UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

REGENERON PHARMACEUTICALS, INC.,
Petitioner,

v.

NOVARTIS PHARMA AG,
NOVARTIS TECHNOLOGY LLC,
NOVARTIS PHARMACEUTICALS CORPORATION,
Patent Owners.

Case IPR2021-00816
Patent 9,220,631

SECOND DECLARATION OF JAMES L. MULLINS, PH.D.

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I, Dr. James L. Mullins, declare as follows:

I. INTRODUCTION

1. My name is Dr. James L. Mullins. I have been retained by petitioner Regeneron Pharmaceutical, Inc. ("Regeneron") to provide opinions on various documents.

2. I am presently Dean Emeritus of Libraries and Esther Ellis Norton Professor Emeritus at Purdue University. My career as a professional and academic/ research librarian spanned more than 44 years including library positions at Indiana University, Villanova University, Massachusetts Institute of Technology, and Purdue University. Appendix A is a true and correct copy of my curriculum vitae my background and experience.

3. In 2018, I founded the firm Prior Art Documentation Librarian Services, LLC, located at 106 Berrow, Williamsburg, VA 23188 after purchasing the intellectual property of and as a successor to Prior Art Documentation, LLC located at 711 South RaceStreet, Urbana, IL 61801. Further information about my firm, Prior Art Documentation Librarian Services, LLC (PADLS), is available at www.priorartdoclib.com.

4. I have been retained by Regeneron to offer my opinion on the authenticity and dates of public accessibility of various documents. For this service, I am being paid my usual hourly fee of $275.00. I have no stake in the outcome of

this proceeding or any related litigation or administrative proceedings, and my compensation in no way depends on the substance of my testimony or the outcome of this proceeding.

II. QUALIFICATIONS

5. My qualifications are laid out in my first declaration (Ex. 1033) and in my CV (Appendix A).

III. BACKGROUND ON PUBLIC ACCESSIBILITY

A. Scope of this Declaration

6. I am not a lawyer, and I am not rendering an opinion on the legal question of whether a particular document is, or is not, a "printed publication" under the law. I am, however, rendering my expert opinion on the authenticity of the document referenced herein and when and how this document was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the document.

7. I am informed by counsel that an item is considered authentic if there is sufficient evidence to support a finding that the item is what it is claimed to be. I am also informed that authenticity can be established based on the contents of the document itself, such as the appearance, content, substance, internal patterns, or otherdistinctive characteristics of the item.

8. I am informed by counsel that a given reference qualifies as "publicly accessible" if it was disseminated or otherwise made available such that a person interested in and ordinarily skilled in the relevant subject matter could locate it through the exercise of ordinary diligence.

9. While I understand that the determination of public accessibility under the foregoing standard rests on a case-by-case analysis of the facts particular to an individual publication, I also understand that a printed publication is rendered "publicly accessible" if it is cataloged and indexed by a library such that a person interested in the relevant subject matter could locate it (*i.e.*, I understand that cataloging and indexing by a library is sufficient, though there are other ways that a printed publication may qualify as "publicly accessible"). One manner of sufficient indexing is indexing according to subject matter. I understand that it is not necessary to prove someone actually looked at the printed publication in order to show it was publicly accessible by virtue of a library's cataloging and indexing thereof. I understand that cataloging and indexing by a single library of a single instance of a particular printed publication is sufficient. I understand that, even if access to a library is restricted, a printed publication that has been cataloged and indexed therein is publicly accessible so long as a presumption is raised that the portion of the public concerned with the relevant subject matter would know of the printed publication. I also understand that the cataloging and indexing of information that would guide a

person interested in the relevant subject matter to the printed publication, such as the cataloging and indexing of an abstract for the printed publication, is sufficient to render the printed publication publicly accessible.

10. I understand that evidence showing the specific date when a printed publication became publicly accessible is not necessary. Rather, routine business practices, such as general library cataloging and indexing practices, can be used to establish an approximate date on which a printed publication became publicly accessible.

B. Person of Ordinary Skill in the Art

11. In forming the opinions expressed in this declaration, I have reviewed the documents and appendices referenced herein. These materials are records created in the ordinary course of business by publishers, libraries, indexing services, and others. From my years of experience, I am familiar with the process for creating many of these records, and I know that these records are created by people with knowledge of the information contained within the record. Further, these records are created with the expectation that researchers and other members of the public will use them. All materials cited in this declaration and its appendices are of a type that experts in my field would reasonably rely upon and refer to in forming their opinions.

12. I have been informed by counsel that the subject matter of this proceeding relates to a terminally sterilized pre-filled syringe for intravitreal injection that includes a VEGF-antagonist solution.

13. I have been informed by counsel that, with respect to claims 1-23 of the '631 Patent, a person of ordinary skill would have had at least an advanced degree (Dipl.Ing, M.S., or Ph.D.), with research experience in mechanical engineering, biomedical engineering, materials science, chemistry, or a related field, or at least 2-3 years of professional experience in one or more of those fields. Furthermore, I understand that a POSITA would have had experience with (i) the design of pre-filled syringes; and (ii) sterilization of drug delivery devices, including those containing sterilization sensitive therapeutics. Such sterilization experience would include experience with microbiology. I have further been informed by counsel that, with respect to claims 24-26 of the '631 Patent, a person of ordinary skill would be an ophthalmologist with experience administering VEGF-antagonist drugs to patients via the intravitreal route.

14. I further understand that Novartis has proposed a different definition of POSITA, under which a POSITA would have had an advanced degree (i.e., an M.S., a Ph.D., or equivalent), and at least 2-3 years of professional experience, in mechanical engineering, biomedical engineering, materials science, chemistry, chemical engineering, or a related field, including experience with the design of a

PFS and/or the development of ophthalmologic drug products or drug delivery devices. Such a person would have been a member of a product development team and would have drawn upon not only his or her own skills, but also the specialized skills of team members in complementary fields including ophthalmology, microbiology and toxicology. My opinions do not change and are equally valid under either definition of POSITA.

15. It is my opinion that such a person would have been actively engaged in academic research and learning through study and practice in the field, and possibly through formal instruction through the bibliographic resources relevant to his or her research. By the 2000s, such a person would have had access to a vast array of print resources, including at least the documents referenced below, as well as to a fast-changing set of online resources.

C. Library Catalog Records and Other Resources

16. Although I have previously provided background on library catalog records (*see* Ex. 1033), some additional background on MARC (Machine-Readable Cataloging) formatted records, OCLC, and *WorldCat* is helpful to understand the library catalog records discussed in this declaration. I am fully familiar with the library cataloging standard known as the MARC standard, which is an industry-wide

standard method of storing and organizing library catalog information.[1] MARC practices have been consistent since the MARC format was developed by the Library of Congress in the 1960s, and by the early 1970s became the U.S. national standard for disseminating bibliographicdata. By the mid-1970s, MARC format became the international standard, and persists through the present. A MARC-compatible library is one that has a catalog consisting of individual MARC records for each of its items. The underlying MARC format (computer program) underpins the online public access catalog (OPAC) that is available to library users to locate a particular holding of a library. Today, MARC is the primary communications protocol for the transfer and storage of bibliographic metadata in libraries.[2] The MARC practices discussed below were in place during the late 1990s period relevant to the documents referenced herein.

17. Online Computer Library Center (OCLC) is a not-for-profit worldwide consortium of libraries. Similar to MARC standards, OCLC's practices have been

[1] The full text of the standard is available from the Library of Congress at http://www.loc.gov/marc/bibliographic/.

[2] Almost every major library in the world uses a catalog that is MARC-compatible. *See, e.g., Library of Congress, MARC Frequently Asked Questions (FAQ)*, https://www.loc.gov/marc/faq.html (last visited Jan. 24, 2018) ("MARC is the acronym for MAchine-Readable Cataloging. It defines a data format that emerged from a Library of Congress-led initiative that began nearly forty years ago. It provides the mechanism by which computers exchange, use, and interpret bibliographic information, and its data elements make up the foundation of most library catalogs used today."). MARC is the ANSI/NISO Z39.2-1994 (reaffirmed 2009) standard for Information Interchange Format.

consistent since the 1970s through the present. Accordingly, the OCLC practices discussed below were in place during the period discussed in my opinions section. OCLC was created "to establish, maintain and operate a computerized library network and to promote the evolution of library use, of libraries themselves, and of librarianship, and to provide processes and products for the benefit of library users and libraries, including such objectives as increasing availability of library resources to individual library patrons and reducing the rate of rise of library per-unit costs, all for the fundamental public purpose of furthering ease of access to and use of the ever-expanding body of worldwide scientific, literary and educational knowledge and information."[3] Among other services, OCLC and its members are responsible for maintaining the *WorldCat* database (http://www.worldcat.org/), used by libraries throughout the world.

18. Libraries worldwide use the machine-readable MARC format for catalog records. MARC-formatted records include a variety of subject access points based on the content of the document being cataloged. A MARC record for a particular work comprises several fields, each of which contains specific data about the work. Each field is identified by a standardized, unique, three-digit code

[3] OCLC Online Computer Library Center, Inc., Amended Articles of Incorporation of OCLC Online Computer Library Center, Inc., Third Article (OCLC, Dublin, Ohio) Revised November 30, 2016, https://www.oclc.org/content/dam/oclc/membership/articles-of-incorporation.pdf.

corresponding to the type of data that follows. For example, a work's title is recorded in field 245, the primary author of the work is recorded in field 100, a work's International Standard Book Number ("ISBN") is recorded in field 020, and the work's Library of Congress call number (assigned by Library of Congress) is recorded in field 050. Some fields can contain subfields, which are indicated by letters. For example, a work's publication date is recorded in field 260 under the subfield "c."

19. The MARC Field 040, subfield "a," identifies the library or other entity that created the catalog record in the MARC format. The MARC Field 008 identifies the date when this first MARC record was created.

20. MARC records also include several fields that include subject matter classification information. An overview of MARC record fields is available through the Library of Congress at http://www.loc.gov/marc/bibliographic/. For example, 6XX fields are termed "Subject Access Fields."[4] Among these, for example, is the 650 field; this is the "Subject Added Entry – Topical Term" field. *See* http://www.loc.gov/marc/bibliographic/bd650.html. The 650 field is a "[s]ubject added entry in which the entry element is a topical term." *Id*. The 650 field entries "are assigned to a bibliographic record to provide access according to generally accepted thesaurus-building rules (e.g., *Library of Congress Subject Headings*

[4] *See* http://www.loc.gov/marc/bibliographic/bd6xx.html.

(LCSH), *Medical Subject Headings* (MeSH))." *Id*. Thus, a researcher can easily discover material relevant to a topic of interest with a search using the terms employed in the MARC Fields 6XX.

21. Further, MARC records include call numbers, which themselves include a classification number. For example, the 050 field is dedicated as the "Library of Congress Call Number"[5] as assigned by the Library of Congress. A defined portion of the Library of Congress Call Number is the classification number, and "source of the classification number is *Library of Congress Classification* and the *LC Classification-Additions and Changes*." *Id.* Thus, included in the 050 field is a subject matter classification. As an example: TK5105.59 indicates books on computer networks – security measures. When a local library assigns a classification number, most often a Library of Congress derived classification number created by a local library cataloger or it could be a Dewey Decimal classification number for example, 005.8, computer networks – security measures, it appears in the 090 field. In either scenario, the MARC record includes a classification number in the call number field that represents a subject matter classification.

22. The 9XX fields, which are not part of the standard MARC 21 format,[6] were defined by OCLC for use by the Library of Congress, processing or holding

[5] *See* http://www.loc.gov/marc/bibliographic/bd050.html.
[6] *See* https://www.oclc.org/bibformats/en/9xx.html.

notes for a local library, and for internal OCLC use. For example, the 955 field is reserved for use by the Library of Congress to track the progress of a new acquisition from the timeit is submitted for Cataloging in Publication (CIP) review until it is published and fully cataloged and publicly available for use within the Library of Congress. Fields 901- 907, 910, and 945-949 have been defined by OCLC for local use and will pass OCLC validation. Fields 905 or 910 are often used by an individual library for internal processing purposes, for example the date of cataloging and/or the initials of the cataloger.

