AAPS PharmSci 2002; 4 (2) article 7 (http://www.aapspharmsci.org).

# Assuring Quality and Performance of Sustained and Controlled Release Parenterals: Workshop Report

*Submitted: March 17, 2002; Published: April 17, 2002*

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## ABSTRACT

This is a summary report of the American Association of Pharmaceutical Scientists, the Food and Drug Administration and the United States Pharmacopoeia co-sponsored workshop on "Assuring Quality and Performance of Sustained and Controlled Release Parenterals." Experts from the pharmaceutical industry, the regulatory authorities and academia participated in this workshop to review, discuss and debate formulation, processing and manufacture of sustained and controlled release parenterals and identify critical process parameters and their control. Areas were identified where research is needed in order to understand the performance of these drug delivery systems and to assist in the development of appropriate testing procedures. Recommendations were made for future workshops, meetings and working groups in this area.

## INTRODUCTION

This report summarizes the outcome of the workshop on "Assuring Quality and Performance of Sustained and Controlled Release Parenterals," which was held in April 2001 in Washington, DC. This workshop was sponsored by the American Association of Pharmaceutical Scientists (AAPS), the Food and Drug Administration (FDA) and the United States Pharmacopoeia (USP). The overall goal of this workshop was to identify future directions for regulatory activity and public standards in the rapidly emerging area of controlled release (CR) parenteral products. Presentations focused on dispersed systems (microspheres, liposomes, gels and suspensions) as well as implants of small molecule and protein/peptide therapeutics for human and animal use. The objectives of the workshop were to:

- Review formulation, processing and manufacture of CR parenterals. Identify and discuss critical process parameters and their control.
- Identify new and emerging methods of in vitro release testing for CR parenterals and their ability to predict product performance.
- Discuss accelerated stability and in vitro release testing methods for CR parenterals.
- Discuss bioavailability, bioequivalence and pharmaceutical equivalence for CR parenterals.
- Explore the opportunity for in vitro-in vivo correlation of CR parenterals.
- Identify future directions for regulatory activity and public standards in this area.

This workshop brought together experts from the pharmaceutical industry, the regulatory authorities and academia to discuss and debate issues pertaining to assuring the quality and performance of sustained and controlled release parenterals. The workshop was divided into formal presentations in the morning and parallel breakout discussion sessions in the afternoon. The breakout sessions served to identify future directions for regulatory activity and public standards in this rapidly emerging area. At the close of each breakout session the moderators were asked to prepare a summary of the key points discussed in their session. This report represents a compilation of these summaries together with background information explaining the need for regulatory activity in this area. Since many of the same concerns and issues were raised in different parallel sessions, this report is not divided by the breakout sessions, but rather by the key issues discussed.

On the first day of the workshop, formulation, development and manufacture of the different products were reviewed and critical process parameters were identified. The breakout sessions focused on chemistry, manufacturing, and control issues and were divided by product (liposomes, microspheres, gels, suspensions and implants). The second day centered on biopharmaceutics issues, including physiology of the parenteral routes, bioavailability and bioequivalence, in vitro release testing and the possibility of in vitro-in vivo correlation.

## BACKGROUND

Controlled release drug delivery systems are used to improve the therapeutic response by providing blood levels that are more consistent and stable compared to immediate release dosage forms. They can result in a reduction in adverse reactions since less drug is required and since the drug may be targeted to the site in vivo avoiding high systemic levels. As a consequence of targeted and controlled release, patient compliance may be improved due to lower dosing frequencies and simpler dosing regimens. With targeting and more sustained, predictable levels, efficacy may also be enhanced. CR parenteral drug delivery systems include: suspensions, liposomes, microspheres, gels and implants. Tiny microspheres and larger implantable devices can be used to modify release over periods of months to years. Suspensions, liposomes and gels may not achieve quite as long durations of action; however, they can be localized at the site of action in vivo and liposomes may achieve targeted delivery both by passive and active means following intravenous administration. These delivery systems are becoming increasingly utilized by the pharmaceutical industry to deliver drugs for treatment or prevention of a variety of diseases.

