxidant efficacy often misleading (12), but other factors such as interaction with the stopper, effectiveness of nitrogen purge, and stability of the antioxidant itself could complicate the entire picture. Other than the antioxidants listed in Table I, tocopherols, ascorbyl palmitate, and butylated hydroxytoluene (BHT), have been recommended for oleaginous vehicles; and thiourea, cysteine, and glutathione for aqueous vehicles

[1] Pluronics, manufactured by Wyandott Chemicals Corp., are surface-active polymers of polyoxyethylene and polyoxypropylenes. Pluronic F-68 was referred as a surfactant for parenteral use in several U.S. patents. The newly developed artificial blood (not sold in this country) uses Pluronic F-68 to emulsify fluorocarbon.

[2] Information furnished by Parenteral Products Development Department, Eli Lilly and Co.

(5, 6). Dithiothreitol is particularly effective to protect thiol compounds (13). However, its safety in parenteral dosage forms has not been established. Oxystearin listed in Upjohn's Depo-Testosterone is an antioxidant added to cottonseed oil by the oil vendor.

Frequently, a combination of antioxidants was employed to confer synergistic effect. For example, Thorazine contains ascorbic acid, sodium sulfite, and sodium bisulfite, and Torecan employs ascorbic acid and sodium metabisulfite. Many oxidation reactions are catalyzed by transition metals. By inhibiting metal catalysis, a proper chelating agent often enhances the effectiveness of antioxidant (14).

Other than benzyl benzoate, oleaginous solvents are all fixed oils. Besides those listed, corn oil is also recommended (15), although no products were found employing this vehicle. The USP states certain specifications for fixed oils. The fixed oil must be of vegetable origin so that it may be metabolized, it must be liquid at room temperature, and it must not become rancid quickly. Fixed oils of natural origin such as sesame oil and corn oil often contain significant amounts of peroxide[3]. Formulators should take heed, therefore, to choose an oleaginous vehicle for drugs that are prone to be oxidized. Fractionated coconut oil[4] or other semi-synthetic oils[5] can be considered for they are mostly low in peroxide content[3].

The lack of tissue irritation, good absorption, low peroxide content, and favorable physicochemical properties of glyceryl triacetate recommend it as a potential vehicle for parenteral use (16)[3]. Ethyl oleate has also been recommended (5). Oleaginous formulations have slipped from popularity and replaced by aqueous suspensions (17). Thus, one would find penicillin G procaine, once popular in a refined vegetable oil (using 2% aluminum stearate as suspending agent), is now only available in aqueous suspension. Because of the longer shelf-life of penicillin G procaine in an oily preparation rather than an aqueous one, the oily preparations remain in veterinary use.

Procaine is almost exclusively the only local anesthetic used. Instead of being an excipient, it is also incorporated as a counter-ion in a salt form of the active substance such as Penicillin Procain and Dicurin Procain. In Dramamine, 5% benzyl alcohol is employed in a 50% propylene glycol solution. Since propylene glycol is capable of preserving the formulation, benzyl alcohol may contribute solvency or local anesthetic activity (18).

Chelating agents are added to complex, and thereby inactivate, trace amounts of metals such as copper, iron, and zinc which catalyze a variety of reactions, e.g., oxidation (19), hydrolysis (20), and deiodination (21). Autoclave sterilization, exposure to light, or simply aging, often caused discoloration. In many cases the coloring substances cannot be identified and the mechanism of discoloration is unknown, yet chelating agents effectively preserve the elegancy of the product. The most widely used chelating agents are salts of edetic acid (EDTA). As a precaution to avoid hypocalcemia, the calcium salts of edetate have recently become the chelating agent of choice.

Citric acid, tartaric acid, glycerin, sorbitol, etc., can also be considered as chelating agents. However, formulators should be aware of the fact that these compounds are less effective, or often ineffective, in preventing metal-catalyzed reactions. It is noteworthy that Japanese formulators often resort to amino acids such as glycine, cysteine, or tryptophan because Japan does not allow the use of EDTA

[3] By American Official Analytical Chemist (AOAC) method, the peroxide content, in micro equivalents thiosulfate, for the following oils is: sesame oil, 26.2; corn oil, 29.2; glyceryl triacetate, 0.2; and Miglyol, I.7. E. Ivashkiv, Analytical R&D Report, Squibb Institute for Medical Research.

[4] Representatives of fractionated coconut oil are Miglyol 810 and 812, mixture of caprylic and capric triglycerides, manufactured by Dynamit Nobel Chemicals, Sweden.