D. Monograph Publications

23. Monograph publications are written on a single topic, presented at length, and distinguished from an article and include books, dissertations, proceedings of a conference, and technical reports. A library typically creates a catalog record when the monograph is acquired by the library. First, it will search OCLC to determine if a record has already been created by the Library of Congress or another OCLC institution. If a record is found in OCLC, the record is downloaded into the library's LMS. The library's LMS typically includes the OPAC (online public access catalog by which researchers locate a particular library holding in a user-friendly format), acquisitions, cataloging, and circulation integrated functions. Once the item is downloaded into the library's LMS, the library adds its identifier to the OCLC database so when a search is completed on *WorldCat*, the library will be

indicated as an owner of the title. Once a record is created in a library's LMS, it is searchable and viewable through the library's OPAC. The record is typically searchable by author, title, and subject heading, at that library and from anywhere in the world through the internet by accessing that library's OPAC. The OPAC also connects with the circulation function of the library which typically indicates whether the record is available, in circulation, etc., with its call number and location in a specific departmental/disciplinary library, if applicable. The OPAC not only provides immediate bibliographic access on site, it also facilitates the interlibrary loan process, which involves loaning a publication from one library to another.

E. Ownership and Date Stamp

24. Every library sets its own practice or policy on whether-or-not to date stamp, but all will have an ownership stamp somewhere in the publication—typically on the cover page, verso of the cover page, or a designated page within the publication, sometimes even on the top, side, or bottom edge of the monograph or periodical. The ownership and date stamp can also vary from one library to another when the stamp is entered on the monograph. It can occur when received in acquisitions after shipment to the library, or it can be at time of cataloging. Therefore, there could be instances when the date of receipt precedes the cataloging date or vice versa.

F. Indexing/Cataloging

25. A researcher may discover material relevant to his or her topic in a variety of ways. One common means of discovery is to search for relevant information in an index of periodical and other publications. Having found relevant material, the researcher will then normally obtain it online, look for it in libraries, or purchase it from the publisher, a bookstore, a document delivery service, or other provider. Sometimes, the date of a document's public accessibility will involve both indexing and library date information. Date information for indexing entries is, however, often unavailable. This is especially true for online indices, including *Wiley Online Library* and *WorldCat.*

26. *WorldCat* is the world's largest public online catalog, maintained by the OCLC, Inc., a not-for-profit international library consortium, and built with the records created by thousands of libraries that are members of OCLC. Prior to *WorldCat,* the OCLC database base was accessible since 1991 through a search engine called *FirstSearch. FirstSearch* required access from an OCLC, Inc. member library, therefore, not open access. In 2006, OCLC's *WorldCat* was separated from *FirstSearch* and was made accessible as an open access data base, freely available to anyone in the world.

27. *WorldCat* requires no knowledge of MARC tags and code and does not require a login or password. *WorldCat* is easily accessible through the World Wide

Web to all who wish to search it; there are no restrictions to be a member of a particular community, etc. The date a given catalog record was created (corresponding to the MARC Field 008) appears in some detailed *WorldCat* records as the Date of Entry but not necessarily all. *WorldCat* does not provide a view of the underlying MARC format for a specific *WorldCat* record. In order to see the underlying MARC format the researcher must locate the book in a holding library listed among those shown in *WorldCat*, and search the online public catalog (OPAC) of a holding library. Whereas *WorldCat* records are widely available, the availability of library specific MARC formatted records varies from library to library. When a specific library wishes to make the underlying MARC format available there will be a link from the library's OPAC display, often identified as a MARC record or librarian/staff view.

28. When a MARC record is created by the Library of Congress or an OCLC member institution, the date of creation for that record is automatically populated in the fixed field (008), with characters 00 through 05 in year, month, day format (YYMMDD).[7] Therefore, the MARC record creation date reflects the date on which the publication associated with the record was first cataloged. Thereafter, the local library's computer system may automatically update the date in field 005

[7] Some of the newer library catalog systems also include hour, minute, second (HHMMSS).

every time the library updates the MARC record (*e.g.*, to reflect that an item has been moved to a different shelving location within the library, or a reload of the bibliographic data with the introduction of a new library management system that creates and manages the OPAC).

G. Periodical Publications.

29. A library typically creates a catalog record for a periodical publication when the library receives its first issue. When the institution receives subsequent issues/volumes of the periodical, the issues/volumes are generally checked in (often using a date stamp), added to the institution's holding records, and made available very soon thereafter – normally within a few days of receipt or (at most) within a few weeks of receipt**.**

30. **ProQuest** – ProQuest's collections span six centuries, all disciplines and the diverse content types needed by researchers, providing the world's largest collection of dissertations and theses; three centuries of newspapers; more than 450,000 academic eBooks; collections of important scholarly journals and other content researchers need such as data; and unique digital vaults of primary source materials . ProQuest's renowned abstracting and indexing enables researchers to find sources in their area of study. *See* https://about.proquest.com/libraries/academic/.

31. ***Wisconsin TechSearch (WTS)* –** WTS offers an array of article delivery and research services to individuals and organizations not affiliated with

the University of Wisconsin or who need the specialized skills of WTS staff in locating and retrieving information. *See* https://wts.wisc.edu/.

IV. OPINION REGARDING AUTHENTICITY AND PUBLIC ACCESSIBILITY

A. Document A: Ex. 1015 & Ex. 1016: Sandeep Nema and John D. Ludwig, editors, *Pharmaceutical Dosage Forms: Parenteral Medications*, 3rd edition. Volume 1: *Formulation and Packaging*; Volume 2: *Facility Design, Sterilization and Processing*. Informa Healthcare, 2010. ("Nema")

32. I have been asked to opine on a book titled: *Pharmaceutical Dosage Forms: Parenteral Medications*, 3rd edition, edited by Sandeep Nema and John D. Ludwig, published in three volumes, for this declaration, Volume 1 - *Formulation and Packaging*; and Volume 2 - *Facility Design, Sterilization and Processing* have been included in this declaration to authenticate and document public access.

1. Authentication

33. I have evaluated the Nema reference several ways: (1) by assessing scans of a copy provided to me by counsel, Ex. 1015 and Ex. 1016; (2) by assessing scans of a print copy held by the National Library of Medicine (NLM), Attachment A-1 (3) by assessing downloads of Nema available to me as an emeritus faculty member of Purdue University through the Purdue University Libraries, from the *ProQuest Ebook Central*, at this URL: https://ebookcentral.proquest.com/lib/purdue/detail.action?pq-origsite=primo&docID=584343.

34. It is available for a fee through *ProQuest Ebook Central* at this URL: https://www.taylorfrancis.com/books/edit/10.1201/b17733/pharmaceutical-dosage-forms-sandeep-nema-john-ludwig.

35. Attachment A-1, obtained by me at my request by Wisconsin TechSearch (WTS) was made from the print copy owned by the National Library of Medicine (NLM). I received Attachment A-1 on March 9, 2022, and it contains scans of Volume 1 of Nema that include: partial back cover with a barcode label that reads "National Library of Medicine" (shown below); spine of the book with a label that reads "2010 L-841 v.1 (shown below); cover of volume 1; front flyleaf with ownership stamp that reads "Property of the National Library of Medicine" (shown below); title page of volume 1; verso of the title page (copyright); Contents [volume 1].

Selected Scans of Volume 1 of Nema (Ex. 1015)

36. Attachment A-1 also contains scans of Volume 2 of Nema that includes: partial back cover with a barcode label that reads "National Library of Medicine" (shown below); spine of the book with a label that reads "2010 L-841 v.2; cover of volume 2 (shown below); front flyleaf with ownership stamp that reads "Property of the

National Library of Medicine" (shown below); title page of volume 2; verso of the title page (copyright); and Contents [volume 2].

Selected Scans of Volume 2 of Nema (Ex. 1016)

37. All identifying characteristics, such as stamps and notations, on Attachment A-1 are consistent with library practice and procedure that I have observed during my career as a professional librarian, specifically with those items held by the National Library of Medicine (NLM). I have no cause for concern about the authenticity or accuracy of these identifying attributes. In addition, Nema was found within the collection of a library, the National Library of Medicine, one of the most likely locations for an authentic publication to be located.

38. Attachment A-2 is a download of Nema from the *ProQuest Ebook Central* database. I completed this download through Purdue University Libraries on March 26, 2022, as an emeritus faculty member at Purdue at this URL: https://ebookcentral.proquest.com/lib/purdue/detail.action?pq-origsite=primo&docID=584343.

39. It is also available for a fee through *ProQuest Ebook Central* at this URL: https://www.taylorfrancis.com/books/edit/10.1201/b17733/pharmaceutical-dosage-forms-sandeep-nema-john-ludwig.

40. After comparing Attachment A-1 and A-2, with the corresponding pages of Ex. 1015 and Ex. 1016, I found no difference between Attachment A-1 and Attachment A-2 with Ex. 1015 or Ex.1016.

41. Therefore, upon finding Nema in the National Library of Medicine, and as a download provided through a research library, Purdue University, from the publisher database, *ProQuest Ebook Central*, I have determined that Ex. 1015 and Ex. 1016, Nema, are authentic documents.

42. I conclude and affirm that Nema, Ex. 1015 and Ex. 1016 are authentic documents.

2. Public Accessibility

43. Attachment A-3 is a true and correct copy of the *WorldCat* entry for Nema. I obtained Attachment A-3 by completing a search on *WorldCat* on March 27, 2022, by searching using Maryland (National Library of Medicine) as the geographical location. The National Library of Medicine was second on the list among the 67 libraries that held Nema worldwide.

44. Attachment A-3 shows that Nema is the document associated with this *WorldCat* entry, as verified by authors: Sandeep Nema and John D. Ludwig; title:

Pharmaceutical Dosage Forms. Parenteral Medications; publisher and publication date: Informa Healthcare in 2010; and ISBN: 978420086539 (three volume set).

45. Nema could have been located by searching for the authors: Sandeep Nema and John D. Ludwig; title: *Pharmaceutical Dosage Forms. Parenteral Medications* or by searching the subject headings: *Parenteral solutions; Pharmaceutical technology;* and/or *Technology Pharmaceutical.*

46. The search discussed above could have been performed anywhere in the world by anyone who accessed *WorldCat* in 2010, openly accessible on the web at that time, and definitely prior to 2011.

47. Attachment A-4 is a download I made from the National Library of Medicine OPAC (online catalog) on March 27, 2022. The document cataloged in this record is Nema as verified on this record are shown as "Creators": Sandeep Nema and John D. Ludwig; title: *Pharmaceutical Dosage Forms. Parenteral Medications;* publisher and publication date: Informa Healthcare in 2010; and ISBN: 978420086539 (three volume set). In addition, the National Library of Medicine call number in Attachment A-4: 2010 L841 matches the call number shown in Attachment A-1 in scan of the back cover and spine of the book, 2010 L841.

48. Nema could have been located in the National Library of Medicine OPAC by searching for the authors on this record shown as "Creators": Sandeep Nema and John D. Ludwig; title: *Pharmaceutical Dosage Forms. Parenteral Medications*;

or by searching the subject headings: *Parenteral solutions; Pharmaceutical technology;* and/or *Technology Pharmaceutical.*

49. Attachment A-5 is the MARC record I downloaded from the National Library of Medicine OPAC on March 27, 2022. The MARC format provides information about the processing of Nema by the National Library of Medicine. As mentioned above, the 9XX field in the MARC format is allocated to local libraries to enter information specific to that library. The National Library of Medicine has used several 9XX fields to indicate dates of processing of the item cataloged.

50. Attachment A-6 is a communication to me from Tina Shrader, Acting Head of Cataloging and Metadata Management Section, Technical Services Division, National Library of Medicine dated March 14, 2022. In this communication she clarifies the use of several 9XX fields by the National Library of Medicine catalogers, below is a quote from the communication from Ms. Shrader, Attachment A-6:

> NLM has locally defined the MARC 992, 993, 994 fields as follows:
>
> 992—Processing Data and Instructions. The date in the $a represents the date that the item described in the record was sent from Acquisitions to Cataloging. The other subfields contain information about the priority level of the item in our cataloging workflow and the encoding level to be assigned to the final bib record.
> 993—CAT Action. Records information about the assignment of the item to a cataloger. The date represents when the item was assigned for cataloging.
> 994—Cataloging Completion. Indicates completion of descriptive and subject cataloging. The date indicates when this work is completed.
>
> There are additional fields that may be tangentially relevant to your question. After cataloging work is completed, most records go through a review process and are not distributed in NLM's MARC files until the 995 Record Authorization/Revision field is coded to indicate the record is authorized for distribution, with the date of authorization. The 999 Processing Status field also contains a code that affects whether the record is distributed.