Not all drugs are candidates for controlled delivery via the parenteral route. The candidate drug should be potent with known toxicity and pharmacokinetic profiles. A CR parenteral dosage form is usually selected when there are problems associated with oral delivery (e.g. gastric irritation, first pass effects or poor absorption) and a need for extended release or targeted delivery (e.g. rapid clearance). Both systemic and localized delivery can be achieved using CR parenterals. In addition, the drug must be compatible with the manufacturing process, which may be fairly harsh for some of these products. Examples of disease applications for CR parenteral delivery include: fertility, hormone therapy, protein therapy, infections (antibiotics and antifungals), cancer therapy, orthopedic surgery and post-operative pain, chronic pain, vaccination/immunization, CNS disorders, and immunosupression. Approved CR parenteral products are listed in Table 1.

**Table 1** - Approved CR Parenteral Products

| Trade Name | Active Ingredient | Approval Date |
|---|---|---|
| Suspension Products | | |
| Depo-Medrol | Methylprednisolone | pre-1982 |
| Depo-Provera | Medoxyprogesterone | pre-1982 |
| Celestone Soluspan | Betamethasone | pre-1982 |
| Insulin | Lente Unltralente NPH | pre-1962 |
| Microsphere Products | | |
| Lupron Depot | Leuprolide | 1989 |
| Sandostatin LAR | Octreotide | 1998 |
| Nutropin Depot | Somatropin | 1999 |
| Trelstar Depot | Triptorelin | 2000 |
| Liposome Products | | |
| Doxil | Daunorubicin | 1995 |
| Daunoxome | Daunorubicin | 1996 |
| Ambisome | Amphotericin B | 1997 |
| Depocyt | Cytarabine | 1999 |
| Lipid Complex Products | | |
| Ambelcet | Amphotericin B | 1995 |
| Amphotec | Amphotericin B | 1997 |
| Visudyne | Verteporfin | 2000 |
| Implant Products | | |
| Norplant | Levonorgestrel | 1990 |
| Gliadel | Carmustine | 1996 |
| Zoladex | Goserelin | 1998 |
| Viadur | Leuprolide | 2000 |

Although CR parenteral products are relatively low volume in sales compared to oral products, they offer significant and distinct therapeutic advantages for certain types of drugs and consequently their use is becoming more prevalent. CR parenterals are complex formulations and thereby present significant challenges in regulation and the development of standards. In addition, they are considered ?high risk? products since they are complex, are designed for prolonged and targeted release and, in the case of dispersed system CR parenterals, are almost impossible to remove from the body once administered. Consequently, there is a pressing need to open a public dialog between industry, FDA and USP on how best to assure the quality and performance of these products. This workshop served to initiate this public dialog.

Of paramount importance is to identify any gaps in our scientific understanding of CR parenteral products and determine regulatory policy issues that need to be addressed. Critical formulation and process variables for individual products must be identified in order to develop the necessary characterization studies that undergird the substance, excipient, and product specifications that allow batch release. Key issues discussed in this workshop include: in vitro drug release testing (need for quality assessment as well as in vivo relevance), the possibility of in vitro-in vivo correlation, stability testing to ensure that specifications are met during shelf-life, as well as in vivo stability, sterility assurance, sterility testing, foreign particulate matter, particle size analysis, bioavailability and bioequivalence assessments, qualification of new biopolymers, residual solvent levels, reconstitution of parenteral products, and nomenclature.

The major issues and recommendations from this workshop are summarized below.

## IN VITRO RELEASE METHODS

Because the issue of in vitro release testing was raised at many of the breakout sessions, attendees generally agreed that an immediate need for guidance in this area exists. This guidance should focus on regulatory and compendial approaches with respect to acceptable apparatus, media and sampling methods, test intervals, and total percent release. Attendees also requested guidance on the method development process for in vitro tests for quality control purposes as well as on how to ensure the in vivo relevance of these tests. A need for guidance on accelerated in vitro testing for routine quality control purposes was also expressed. The issue of in vitro - in vivo correlation was discussed.

Although workshop attendees did not want a single approach to be set for in vitro release testing given the wide range of CR parenteral products, they noted a need for general guiding principles and encouraged research to ensure a scientific basis for the development of different tests, procedures (to include apparatus) and acceptance criteria. These general approaches could then be modified, as appropriate, for specific products. For example, a given product may have specific requirements with respect to media, sampling interval or temperature.