[5] Example is Neobee M5, a fractionated triglyceride of coconut oil origin that has been reconstituted to produce an alcohol soluble oil. Neobee is manufactured by Drew Chemical Corp., Boonton, NJ.

TABLE II.

pH Range
1.8–2.8
2.0–3.8
3
3–5.5
3.0–5.5
3.4 ± 0.
3.75 ± 0.
3.85 ± 0.
4.0–5.0
4.0–6.0
4.5–5.2
4.8–5.2
5.0–7.5
5.5–6.5
5.9
6.0–7.0
6.2 ± 0.
6.5–7.7
7–10.
8.5
8.5
8.6–9.0
8.5–10.
9.0
9.2
9.5
9.6–10.
11.6
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TABLE II. Parenteral Product pH's

pH Range	Adjusted with	Product
1.8–2.8	—	Tetracycline HCl (2)
2.0–3.8	HCl/NaOH	Hexa-Betalin (Lilly)
3	Maleic acid/NaOH	Librium (Roche)
3–5.5	—	Lincocin (Upjohn) (3)
3.0–5.5	Sodium citrate/citric acid	Neo-Synephrine (Winthrop)
3.4 ± 0.2	Lactic acid	Haldol (McNeil)
3.75 ± 0.5	Methanesulfonic acid/NaOH	D.H.E. 45 (Sandoz)
3.85 ± 0.15	Tartaric acid	Gynergen (Sandoz)
4.0–5.0	Lactic acid/NaOH	Talwin (Winthrop)
4.0–6.0	HCl/NaOH	Pronestyl (Squibb)
4.5–5.2	HCl/NaOH	Vesprin (Squibb)
4.8–5.2	HCl/NaOH	Prolixin (Squibb)
5.0–7.5	HCl/NaOH	Kenalog (Squibb)
5.5–6.5	HCl/NaOH	Kinevac (Squibb)
5.9	Acetic acid/NaOH	Prostigmin (Roche)
6.0–7.0	HCl/NaOH	Nydrazid (Squibb)
6.2 ± 0.3	Citric acid	Cedilanid-D (Sandoz)
6.5–7.7	Sodium carbonate/HCl	Hypaque (Winthrop)
7–10.5	—	Hexadrol Phosphate (Organon)
8.5	NaOH	Methotrexate (Lederle)
8.5	NaOH	Mexate (Bristol)
8.6–9.0	NaOH	Adrucil (Adria)
8.5–10.5	—	Sulfadiazine Sodium (2)
9.0	NaOH	Fluorouracil (Roche)
9.2	NaOH	Diamox (Lederle)
9.5	NaOH	Dantrium (Norwich-Eaton)
9.6–10.4	—	Amytal Sodium (Lilly) (2)
11.6	NaOH	Hyperstat (Schering)
12	NaOH	Dilantin (Parke-Davis)

in any parenteral products (22).

In the area of radiopharmaceuticals, diethylenetriamine pentaacetic acid (DTPA) has been used in various products as a chelating agent (example: Renotec). Stability constants for metal-DTPA complex are all greater than those of edetate (23). DTPA has been used in Europe to treat heavy metal poisoning; thus, it could be safe to use for chelating purposes (24).

In the category of specific stabilizers, some unique examples were found; the physical stability of steroid solutions prepared with the phosphates of hydrocortisone, cortisone, prednisone, or prednisolone, can be increased by the addition of niacinamide or creatinine, as exemplified by Estradurin or Decadron, respectively (25). It is believed that these nitrogen-containing compounds prevent the formation of precipitates by solubilizing steroid alcohol which would otherwise precipitate as a result of hydrolysis during storage (26). However, the chemical stability of these steroids, as described in another patent, were increased by saccharin (27). Although no steroid product was found to contain saccharin. The use of a soluble saccharin derivative, in very small amounts, however, is efficient in stabilizing phenothiazine derivatives (28). The mechanism of stabilization was attributed to

the formation of a "probability complex" (29).

In most cases, employment of extreme pH's are necessary for solubility reasons. At high pH's, barbiturates and sulfonamides are typical examples. In order to solubilize weak basic substances, low pH's are required. Stability is another major concern in selecting optimal pH's. Hyperstat is a good example of adjusting pH to the minimum (11.6) on a rate-pH profile (30).

Conceivably, a properly designed formulation is a key to a successful parenteral product. Formulators should always bear in mind that the ideal formulation is the one without excipient at all. If it is necessary to use any excipients to preserve potency, elegancy, safety, etc., one should use extreme caution in selecting proper excipients and use them at optimal concentration. It is hoped that this review will serve as a handy reference for formulators to learn from existing products.

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