51. The 992, 993, 994, 995, and 999 MARC Fields indicate the processing and cataloging of Nema after acquisition by the National Library of Medicine. The MARC 992, 993, 994, and 995 fields as shown on Attachment A-5 are as follows:

992	__ | **p**P1**e**EF**a**20101116
993	__ | **a**JCY**b**20101118
994	__ | **a**CDN**b**20101118
995	__ | **a**AUTH**b**20100721**c**REV**d**20180131
996	__ | **a**rev. CIP**b**20101118

52. In the MARC record above the 992 MARC Field, after the "a" delimiter reads: 20101116, i.e.,: 2010 = 2010; 11 = November; 16 =16th; November 16, 2010, this is the date Nema was received from acquisitions by the cataloging department. The 993 MARC Field after the "b" delimiter reads: 20101118, i.e.,: 2010 = 2010; 11 = November; 18 =18th; November 18, 2010 indicates when Nema was assigned for cataloging. The 994 MARC Field after the "b" delimiter reads: 20101118, i.e.,: 2010 = 2010; 11 = November; 18 =18th; November 18, 2010 indicates when cataloging was completed for Nema.

53. The physical copy of Nema at the National Library of Medicine would have been available for public access, consistent with standard library practice, within one week to ten days after cataloging was completed on November 18, 2010. Therefore, Nema would have been accessible to the public in the National Library of Medicine no later than November 29, 2010.

3. Conclusion

54. I conclude that Nema, Ex. 1015 and Ex. 1016, is an authentic document and would have been publicly accessible in the National Library of Medicine on or about November 29, 2010, well before July, 2011.

B. Document B: Ex. 1214: Shawn Kinney, et al., "A Rational Approach to Determining the Maximum Product Sterility", *Drug Delivery Technology*, Volume 9, Number 2. February, 2009. Pages: 42-47. ("Kinney")

55. I have been asked to opine on an article titled: "A Rational Approach to Determining the Maximum Product Sterility" published in *Drug Delivery Technology* in its volume 9, issue number 2, February, 2009 on pages 42-47. In this declaration when "Kinney" is used, it refers not only to the article titled "A Rational Approach to Determining the Maximum Product Sterility" it also can refer, depending upon the context, to *Drug Delivery Technology,* volume 9, issue number 2, February, 2009.

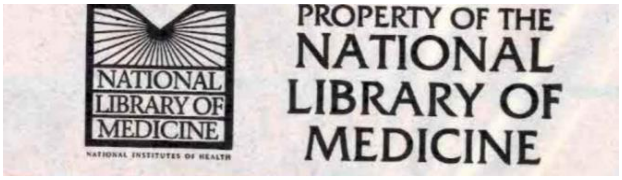
1. Authentication

56. I have evaluated the Kinney reference several ways: (1) by assessing scans of a copy provided to me by counsel, Ex. 1214; (2) by assessing scans of a print copy held by the National Library of Medicine (NLM) provided to me by Wisconsin TechSearch (WTS), Attachment B-1; (3) by assessing scans of a print copy provided to me by Wisconsin TechSearch (WTS) from the British Lending Library, Attachment B-2; (4) by assessing scans of a print copy provided to me by

Wisconsin TechSearch (WTS) from the Butler University Library, Indianapolis, Indiana, Attachment B-3.

57. Attachment B-1, obtained for me at my request by Wisconsin TechSearch (WTS) was made from the print copy owned by the National Library of Medicine (NLM). I received Attachment B-1 on March 14, 2022, and it contains scans of Kinney that includes: cover of *Drug Delivery Technology,* volume 9, number 2, February, 2009 with a stamp in the upper left corner as shown below:

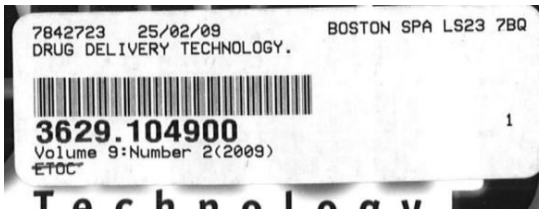
The cover of Attachment B-1 also includes a stamp indicating that the copy is owned by the National Library of Medicine:



58. All identifying characteristics, such as stamps and notations, on Attachment B-1 are consistent with library practice and procedure that I have observed during my career as a professional librarian, specifically with those items held by the National Library of Medicine (NLM). I have no cause for concern about the authenticity or accuracy of these identifying attributes. In addition, Kinney was

found within the collection of a library, the National Library of Medicine, one of the most likely locations for an authentic publication to be located.

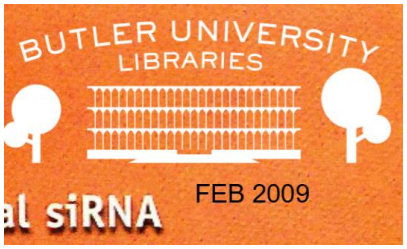
59. Attachment B-2, obtained for me at my request by Wisconsin TechSearch (WTS) was made from the print copy owned by the Boston Spa Library of the British Library, United Kingdom. I received Attachment B-1 on March 31, 2022 it contains scans of Kinney that includes: cover of *Drug Delivery Technology*, volume 9, number 2, February, 2009 with a label in the upper right corner as shown as below; periodical information sheet; table of contents; and Kinney article on pages 42-47.



60. All identifying characteristics, such as stamps and notations, on Attachment B-2 are consistent with library practice and procedure that I have observed during my career as a professional librarian. In addition, Kinney was found within the collection of a library, the Boston Spa Center of the British Library of the United Kingdom, one of the most likely locations for an authentic publication to be located.

61. Attachment B-3, obtained for me at my request by Wisconsin TechSearch (WTS) was made from the print copy owned by the Butler University

Library, Indianapolis, Indiana. I received Attachment B-3 on March 18, 2022 and contains scans of Kinney that includes: cover of Drug Delivery Technology, volume 9, number 2, February, 2009; periodical information sheet; table of contents with a stamp that reads "Butler University Libraries FEB 2009" (as shown below); and Kinney article on pages 42-47.



62. All identifying characteristics, such as stamps and notations, on Attachment B-3 are consistent with library practice and procedure that I have observed during my career as a professional librarian. In addition, Kinney was found within the collection of a library, the Butler University Library, a likely locations for an authentic publication to be located.

63. After comparison between Attachment B-1, B-2, and B-3 with the corresponding pages of Ex. 1214, I found no difference between Attachment B-1, Attachment B-2, and Attachment B-3 with Ex. 1214.

64. Therefore, upon finding Kinney in the National Library of Medicine, The Boston Spa Center of the British Library, and the Butler University Library, I have determined that Ex. 1214, Kinney, is an authentic document.

65. I conclude and affirm that Kinney, Ex. 1214 is an authentic document.

2. Public Accessibility

66. Attachments B-4, B-5, and B-6 are true and correct copies of the *WorldCat* entries for Kinney. I obtained Attachment B-4, B-5, and B-6 by completing searches on *WorldCat* on April 3, 2022, by using Maryland (National Library of Medicine) as a geographical location; by using United Kingdom as a geographical location, Boston Spa Center, British Library; and by using Indiana as a geographical location, Butler University.

67. On Attachment B-4 National Library of Medicine was second; on Attachment B-5: The British Library, On Demand (Boston Spa) was fourth; and on Attachment B-6, Butler University was first on the list among the 45 libraries that hold Kinney worldwide.

68. Attachments B-4, B-5, and B-6 show that Kinney is the document associated with these *WorldCat* entries, as verified by title: *Drug Delivery Technology*; and publisher: Drug Delivery Technology, LLC; and ISSN: 1537-2898 (ISSN for print edition).

69. Kinney could have been located by searching for the title: *Drug Delivery Technology* and/or by searching the subject headings: *Drug delivery systems – Periodicals; Drug delivery systems*; and/or *Biological Transport.*

70. The search discussed above could have been performed anywhere in the world by anyone who accessed *WorldCat* in 2009, openly accessible on the web at that time, and definitely prior to 2011.

71. Attachment B-7 is a download I made from the National Library of Medicine OPAC (online catalog) on April 3, 2022. The document cataloged in this record is Kinney as verified on this record are shown by title: *Drug Delivery Technology;* publisher: Drug Delivery Technology, LLC. In addition, the National Library of Medicine call number in Attachment B-7: W1 DR514BK, matches the call number shown in Attachment B-1 in the label on the cover of *Drug Delivery Technology*, Volume 9, Number 2. February, 2009.

72. Kinney could have been located in the National Library of Medicine OPAC by searching for the title: *Drug Delivery Technology* and/or by searching the MESH subject headings: *Drug Delivery Systems; Biological Transport; Drug Industry;* and/or *Technology, Pharmaceutical*. Kinney could have been located in the National Library of Medicine OPAC by searching for the title: *Drug Delivery Technology* and/or by searching the MESH subject headings: *Drug Delivery Systems; Biological Transport; Drug Industry;* and/or *Technology, Pharmaceutical*.

73. Attachment B-8 is a download I made from the British Library OPAC (online catalog) on April 3, 2022. The document cataloged in this record is Kinney

as verified on this record are shown by title: *Drug Delivery Technology;* publisher: Drug Delivery Technology, LLC.

74. Kinney could have been located in the British Library by searching for the title: *Drug Delivery Technology* and/or by searching the subject headings: *Drug Delivery Systems - Periodicals; Biological Transport - Periodicals; Drug Industry - Periodicals;* and/or *Technology, Pharmaceutical - Periodicals*.

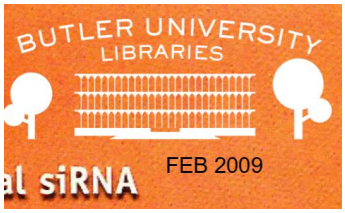
75. Attachment B-9 is a download I made from the Butler University Library OPAC (online catalog) on April 3, 2022. The document cataloged in this record is Kinney as verified on this record are shown by title: *Drug Delivery Technology;* publisher: Drug Delivery Technology, LLC.

76. Kinney could have been located in the British Library by searching for the title: *Drug Delivery Technology* and/or by searching the Library of Congress subject heading: *Drug Delivery Systems - Periodicals; and/or MESH Subject Headings: Drug Delivery Systems; Biological Transport;* and/or *Drug Industry.*

77. The physical copy of Kinney at the National Library of Medicine, British Library and Butler University Library would have been available for public access, consistent with standard library practice, within one week to ten days after receipt as shown on the label (Attachment B-2) or stamp (Attachment B-3).

78. On Attachment B-2, the label, shown below, has a date embedded in it that, more likely than not, 25/02/09, that is the date of receipt of *Drug Delivery Technology*, volume 9, number 2, February 2009, i.e., February 25, 2009.

79. On Attachment B-2, the stamp shown below, has only a month and year, "FEB 2009."



80. Therefore, the physical copy of Kinney at the British Library and Butler University Library would have been available for public access, consistent with standard library practice, within one week to ten days after receipt as shown on the label (Attachment B-2) or stamp (Attachment B-3). That is, at the British Library by March 6, 2009, and using the end of February, February 28, as the latest date the stamp would have been applied to the print copy held by the Butler Library, of March 10, 2009. The National Library of Medicine print copy did not have a date of receipt

to verify the date of receipt, so it is not used to prove public accessibility, only authenticity.

81. Additional evidence that a publication was known to the research community is a citation to the publication (article, thesis, or paper). Attachment B-10 is an article by: Edwin Chan, et al., titled: "Investigating Liquid Leak from Pre-filled Syringes upon Needle Shield Removal: Effect of Air Bubble Pressure," published in *PDA Journal of Pharmaceutical Science and Technology*, volume 65, number 4, July-August, 2011, pages 363-371. ("Chan").

82. I downloaded Chan, for a fee, from this link: https://www.researchgate.net/publication/292012903_A_rational_approach_to_determining_the_maximun_allowable_Gas_bubble_inside_a_prefilled_syringe_to_minimize_stopper_movement_protect_product_sterility/citations

83. On page 371 of Chan, is a list of "References". Number 3 on this list reads as shown below:

> 3. Kinney, H.; Wagner, A.; Phillips, C. W. A rational approach to determining the maximum allowable gas bubble inside a prefilled syringe to minimize stopper movement and protect product sterility. *Drug Deliv. Technol.* **2009,** *9,* 42– 47.