### *Apparatus*

Current USP apparatus for in vitro release testing are designed for oral and transdermal products and may not be optimal for controlled release parenteral products. USP apparatus 1 (basket) and 2 (paddle) were designed

for immediate- and modified-release oral formulations. USP apparatus 5 (paddle over disc), 6 (cylinder) and 7 (reciprocating holder) were designed for the transdermal route. USP apparatus 3 (reciprocating cylinder) and 4 (flow through cell) were designed for extended-release oral formulations. These latter two methods may be the most relevant to CR parenterals and may be suitable following appropriate modification. Alternative apparatus, such as small sample vials and vessels, with and without agitation, are currently used for CR parenterals. Problems that may be associated with these alternative apparatus include: lack of sink conditions and sample aggregation.

Research is required to determine the scientific basis for the tests, procedures, including apparatus (e.g., geometry and hydrodynamics), and acceptance criteria for CR parenterals. The apparatus and media used should take into account the release mechanism and the physical properties of the product (e.g. size and stability). In addition, in vitro release tests must also discriminate between the performance of different formulation variants and ideally should have bio-relevance.

### *Method development*

Attendees considered the purpose of in vitro release testing since method design may vary according to the purpose of the test. Current uses of in vitro release testing include: 1) formulation development, to include assessment of dose-dumping and in vivo stability (e.g., Stealth-type liposomes, which should remain stable without significant drug release until uptake at the target site in vivo); 2) quality control to support batch release, 3) evaluation of the impact of manufacturing process changes on product performance, 4) substantiation of label claims; and 5) compendial testing.

Although in vitro release testing of CR parenterals is primarily utilized for quality control purposes, many attendees agreed that in vitro release tests should be developed with regard to clinical outcomes (bio-relevance). The rationale for this understanding is that the ultimate purpose of quality control testing is to ensure the clinical performance, i.e., efficacy and safety of the product. In order to achieve in vivo relevance, physiological variables at the site need to be considered including: body temperature and metabolism (both can significantly affect blood flow), muscle pH, buffer capacity, vascularity, level of exercise, as well as volume and osmolarity of the products. Any tissue response, such as inflammation and/or fibrous encapsulation of the product may need to be considered. In vitro release methods should be designed based on in vivo release mechanisms. With this understanding, attendees noted the following general approaches for in vitro test method design: 1) identification of release media and conditions that result in reproducible release rates; 2) preparation of formulation variants that are expected to have different biological profiles; 3) testing of formulation variants in vitro as well as in vivo; and 4) modification of in vitro release methods to allow discrimination between formulation variants that have different in vivo release profiles.

Attendees also discussed the relevance of sink conditions in in vitro test design for CR parenterals, considering that sink conditions may not exist at a particular in vivo site. General agreement was that sink conditions should be used for in vitro testing for quality control purposes provided that the study design allowed for discrimination between formulation variants with different in vivo release profiles. However, participants argued that non-sink conditions may be necessary if the purpose of the in vitro test is to establish in vitro-in vivo correlation (IVIVC). Although IVIVC is not utilized at present for CR parenterals, with sufficient bio-relevance built into the in vitro tests to support an IVIVC it may allow subsequent waiver of in vivo studies (see the IVIVC section below).

Attendees also considered other issues, including the percent total release required (e.g., 70%, 80%) and the value of physical/chemical properties in lieu of release data for some quality control purposes (e.g., for stable liposomal formulations that are designed for no release until uptake at the site).

### *Development of IVIVC for CR parenterals*

Although IVIVC may not be possible for all CR parenteral products, many attendees agreed that this is an important area for research. The principles used in IVIVC of oral extended-release products may be applied to parenterals with appropriate modification, justified on a scientific basis. IVIVC modeling and measurements may be different for different types of products (e.g. targeted release versus extended release products). Similarly, in vitro release methods and media are likely to vary depending on the product and should be developed based on in vivo relevance. For example, in vitro cellular tests may be acceptable as long as they are reproducible and can be validated. Similarly, in vivo measurements may vary and may include plasma concentrations, efficacy/safety data, surrogate endpoint data, as well as tissue concentrations. Discussions stressed that both in vitro and in vivo measurements must be justified scientifically. In the case of some products, such as liposomes, it may be necessary to measure in vivo concentrations of both free and encapsulated drug. Models that represent multiple processes (e.g., physical and biological) should be considered, as appropriate.