84. Therefore, having located Kinney in three research libraries with evidence that it was available within two of those libraries, more likely than not, by March 10, 2009, as well as locating a citation to Kinney that was published in a

journal dated July/August 2011, I conclude and affirm that Kinney would have been publicly accessible no later than March 10, 2009, well before July 2011.

3. Conclusion

85. I conclude that Kinney, Ex. 1214 is an authentic document and would have been publicly accessible in the British Library and the Butler University Library National Library on or about March 10, 2009 well before July, 2011.

V. AVAILABILITY FOR CROSS-EXAMINATION

86. In signing this Declaration, I recognize that this Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the U.S. Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

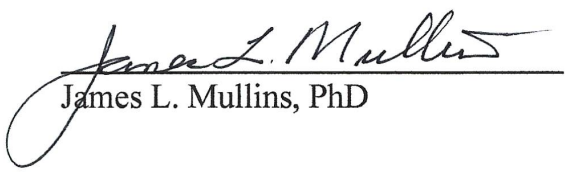
VI. RIGHT TO SUPPLEMENT

87. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner raises and to take into account new information as it becomes available to me.

VII. JURAT

88. I declare that all statements made herein of my 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 full knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code.

Dated: April 6, 2022 Respectfully submitted,



Williamsburg, Virginia James L. Mullins, PhD

ATTACHMENT A-1

Executive Director,
Therapeutics Pharmaceutical
ouis. Since graduating in 1992
ema has been involved with
ll molecule and protein drugs
rst at Mallinckrodt Medical
e, Pharmacia), and has led the
ched products. He is active in
n of Pharmaceutical Scientists
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veral meetings and focus
an adjunct faculty appointment
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is Vice President, Business
d Clinical Supply Planning,
ceutical Sciences at Pfizer, and
pany's St. Louis Laboratories.
S. degree in Pharmacy and
ceutics from the University of
d has held numerous research
ons at Burroughs Wellcome
ia, Inc., and Pfizer. He is
Association of Pharmaceutical
e Parenteral Drug Association
arch Institute, where he has
ng professional training courses
d as an instructor.

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VOLUME
1

Nema
Ludwig

Pharmaceutical Dosage Forms: Parenteral Medic
Third Edition Volume 1: Formulation and Packaging

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Third Edition
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Pharmaceutical Dosage Forms:

Parenteral Medications

Third Edition

Volume 1: Formulation and Packaging

Edited by
Sandeep Nema
John D. Ludwig

informa
healthcare

Pharmaceutical Dosage Forms

Parenteral Medications
Third Edition

Volume 1
Formulation and Packaging

Edited by

Sandeep Nema
Pfizer, Inc.
Chesterfield, Missouri, U.S.A.

John D. Ludwig
Pfizer, Inc.
Chesterfield, Missouri, U.S.A.

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healthcare
New York London

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Contents

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About the editors

SANDEEP NEMA Ph.D. is Executive Director, Pharmaceutical R&D, BioTherapeutics Pharmaceutical Sciences at Pfizer in St. Louis. Since graduating in 1992 with his doctorate, Dr. Nema has been involved with the development of small molecule and protein drugs via parenteral delivery, first at Mallinckrodt Medical and then at Pfizer (Searle, Pharmacia), and has led the formulation of four launched products. He is active in the American Association of Pharmaceutical Scientists (AAPS) and the Parenteral Drug Association (PDA), where he has chaired several meetings and focus groups. Dr. Nema holds an adjunct faculty appointment at the University of Tennessee.

JOHN D. LUDWIG Ph.D. is Vice President, Business Strategy, Operations, and Clinical Supply Planning, BioTherapeutics Pharmaceutical Sciences at Pfizer, and Site Director for the company's St. Louis Laboratories. Dr. Ludwig received a B.S. degree in Pharmacy and Ph.D. degree in Pharmaceutics from the University of Tennessee, Memphis and has held numerous research and development positions at Burroughs Wellcome Co, Searle, Inc., Pharmacia, Inc., and Pfizer. He is active in the American Association of Pharmaceutical Scientists (AAPS) and the Parenteral Drug Association (PDA) Training and Research Institute, where he has contributed to developing professional training courses and has regularly served as an instructor.

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VOLUME 2

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Ludwig

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Pharmaceutical Dosage Forms:

Parenteral Medications

Third Edition

Volume 2: Facility Design, Sterilization and Processing



Edited by
Sandeep Nema
John D. Ludwig

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healthcare

Pharmaceutical Dosage Forms

Parenteral Medications
Third Edition

Volume 2
Facility Design, Sterilization and Processing

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ATTACHMENT A-2

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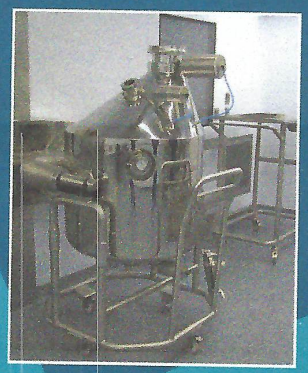
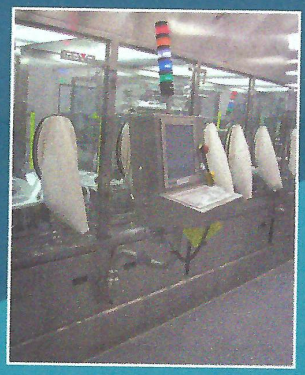
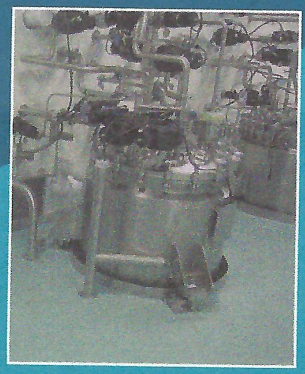
IPR2021-00816

Pharmaceutical Dosage Forms:

Parenteral Medications

Third Edition

Volume 1: Formulation and Packaging

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Foreword

I was a faculty member at the University of Tennessee and a colleague of Dr. Kenneth Avis when he conceived, organized, and edited (along with H.A. Lieberman and L. Lachman) the first edition of this book series that was published in 1984. It was so well received by the pharmaceutical science community that an expanded three-volume second edition was published in 1992. Dr. Avis did not survive long enough to oversee a third edition, and it was questionable whether a third edition would ever be published until two of his graduate students, Drs. Nema and Ludwig, took it upon themselves to carry on Dr. Avis' tradition.

Their oversight of this third edition is work that their mentor would be highly pleased and proud of. From 29 chapters in the second edition to 43 chapters in this new edition, this three-volume series comprehensively covers both the traditional subjects in parenteral science and technology as well as new and expanded subjects. For example, separate chapter topics in this edition not found in previous editions include solubility and solubilization, depot delivery systems, biophysical and biochemical characterization of peptides and proteins, container-closure integrity testing, water systems, endotoxin testing, focused chapters on different sterilization methods, risk assessment in aseptic processing, visual inspection, advances in injection devices, RNAi delivery, regulatory considerations for excipients, techniques to evaluate pain on injection, product specifications, extractables and leachables, process analytical technology, and quality by design.

The editors have done an outstanding job of convincing so many top experts in their fields to author these 43 chapters. The excellent reputations of the authors and editors of this book will guarantee superb content of each chapter. There is no other book in the world that covers the breadth and depth of parenteral science and technology better than this one. In my opinion, the editors have achieved their primary objectives—publishing a book that contains current and emerging sterile product development and manufacturing information, and maintaining the high standard of quality that readers would expect.

Michael J. Akers
Baxter BioPharma Solutions
Bloomington, Indiana, U.S.A.

Preface

Pharmaceutical Dosage Forms: Parenteral Medications was originally published in 1984 and immediately accepted as a definitive reference in academic institutions and the pharmaceutical industry. The second edition was published in 1993. The ensuing years have produced incredible technological advancement. Classic small-molecule drugs are now complemented by complex molecules such as monoclonal antibodies, antibody fragments, aptamers, antisense, RNAi therapeutics, and DNA vaccines. There have been significant innovations in delivery devices, analytical techniques, in-silico modeling, and manufacturing and control technologies. In addition, the global regulatory environment has shifted toward greater emphasis on science-based risk assessment as evidenced by the evolving cGMPs, quality by design (QbD), process analytical technology (PAT), continuous processing, real time release, and other initiatives. The rapidly changing landscape in the parenteral field was the primary reason we undertook the challenging task of updating the three volumes. Our objectives were to (*i*) revise the text with current and emerging sterile product development and manufacturing science and (*ii*) maintain the high standard of quality the readers expect.

The third edition not only reflects enhanced content in all the chapters, but also more than half of the chapters are new underscoring the rapidly advancing technology. We have divided the volumes into logical subunits—volume 1 addresses formulation and packaging aspects; volume 2, facility design, sterilization and processing; and volume 3, regulations, validation and future directions. The authors invited to contribute chapters are established leaders with proven track records in their specialty areas. Hence, the textbook is authoritative and contains much of the collective experience gained in the (bio)pharmaceutical industry over the last two decades. *We are deeply grateful to all the authors who made this work possible.*

Volume 1 begins with a historical perspective of injectable drug therapy and common routes of administration. Formulation of small molecules and large molecules is presented in depth, including ophthalmic dosage forms. Parenteral packaging options are discussed relative to glass and plastic containers, as well as elastomeric closures. A definitive chapter is provided on container closure integrity.

Volume 2 presents chapters on facility design, cleanroom operations, and control of the environment. A chapter discussing pharmaceutical water systems is included. Key quality attributes of sterile dosage forms are discussed, including particulate matter, endotoxin, and sterility testing. The most widely used sterilization techniques as well as processing technologies are presented. Volume 2 concludes with an in-depth chapter on lyophilization.

Volume 3 focuses on regulatory requirements, risk-based process design, specifications, QbD, and extractables/leachables. In addition, we have included chapters on parenteral administration devices, siRNA delivery systems, injection site pain assessment, and control, PAT, and rapid microbiology test methods. Volume 3 concludes with a forward-looking chapter discussing the future of parenteral product manufacturing.

These three volumes differ from other textbooks in that they provide a learned review on developing parenteral dosage forms for *both* small molecules and biologics. Practical guidance is provided, in addition to theoretical aspects, for how to bring a drug candidate forward from discovery, through preclinical and clinical development, manufacturing, validation, and eventual registration.

The editors wish to thank Judy Clarkston and Lynn O'Toole-Bird (Pfizer, Inc.) for their invaluable assistance and organizational support during this project, and Sherri Niziolek and Bianca Turnbull (Informa Healthcare) for patiently leading us through the publishing process.

We also acknowledge the assistance of Pfizer, Inc. colleagues Lin Chen and Min Huang for reviewing several of the chapters.

We would like to express special gratitude to the late Kenneth E. Avis (University of Tennessee College of Pharmacy) for his dedication to teaching and sharing practical knowledge in the area of parenteral medications to so many students over the years, including us. Finally, we acknowledge the contributions of Dr Avis, Leon Lachman, and Herbert A. Lieberman who edited the earlier editions of this book series.

Sandeep Nema
John D. Ludwig

We dedicate this work to those who have inspired us.
To my parents Walter and Ruth Ludwig and my wife Sue Ludwig
To my parents Hari and Pratibha Nema and my wife Tina Busch-Nema

Contents

Contributors

Balaji Agoram Pfizer, Inc., Sandwich, U.K.

Paramita Bandyopadhyay Bausch & Lomb, Rochester, New York, U.S.A.

Himanshu Bhattacharjee Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, Memphis, Tennessee, U.S.A.

James A. Carroll BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc., Chesterfield, Missouri, U.S.A.

Martin J. Coffey Bausch & Lomb, Rochester, New York, U.S.A.

James J. Cunningham Pharmaceutical Research and Development Sciences, Merck Research Laboratories, West Point, Pennsylvania, U.S.A.

Tapan K. Das BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc., Chesterfield, Missouri, U.S.A.

Frances L. DeGrazio West Pharmaceutical Services, Inc., Lionville, Pennsylvania, U.S.A.

Patrick P. DeLuca Pharmaceutical Sciences, University of Kentucky College of Pharmacy, Lexington, Kentucky, U.S.A.

Dana Morton Guazzo RxPax, LLC, Bridgewater, New Jersey, U.S.A.

Michael Hageman Bristol-Myers Squibb Research, Princeton, New Jersey, U.S.A.

Renaud Janssen Helvoet Pharma, Alken, Belgium

Madhav Kamat Biopharmaceutics R&D, Bristol-Myers Squibb Company, New Brunswick, New Jersey, U.S.A.

Marc J. Kirchmeier Vaccine Formulation Development, Variation Biotechnologies, Inc., Cambridge, Massachusetts, U.S.A.

John D. Ludwig BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc., Chesterfield, Missouri, U.S.A.

Sachin Mittal Pharmaceutical Research and Development Sciences, Merck Research Laboratories, West Point, Pennsylvania, U.S.A.

Kazuko Sagawa Pfizer Global R&D, Groton, Connecticut, U.S.A.

Ravi M. Shanker Pfizer Global R&D, Groton, Connecticut, U.S.A.

Mohannad Shawer Bausch & Lomb, Rochester, New York, U.S.A.

Satish K. Singh BioTherapeutics Pharmaceutical Sciences, Pfizer, Inc., Chesterfield, Missouri, U.S.A.

Ching-Chiang Su Bristol-Myers Squibb Research, Princeton, New Jersey, U.S.A.

Robert Swift Amgen, Inc., Thousand Oaks, California, U.S.A.

Laura A. Thoma Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, Memphis, Tennessee, U.S.A.

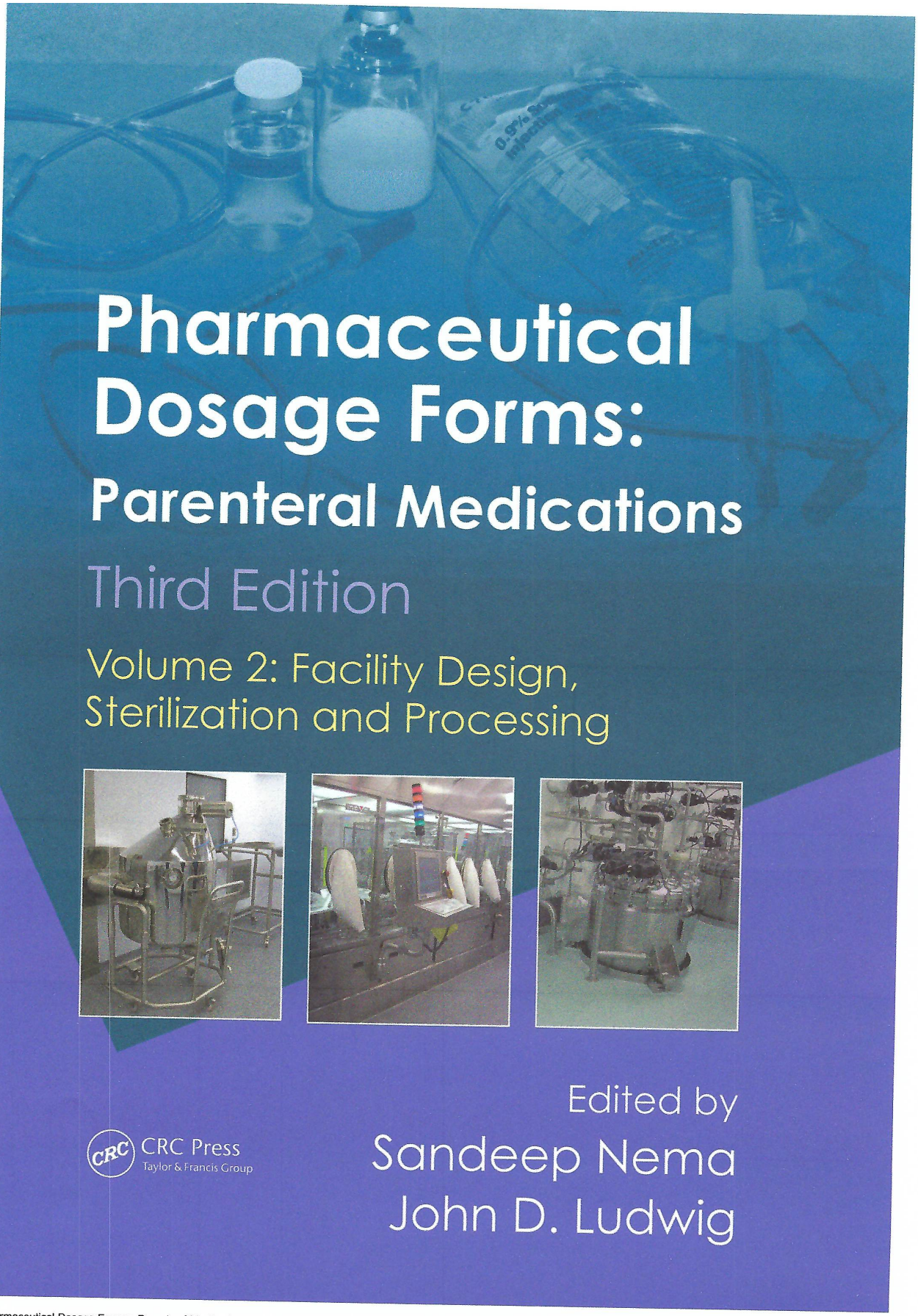
N. Murti Vemuri Sanofi-Aventis, Bridgewater, New Jersey, U.S.A.

Vinod D. Vilivalam West Pharmaceutical Services, Inc., Lionville, Pennsylvania, U.S.A.

Y. John Wang Genentech, South San Francisco, California, U.S.A.

Lan Xiao Bristol-Myers Squibb Research, Princeton, New Jersey, U.S.A.

Gaozhong Zhu Shire Human Genetic Therapies, Inc., Cambridge, Massachusetts, U.S.A.



Pharmaceutical Dosage Forms:

Parenteral Medications

Third Edition

Volume 2: Facility Design, Sterilization and Processing

Edited by

Sandeep Nema

John D. Ludwig

CRC Press
Taylor & Francis Group

Pharmaceutical Dosage Forms

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Parenteral Medications
Third Edition

Volume 2
Facility Design, Sterilization and Processing

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Sandeep Nema
Pfizer, Inc.
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Foreword

I was a faculty member at the University of Tennessee and a colleague of Dr. Kenneth Avis when he conceived, organized, and edited (along with H.A. Lieberman and L. Lachman) the first edition of this book series that was published in 1984. It was so well received by the pharmaceutical science community that an expanded three-volume second edition was published in 1992. Dr. Avis did not survive long enough to oversee a third edition, and it was questionable whether a third edition would ever be published until two of his graduate students, Drs. Nema and Ludwig, took it upon themselves to carry on Dr. Avis' tradition.

Their oversight of this third edition is work that their mentor would be highly pleased and proud of. From 29 chapters in the second edition to 43 chapters in this new edition, this three-volume series comprehensively covers both the traditional subjects in parenteral science and technology as well as new and expanded subjects. For example, separate chapter topics in this edition not found in previous editions include solubility and solubilization, depot delivery systems, biophysical and biochemical characterization of peptides and proteins, container-closure integrity testing, water systems, endotoxin testing, focused chapters on different sterilization methods, risk assessment in aseptic processing, visual inspection, advances in injection devices, RNAi delivery, regulatory considerations for excipients, techniques to evaluate pain on injection, product specifications, extractables and leachables, process analytical technology, and quality by design.

The editors have done an outstanding job of convincing so many top experts in their fields to author these 43 chapters. The excellent reputations of the authors and editors of this book will guarantee superb content of each chapter. There is no other book in the world that covers the breadth and depth of parenteral science and technology better than this one. In my opinion, the editors have achieved their primary objectives—publishing a book that contains current and emerging sterile product development and manufacturing information, and maintaining the high standard of quality that readers would expect.

Michael J. Akers
Baxter BioPharma Solutions
Bloomington, Indiana, U.S.A.

Preface

Pharmaceutical Dosage Forms: Parenteral Medications was originally published in 1984 and immediately accepted as a definitive reference in academic institutions and the pharmaceutical industry. The second edition was published in 1993. The ensuing years have produced incredible technological advancement. Classic small-molecule drugs are now complemented by complex molecules such as monoclonal antibodies, antibody fragments, aptamers, antisense, RNAi therapeutics, and DNA vaccines. There have been significant innovations in delivery devices, analytical techniques, in-silico modeling, and manufacturing and control technologies. In addition, the global regulatory environment has shifted toward greater emphasis on science-based risk assessment as evidenced by the evolving cGMPs, quality by design (QbD), process analytical technology (PAT), continuous processing, real time release, and other initiatives. The rapidly changing landscape in the parenteral field was the primary reason we undertook the challenging task of updating the three volumes. Our objectives were to (*i*) revise the text with current and emerging sterile product development and manufacturing science and (*ii*) maintain the high standard of quality the readers expect.

The third edition not only reflects enhanced content in all the chapters, but also more than half of the chapters are new underscoring the rapidly advancing technology. We have divided the volumes into logical subunits—volume 1 addresses formulation and packaging aspects; volume 2, facility design, sterilization and processing; and volume 3, regulations, validation and future directions. The authors invited to contribute chapters are established leaders with proven track records in their specialty areas. Hence, the textbook is authoritative and contains much of the collective experience gained in the (bio)pharmaceutical industry over the last two decades. *We are deeply grateful to all the authors who made this work possible.*

Volume 1 begins with a historical perspective of injectable drug therapy and common routes of administration. Formulation of small molecules and large molecules is presented in depth, including ophthalmic dosage forms. Parenteral packaging options are discussed relative to glass and plastic containers, as well as elastomeric closures. A definitive chapter is provided on container closure integrity.

Volume 2 presents chapters on facility design, cleanroom operations, and control of the environment. A chapter discussing pharmaceutical water systems is included. Key quality attributes of sterile dosage forms are discussed, including particulate matter, endotoxin, and sterility testing. The most widely used sterilization techniques as well as processing technologies are presented. Volume 2 concludes with an in-depth chapter on lyophilization.

Volume 3 focuses on regulatory requirements, risk-based process design, specifications, QbD, and extractables/leachables. In addition, we have included chapters on parenteral administration devices, siRNA delivery systems, injection site pain assessment, and control, PAT, and rapid microbiology test methods. Volume 3 concludes with a forward-looking chapter discussing the future of parenteral product manufacturing.

These three volumes differ from other textbooks in that they provide a learned review on developing parenteral dosage forms for *both* small molecules and biologics. Practical guidance is provided, in addition to theoretical aspects, for how to bring a drug candidate forward from discovery, through preclinical and clinical development, manufacturing, validation, and eventual registration.

The editors wish to thank Judy Clarkston and Lynn O'Toole-Bird (Pfizer, Inc.) for their invaluable assistance and organizational support during this project, and Sherri Niziolek and Bianca Turnbull (Informa Healthcare) for patiently leading us through the publishing process.

We also acknowledge the assistance of Pfizer, Inc. colleagues Lin Chen and Min Huang for reviewing several of the chapters.

We would like to express special gratitude to the late Kenneth E. Avis (University of Tennessee College of Pharmacy) for his dedication to teaching and sharing practical knowledge in the area of parenteral medications to so many students over the years, including us. Finally, we acknowledge the contributions of Dr Avis, Leon Lachman, and Herbert A. Lieberman who edited the earlier editions of this book series.

Sandeep Nema
John D. Ludwig

We dedicate this work to those who have inspired us.
To my parents Walter and Ruth Ludwig and my wife Sue Ludwig
To my parents Hari and Pratibha Nema and my wife Tina Busch-Nema

Contents

Contributors

James Agalloco Agalloco & Associates, Belle Mead, New Jersey, U.S.A.

D. Scott Aldrich Ultramikro, LLC, Richland, Michigan, U.S.A.

Anne F. Booth Booth Scientific, Inc., Hendersonville, North Carolina, U.S.A.

Mark Caldwell Jacobs Engineering Group, Inc., Conshohocken, Pennsylvania, U.S.A.

Michael E. Dawson Associates of Cape Cod, Inc., Falmouth, Massachusetts, U.S.A.

Donald A. Eisenhauer Abbott Laboratories, North Chicago, Illinois, U.S.A.

Barry P. Fairand Sterigenics International, Dublin, Ohio, U.S.A.

Larry A. Gatlin PK, LLC, Groton, Connecticut, U.S.A.