The use of animals was considered to be acceptable to prove that an in vitro release system is discriminating. However, the use of animal models was considered inappropriate to prove an IVIVC for regulatory purposes. Instead, bio-relevance should be developed using

clinical data. Nevertheless, IVIVC modeling using animal data would be suitable for "proof of principle" for initial research purposes. Research in this area should be encouraged, possibly coordinated through Product Quality Research Initiative (PQRI).

The issue of data variability with respect to IVIVC was discussed and the following potential solutions were suggested:

- Increase the number of dosage units or individuals.
- Variability may be acceptable as long as its source can be estimated and a valid IVIVC is obtained.
- If the source and importance of the variability can be determined, it may be possible to minimize it.

Attendees noted that tissue responses, such as fibrous encapsulation, may affect release in vivo and this needs to be considered in establishing an IVIVC. However, these types of tissue response may be difficult to simulate in vitro.

### *Use of animal models in release testing*

In the development of in vitro release methods, animal data may be used to obtain tissue distribution and pharmacokinetic information. Plasma levels may not be the best measure of in vivo behavior for CR parenteral products intended for local delivery or targeted release, and therefore, discussion in some sessions centered on the use of animal models to investigate in vivo product performance. More extensive bio-data can be obtained using animal models, including tissue levels at the local site. Animal models were considered to be invaluable and serial tissue samples might be used to compare product performance before and after manufacturing changes for CR parenterals with tissue-specific delivery. Although data will be useful in initial development, ultimately human data must be used to establish an IVIVC.

Selection of an appropriate animal model was discussed and it was suggested that comparative studies be performed between injection sites in humans and animals in order to establish interspecies differences in drug release. Larger animals such as sheep and dogs may be more representative of humans with regard to interspecies differences than would small laboratory animals. This may be particularly important with regard to issues such as injection volume. Since inter-subject variability significantly impacts in vivo data, inbred animals may be useful in identifying variables that affect the drug release and absorption processes. Extensive inter- and intra-subject variability may mask critical formulation and manufacturing variables unless very large human populations are utilized. The identification of an appropriate animal model for CR parenteral products was recommended as a research project, possibly for investigation through PQRI. The initial step of this research project should be a retrospective literature review of parenteral bioavailability data to develop initial correlation predictions between humans and animals. This research study should include different animals as well as different sites and should attempt to establish correlations between human and animal data relating the findings to physiological parameters. Different dosage forms and drugs should be investigated to determine whether the results are drug- and/or dosage form-dependant.

Animal models could potentially be utilized in pharmaceutical development. For SUPAC-type changes, attendees recommended that an animal-human correlation be established so that animal models can be used (along with in vitro specifications) in lieu of extensive post-approval human trials. To achieve this, out of specification batches would be used to test the sensitivity of the animal model. Tests should also examine the sensitivity of the animal model to changes in product performance when the duration of testing is truncated (e.g., 3-month release testing for a one-year release product).

Concerns were raised with respect to animal lifespan as well as physiological and metabolic differences between species. Animal lifespan may be a concern for extended release dosage forms with unusually long durations of action. Metabolic differences were considered not to be of importance for formulation comparisons. However, such differences may be very significant if animal models were to be used as a surrogate for efficacy. Another potential problem area is antibody production when using human derived proteins. Since immuno-suppression may be a possibility, the impact of this on pharmacokinetic and pharmacodynamic responses needs to be considered.

### *Accelerated in vitro release testing*

The need for accelerated release testing was discussed, particularly for extended release products. Accelerated release testing is desirable for routine quality control purposes. Attendees generally agreed that these tests should have relevance to "real time" in vitro release tests conducted under conditions that simulate the in vivo situation as closely as possible. "Real time" in vitro tests for the full product duration should be conducted during product development and are essential for validating accelerated release rate tests. Accelerated tests should be bio-relevant and the mechanism of drug release should not be altered in accelerated tests, rather it should only be speeded up. For example, in the case of PLGA microspheres that release drug primarily via polymer erosion the accelerated test should speed up the polymer erosion process. In the design of

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