Deborah Havlik R&D Microbiology, Hospira, Inc., Lake Forest, Illinois, U.S.A.

Bob Helt Jacobs Engineering Group, Inc., Conshohocken, Pennsylvania, U.S.A.

Beth Holden Jacobs Engineering Group, Inc., Conshohocken, Pennsylvania, U.S.A.

Maik W. Jornitz Sartorius Stedim North America, Inc., Bohemia, New York, U.S.A.

Joseph J. Manfredi GMP Systems, Inc., Fairfield, New Jersey, U.S.A.

Christine Martin Abbott GmbH & Co. KG, Ludwigshafen, Germany

Francesca McBride Jacobs Engineering Group, Inc., Conshohocken, Pennsylvania, U.S.A.

Theodore H. Meltzer Capitola Consultancy, Bethesda, Maryland, U.S.A.

William H. Miele Pfizer Global Manufacturing, Kalamazoo, Michigan, U.S.A.

Jeanne Moldenhauer Excellent Pharma Consulting, Mundelein, Illinois, U.S.A.

Steven L. Nail Baxter Pharmaceutical Solutions, Bloomington, Indiana, U.S.A.

Dusan Razem Ruder Boskovic Institute, Zagreb, Croatia

Roland Schmidt Abbott GmbH & Co. KG, Ludwigshafen, Germany

Kevin Schreier Jacobs Engineering Group, Inc., Conshohocken, Pennsylvania, U.S.A.

Steven G. Schultz Abbott Laboratories, North Chicago, Illinois, U.S.A.

Scott V. W. Sutton Microbiology Network, Inc., Rochester, New York, U.S.A.

Kevin Trupp Global Sterilization Engineering, Hospira, Inc., Lake Forest, Illinois, U.S.A.

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Author: Sandeep Nema; John D Ludwig

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Summary: "A historical perspective of injectable drug therapy, common routes of administration, and biopharmaceutics of NCEs and NBEs. - An in-depth discussion on the preformulation and formulation of small and large molecules, including ophthalmic dosage forms. - A presentation of parenteral primary packaging options - glass and plastic containers, as well as elastomeric closures. - A definitive chapter on container-closure

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Pharmaceutical dosage forms. Parenteral medications.

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To: Shrader, Tina (NIH/NLM) [E]
Subject: RE: Response from NLM re: 992, 993, 994 MARC fields

James L Mullins, PhD
Dean Emeritus of Libraries and
Esther Ellis Norton Professor Emeritus
jmullins@purdue.edu
Jlmullins1@cox.net
765 479 4956
205 St Cuthbert
Williamsburg, VA 23188

From: Shrader, Tina (NIH/NLM) [E] <tina.shrader@nih.gov>
Sent: Monday, March 14, 2022 7:36 AM
To: MULLINS, JAMES L. <jmullins@purdue.edu>; jlmullins1@cox.net
Cc: Marill, Jennifer (NIH/NLM) [E] <marillj@mail.nlm.nih.gov>
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Dr. Mullins,

I'm responding on behalf of Jennifer Marill to the voice mail you left on Friday. Diane Boehr retired last year, and I'm currently filling in as Acting Head of our Cataloging and Metadata Management Section.

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Please don't hesitate to contact me by email or phone (301-827-1633) if you have other questions.

Tina Shrader (she/her)
Acting Head
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Technical Services Division
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Drug Delivery® Technology

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Delivering Therapeutic siRNA

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Frank Y. Xie, PhD
Systemic Delivery of Therapeutic siRNA: Opportunities & Challenges

Maria J. Gutierrez, MD
A Spring-Powered Device for Subcutaneous, Intramuscular & Intradermal Injections Using an Auto-Disable Syringe

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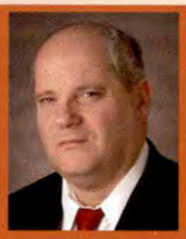

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PUBLISHER/PRESIDENT
Ralph Vitaro

EXECUTIVE EDITORIAL DIRECTOR
Dan Marino, MSc
dmarino@drugdeliverytech.com

CREATIVE DIRECTOR
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CONTROLLER
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Cindy H. Dubin
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TECHNICAL OPERATIONS
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Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
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Advertising Sales Offices

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West Coast
Warren De Graff
Western Regional Manager
818 5th Avenue, Suite 301
San Rafael, CA 94901
Tel: (415) 721-0644
Fax: (415) 721-0665
E-mail: wjdegraff@drugdeliverytech.com

International
Ralph Vitaro
219 Changebridge Road
Montville, NJ 07045
Tel: (973) 299-1200
Fax: (973) 299-7937
E-mail: rvitaro@drugdeliverytech.com

Mailing List Rental
Candy Brecht
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Therapeutic siRNA

"Compared to the local siRNA deliveries that were used in many early siRNA clinical trials, systemic siRNA delivery faces more challenges and hurdles that have slowed down the expansion of siRNA therapeutics. With increasing efforts dedicated to the development of more efficient systemic siRNA delivery technologies, it is conceivable the key delivery hurdles could be overcome and the potential of RNAi-based therapeutics may be realized in a not too distant future."

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PREFILLED SYRINGES

A Rational Approach to Determining the Maximum Allowable Gas Bubble Inside a Prefilled Syringe to Minimize Stopper Movement & Protect Product Sterility

By: Shawn Kinney, PhD; Andrea Wagner, PhD; and Christian W. Phillips

ABSTRACT

Prefilled syringes are a fast-growing alternative to vials in the parenteral product market due to the many advantages they offer relative to vials. These include reduced overfill requirements, ease of use, more accurate dosing, decreased waste, and enhanced product differentiation.

Conventional syringe-filling processes typically leave a large air bubble in a syringe that can negatively impact product sterility and package integrity. Using a series of equations and hypothetical scenarios, this article will demonstrate the potential impact of a bubble on stopper movement during periods of reduced atmospheric pressure. It will also propose a rational approach for determining the maximum allowable size of a gas bubble inside a prefilled syringe taking into account several critical factors. After weighing some of the alternatives for limiting stopper movement during shipping as well as one additional benefit of bubble-free filling, this article will make the case that reducing or eliminating the bubble inside a prefilled syringe is a preferred means for ensuring product sterility while enhancing the benefits of a prefilled syringe.

INTRODUCTION

The internal environments of a glass vial and a glass syringe have a number of features in common, as shown in Figure 1. Both presentations are essentially glass cylinders that are sealed by an elastomeric closure, or stopper, and both contain a gaseous headspace, or bubble. However, there is one noteworthy difference. A vial's stopper is held in place by a crimp, while a syringe's stopper is designed to move in order to allow injection of the drug product. This freedom of movement, when coupled with a gas bubble (which is not intrinsic to a syringe but is a byproduct of sub-optimal filling processes) can potentially cause significant challenges with regard to package integrity and product sterility, particularly when the syringe is exposed to repeated changes in atmospheric pressure, such as during shipping. Reducing or eliminating the

FIGURE 1

Comparison of a vial and a syringe. Both are essentially glass tubes sealed with an elastomeric closure and contain a gas headspace.

bubble inside the syringe would limit stopper movement, potentially enhancing sterility assurance of the product.[1]

In a preliminary study of the impact of a bubble on stopper movement in a prefilled syringe, three syringes were placed inside a Hypak vacuum chamber. One syringe contained a 2.5-mm bubble, one a 5.0-mm bubble, and yet another contained no bubble at all. Next, a vacuum was pulled at 8 inches of mercury and then again at 15 inches while the syringes were closely monitored for signs of stopper movement. The procedure was then repeated five more times, with a new set of syringes each time, to substantiate the initial findings, which included the following:

- In the syringes containing a bubble, the stopper was seen rising into non-sterile areas of the syringe barrel each time the vacuum was pulled.
- In the syringes containing no gas bubble, however, the stopper was not seen rising at all.
- The size of the bubble inside the syringe made a difference in the amount of stopper movement. The syringes filled with a 2.5-mm bubble experienced less movement than the syringes filled with a 5.0-mm bubble. When the vacuum was released and the pressure returned to original levels, the stoppers in the syringes containing a bubble returned to their original position with no indication that they had moved.

Due to the difficulty of controlling for all of the variables that affect stopper movement in a prefilled syringe, a series of equations were devised to show, on a theoretical level, the relationship between the size of the gas bubble and stopper movement. Using Boyle's Law, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to changes in pressure, and the amount of stopper movement that occurs as a result of that expansion and contraction was calculated.

TABLE 1

Gas Bubble Size	H_{sb} = 6.2 mm Approximate Elevation (1,000s ft)	H_{sb} = 4.3 mm Approximate Elevation (1,000's ft)
0.5 mm	21	19
1.0 mm	16	14
2.5 mm	13	7
5.0 mm	7	<5

Approximate elevation (in feet above sea level) at which a stopper will have moved 1/5 H_{sb}.

Plugging these calculations into a hypothetical situation in which a syringe is shipped multiple times from the manufacturer to the end-user, a rational approach was developed for determining the maximum allowable size of a gas bubble inside a prefilled syringe. Among the factors taken into account were stopper height, the elevations to which a syringe will likely be exposed and the consequent changes in pressure which it will undergo, as well as the number of times a syringe will be subjected to reduced atmospheric pressure.

STERILE BARRIER HEIGHT: H_{SB}

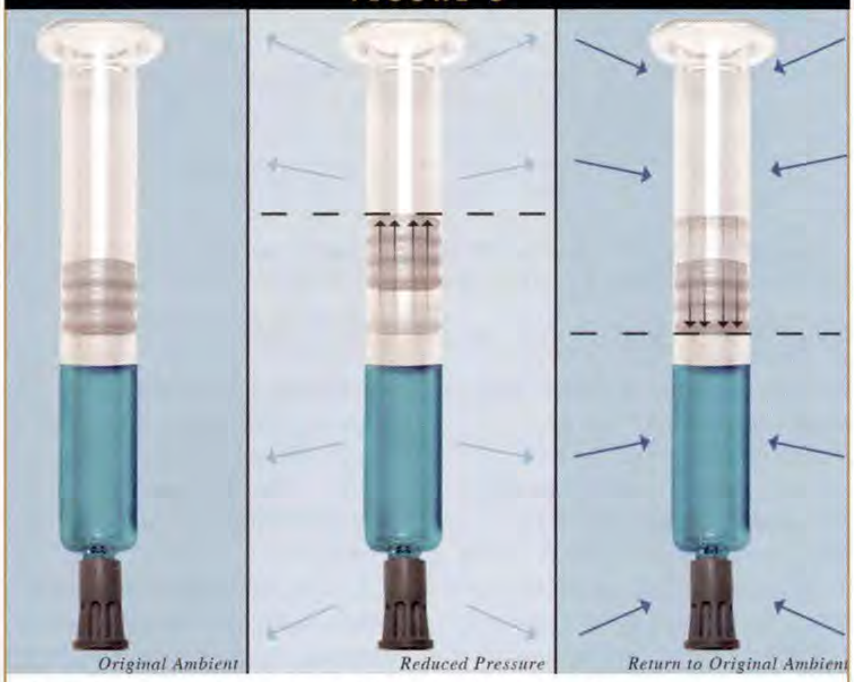
In a prefilled syringe, a sterile barrier is created in which the stopper is in intimate contact with the glass barrel of the syringe, as shown in Figure 2. The sterile barrier height, or H_{sb}, spans the entire distance from the uppermost to the lowermost point of stopper contact and represents the limit of upward stopper movement, which the stopper can undergo before product sterility is potentially compromised.

A gas bubble sealed inside a prefilled syringe acts like a spring, expanding and contracting with changes in temperature or external ambient pressure. If the external ambient temperature increases or pressure decreases, the gas bubble expands, pushing the stopper up until the pressure in the syringe is equivalent to the external pressure. When the external ambient pressure and/or temperature return to their original levels, the gas bubble in the syringe contracts until the pressure in the syringe is equal to the external pressure. This causes the stopper to return to its

FIGURE 2

Syringes and stoppers. The distance from the uppermost to the lowermost point of contact between the stopper and the syringe is known as the sterile barrier height or H_{sb}.

FIGURE 3



A gas bubble will expand or contract under changes in ambient pressure. This expansion/contraction will cause stopper movement in a syringe with no visible evidence that the stopper has moved when external conditions are returned to their original levels.

original position, leaving no visible evidence that the stopper has moved (Figure 3).[2]

If the stopper in a syringe moves more than the distance of H_{sb}, it can pull microorganisms or contaminants from the non-sterile portion of the syringe into the drug product, potentially causing a sterility failure. This same phenomenon could occur when a stopper moves less than the distance of H_{sb} if it moves multiple times and the sum of all stopper movements exceeds H_{sb}, as demonstrated in Figure 4.

PRESSURE & THE VOLUME OF A GAS BUBBLE

The amount of change in the volume of a gas bubble is relatively small over the reasonable temperatures to which a syringe might be exposed (total range of approximately 40°C); however, the volume change due to pressure changes alone can be significant, as demonstrated in the calculations that appear further on.

Assuming that temperature remains constant, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to pressure changes can be calculated using Boyle's Law (Equation 1).

Equation 1.

$$P_1V_1 = P_2V_2$$

Where P_1 = pressure condition 1, V_1 = volume condition 1, P_2 = pressure condition 2, and V_2 = volume condition 2. The volume (V) of a cylinder, such as a syringe, is given by Equation 2.

Equation 2.

$$V = \pi r^2 h$$

Where r = internal radius of the syringe barrel, and h = height of the gas bubble/air gap (assuming the bubble spans the entire diameter of the syringe). If Equation 2 is substituted for V in Equation 1, and both sides are divided by πr^2, the result is as Equation 3.

Equation 3.

$$P_1h_1 = P_2h_2$$

Where P_1 = pressure condition 1, h_1 = height condition 1, P_2 = pressure condition 2, and h_2 = height condition 2. Thus in Equation 4, the theoretical height of the gas space in the syringe at a given external pressure can be determined based on the initial conditions (condition 1).[2]

Equation 4.

$$h_2 = P_1h_1/P_2$$

The percentage of total stopper movement beyond the initial sterility barrier (H_{sb}) can be calculated by subtracting the initial height (H_1) from the height calculated in Equation 4 (H_2) and dividing the result by Hsb, as shown in Equation 5.

Equation 5.

$$\text{Percent } H_{sb} = 100*(H_2 - H_1)/H_{sb}$$

Figures 5b and 5c show the percentage of H_{sb} that a stopper will move in syringes with an H_{sb} of 6.2 and 4.3 mm, respectively, and initial bubble sizes ranging from 0.5 mm to 5 mm, the most common size range for a bubble. The points on the x axis in Figures 5b and 5c represent feet of elevation rather than absolute pressure to demonstrate the effect that reduced pressure (due to changes in elevation) will have on a syringe. These points were determined using a conversion of 1 inch Hg vacuum equal to 1000 feet of elevation (Figure 5a).

The *y* axis in Figures 5b and 5c represents the percentage of H_{sb}, which the stopper in a syringe will move, while the red line at 100% shows the point at which the stopper will enter a non-sterile area of the syringe, potentially compromising product sterility.

In the example in Figure 5b, in which H_{sb} is 6.2 mm and the initial bubble size is 2.5 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 23,000 feet. When the initial bubble is 5.0 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 20,000 feet.[2]

Because the cargo hold of an airplane is generally maintained at a pressure equal to 8,000 feet of elevation, and ground elevations during shipment do not often exceed 10,000 feet, a stopper is not likely to move more than H_{sb} in a single exposure. However, during shipment, a syringe could possibly be exposed to reduced pressure on several occasions which, taken together, increases the potential for total stopper movement to exceed H_{sb}.

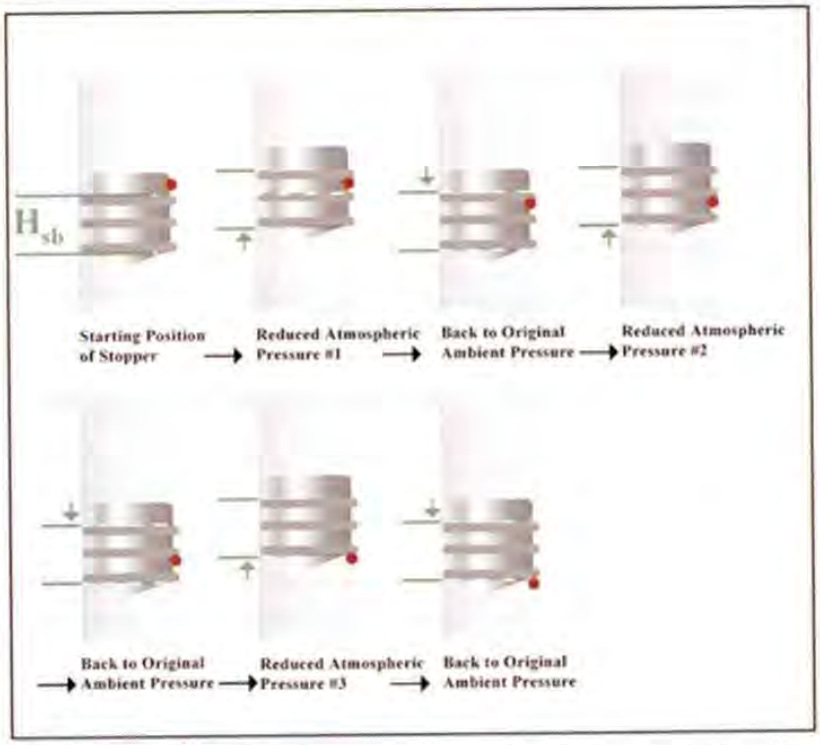
Consider, for example, a syringe that is shipped from a CMO's manufacturing site to the sponsor company's facility to a distribution center and finally to the end-user's site, for a total of three shipments. It is possible that one or more legs of the product's journey could involve more than one flight, creating additional opportunities for the stopper to rise and fall. Under those conditions, it is conceivable that a syringe could be exposed to changes in pressure on five occasions, resulting in five up and down stopper movements. In that case, a stopper would only need to rise 1/5 H_{sb} each time to potentially pull non-sterile material, such as silicon, or other contaminants into the product causing a sterility failure.

Table 1 shows the approximate elevations at which the stopper would exceed 1/5 of H_{sb} given several different sized bubbles. To prevent stopper movement as a result of changes in ambient pressure, syringes should ideally be filled without any gas bubbles. However, in practice, most syringe filling equipment does not have the capability to remove all of the gas in a syringe. When that is the case, the maximum acceptable size of a gas bubble for a given stopper in a prefilled syringe should be determined. This can be done by factoring in the differential pressure changes to which a syringe will likely be exposed, the number of times it will be subjected to reduced pressure, and the height of the sterile barrier.

DETERMINING THE MAXIMUM SIZE OF A GAS BUBBLE

Using the aforementioned equations, the size of the bubble that will lead to a movement of the stopper equal to 1/5 of H_{sb} can be calculated at a number of different elevations. For example, Figure 6 shows the results of calculations performed using elevations of 8,000 and 12,000 feet with a range of H_{sb} from 1 to 15 mm. In situations where H_{sb} is 4.0 and elevation is 8,000 feet, the maximum acceptable size of the gas bubble is approximately 2.0 mm. When the elevation reaches 12,000 feet, however, the maximum acceptable size of the gas bubble decreases to approximately 1.6 mm.[2] The aforementioned analysis is a worst-case scenario and does not take into account frictional forces and break loose forces. Frictional forces caused by the stopper rubbing against the syringe, and the break loose force, which is required to start the stopper moving, should reduce stopper movement. Break loose forces, which increase over the life of the syringe, would improve resistance to stopper movement the longer the product was in transit, requiring greater force to initiate the movement of the stopper. However, it is not unreasonable to assume that a newly filled prefilled glass syringe with silicon has very little break loose force. In fact, we have confirmed in our laboratories that standard, commercially available glass syringes and elastomeric stoppers with silicon show actual stopper movement that is approximately 75% of that which has been theoretically calculated in this article. We did not perform an extensive study of all factors that could affect glide and breakloose forces; therefore, we have used theoretical calculations to demonstrate

FIGURE 4



If the stopper moves more than H_{sb}, contaminants may be pulled into the sterile liquid. This effect can occur with multiple movements if the sum of all stopper movements exceeds H_{sb}.

several worst-case scenarios for stopper movement.

The aforementioned analysis is also based on the assumption that pressures are controlled at consistent levels throughout shipment when, in fact, the actual magnitude of reduced/increased pressure to which syringes are exposed is generally not known. Cargo is shipped by a variety of carriers, many of whom may not consistently control, measure, or report changes in pressure. Atmospheric pressure in a cargo hold could rise and fall during flight, and the drug manufacturer would not be aware of it upon inspection at the final destination.

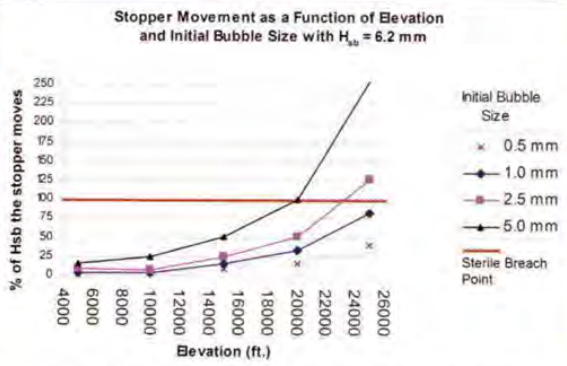
There are alternative means to prevent contamination due to stopper movement other than reducing the size of the gas bubble or increasing H_{sb}. For example, the stopper can be locked in place with a device placed inside the barrel, or the entire syringe can be sealed inside a sterile container (protecting the sterility of the barrel above the stopper), or the syringe can be placed in a holder that secures the plunger rod in place. However, each of these approaches adds cost and requires additional packaging and does not provide the added benefits of a bubble-free syringe.

FIGURE 5A

Elevation	" Hg Vac.	psi	torr
0	0	14.7	760
8,000	8"	10.7	555
10,000	10"	9.8	506
12,000	12"	8.9	455
15,000	15"	7.3	379
18,000	18"	5.9	302
25,000	25"	2.4	125
27,000	27"	1.4	74

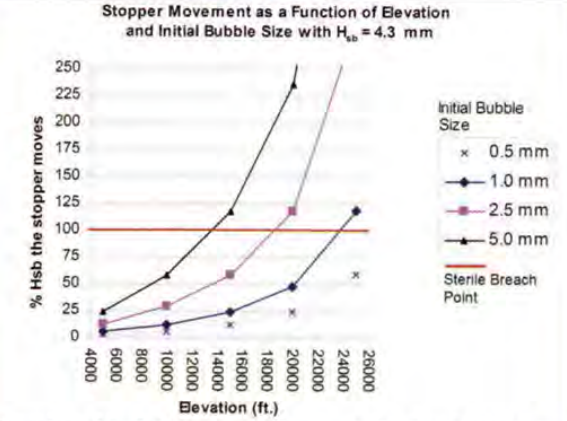
Conversion of 1-inch Hg vacuum equal to 1000 feet of elevation.

FIGURE 5B



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 6.2 mm.

FIGURE 5C



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 4.3 mm.

ELIMINATING PRODUCT LOSS

One added benefit of a bubble-free syringe is the reduction in the amount of product inadvertently lost during use. In a side-by-side analysis, 15 syringes were filled with gas bubbles of varying sizes, while 15 syringes were filled with no bubble. As the tip caps on each set of syringes were removed, the needles were watched for any sign of dripping or product leaks. In the set that were filled with a bubble, product was observed leaking from needle over 75% of the time when the tip cap was removed. Conversely, in the needles that were bubble-free, no product was seen leaking from the needle any time the tip caps were removed (Figure 7).[2]

This is because in a bubble-free syringe, there is no expansion and contraction of the bubble as a result of the small vacuum that is created when the tip cap is removed. Without a drip, there is added assurance that the end-user will receive the entire deliverable dose. There is also less risk that the administrator or end-user will be exposed to cytotoxic or potent compounds, as well as a reduction in product wasted.

CONCLUSION

Although, on the surface, syringes may appear very similar to vials, the freedom of stopper movement in a prefilled syringe, coupled with a gas bubble, will result in challenges to package integrity and product sterility when the syringe is exposed to changes in atmospheric pressure. A gas bubble is not intrinsic to a syringe but is the result of a sub-optimal filling process and therefore, can be reduced or eliminated using alternative filling methods.

Manufacturers go to great lengths to monitor and control the temperature to which products are exposed during shipping. Yet the same attention has not been paid to changes in differential pressures to which a product is exposed. Given that a number of today's parenteral products are shipped several times before reaching the end-user, undergoing several changes in atmospheric pressure and several potential

movements of the stopper, such attention is warranted. Just as exposure to elevated temperatures may impact the shelf-life and efficacy of products, exposure to reduced pressure may potentially impact the sterility and safety of an injectable product in a prefilled syringe if one is not aware of the importance of reduced bubble size and stopper design.

In this discussion, we have proposed one way to determine the maximum acceptable size of a gas bubble that can be left inside a syringe based on stopper height as well as other variables. There are alternative ways to protect prefilled syringes from contamination due to stopper movement, but these require additional packaging and do not offer the added benefits of a bubble-free syringe, such as enhanced dosing accuracy and safety as well as reduced waste due to the elimination of a product drip at the needle when the tip cap is removed.[3]

As prefilled syringes continue to find favor as an alternative to vials for many of today's parenteral products, reduced gas bubble filling should likewise become increasingly popular as an alternative to traditional filling methods and may one day become the industry standard.

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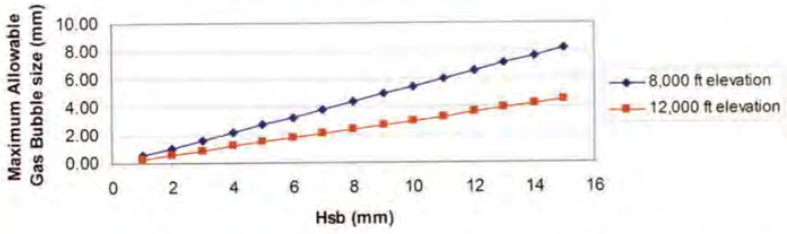
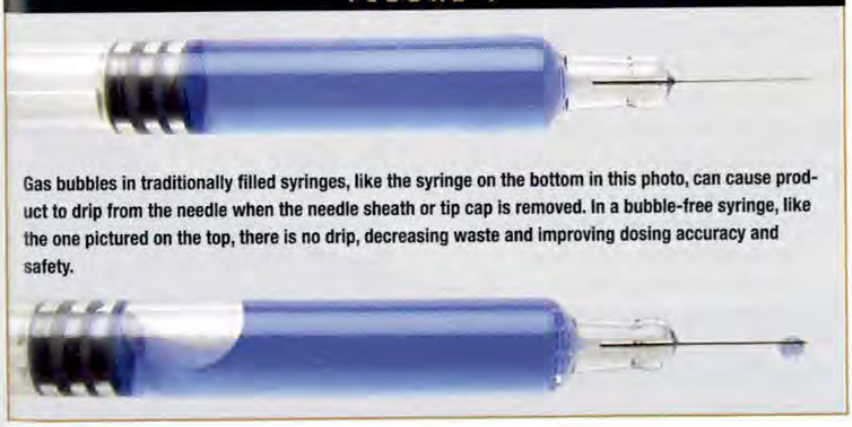
3. Kinney SD. Innovative Solutions Seminar. New Brunswick, NJ, October 30, 2007.

FIGURE 6



The data demonstrates that smaller gas bubbles and stoppers with larger H_{sb} reduce the risk of stopper movement exceeding 1/5 H_{sb}.

FIGURE 7



Gas bubbles in traditionally filled syringes, like the syringe on the bottom in this photo, can cause product to drip from the needle when the needle sheath or tip cap is removed. In a bubble-free syringe, like the one pictured on the top, there is no drip, decreasing waste and improving dosing accuracy and safety.

BIOGRAPHIES

Dr. Shawn D. Kinney, President of Hyaluron Contract Manufacturing (HCM), founded HCM in 1999 to provide aseptic manufacturing and filling services to the pharmaceutical, biotech, and medical device industries. Dr. Kinney earned his PhD in Chemistry from the University of Massachusetts at Amherst, a Masters in Medicinal Chemistry from Northeastern University, and a BS in Chemistry from the University of Massachusetts at North Dartmouth. Dr. Kinney has worked at Anika Therapeutics, Wyeth-Ayerst, and Millipore and has more than 20 years of experience in the pharmaceutical industry. He has extensive experience in the development of sterile formulation and filling processes, including viscous and difficult-to-fill products. Prior to founding HCM, he was responsible for the sterile formulation and filling of hyaluronate into prefilled syringes in his role as VP of Operations at Anika Therapeutics. Recently, Dr. Kinney has pioneered a new technology in online vacuum filling and stoppering (Bubble-Free Filling®) and has been granted a patent. He continues to oversee HCM's expansion and leadership in the aseptic contract manufacturing industry. He can be reached at shawn@hyaluron.com or (781) 270-7900, ext. 218.

Dr. Andrea Wagner is the Vice President of Business Development at HCM, a position she has held for 7 years. Prior to joining HCM, she was employed by the New Jersey Institute of Technology in the capacity of Senior Scientist in a national training program. Simultaneously, she worked as a Manager at Thermo Fisher Scientific as a Manager in business development of pharmaceutical applications for their XRF Analyzers. After earning her PhD in Toxicology, she managed a center devoted to innovative testing technologies in the Chemistry Department at Tufts University in Massachusetts. Dr. Wagner also earned her a MS in Analytical Chemistry and her BS in Chemistry. She can be reached at andrea@hyaluron.com or (781) 270-7900, ext. 106.

Christian W. Phillips is the Director of Process Engineering, at HCM. Mr. Phillips has 14 years of experience in R&D, Process Development, Tech Transfer, and Manufacturing environments suited for the introduction of novel biotherapeutics and generics, including fill/finish applications. Prior to HCM, Mr. Phillips was employed by Transkaryotic Therapies (now Shire HGS). Mr. Phillips earned his a BS in Biology from St. Michael's College and is the co-inventor with Shawn Kinney of HCM's Bubble-Free Filling® technology. He can be reached at cphillips@hyaluron.com or (781) 270-7900, ext. 181.

ATTACHMENT B-2

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Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
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Therapeutic siRNA

"Compared to the local siRNA deliveries that were used in many early siRNA clinical trials, systemic siRNA delivery faces more challenges and hurdles that have slowed down the expansion of siRNA therapeutics. With increasing efforts dedicated to the development of more efficient systemic siRNA delivery technologies, it is conceivable the key delivery hurdles could be overcome and the potential of RNAi-based therapeutics may be realized in a not too distant future."

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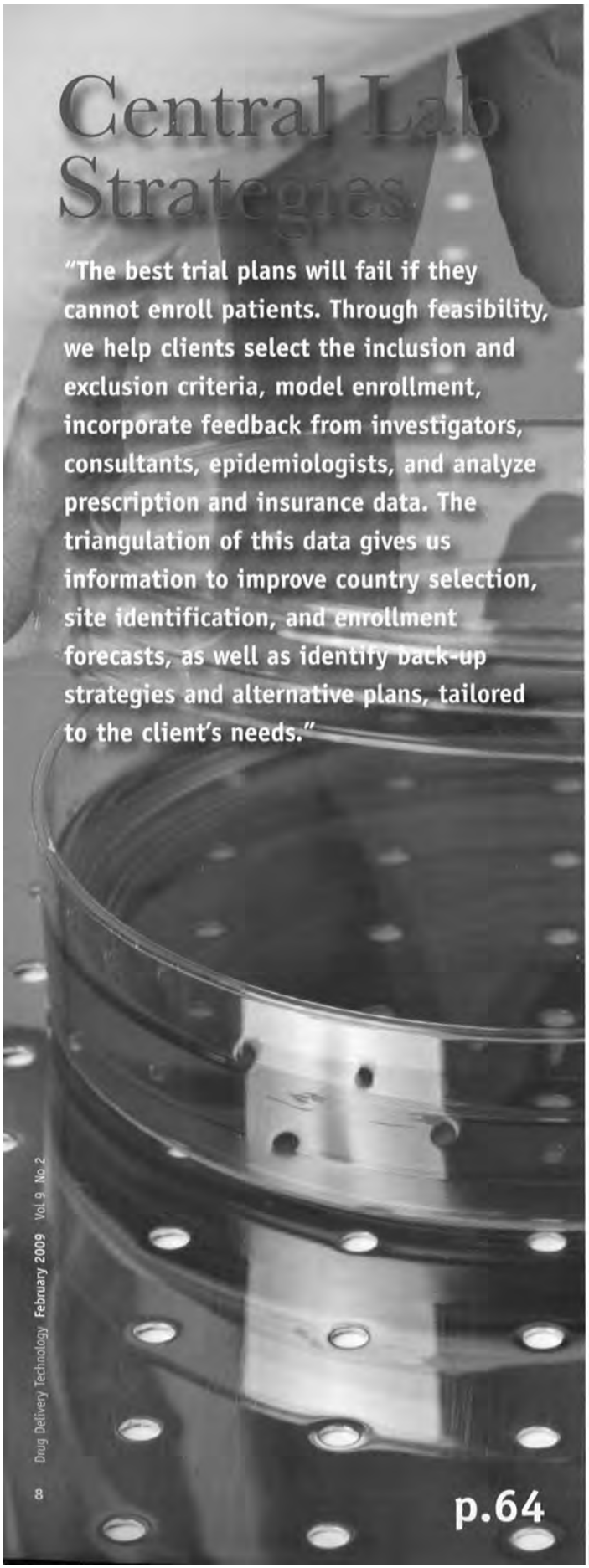

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PREFILLED SYRINGES

A Rational Approach to Determining the Maximum Allowable Gas Bubble Inside a Prefilled Syringe to Minimize Stopper Movement & Protect Product Sterility

By: Shawn Kinney, PhD; Andrea Wagner, PhD; and Christian W. Phillips

ABSTRACT

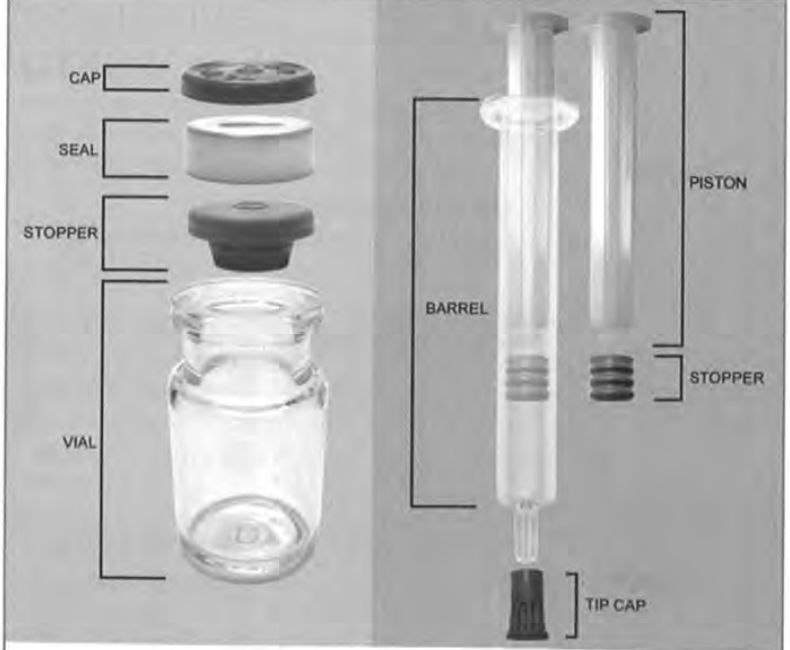
Prefilled syringes are a fast-growing alternative to vials in the parenteral product market due to the many advantages they offer relative to vials. These include reduced overfill requirements, ease of use, more accurate dosing, decreased waste, and enhanced product differentiation.

Conventional syringe-filling processes typically leave a large air bubble in a syringe that can negatively impact product sterility and package integrity. Using a series of equations and hypothetical scenarios, this article will demonstrate the potential impact of a bubble on stopper movement during periods of reduced atmospheric pressure. It will also propose a rational approach for determining the maximum allowable size of a gas bubble inside a prefilled syringe taking into account several critical factors. After weighing some of the alternatives for limiting stopper movement during shipping as well as one additional benefit of bubble-free filling, this article will make the case that reducing or eliminating the bubble inside a prefilled syringe is a preferred means for ensuring product sterility while enhancing the benefits of a prefilled syringe.

INTRODUCTION

The internal environments of a glass vial and a glass syringe have a number of features in common, as shown in Figure 1. Both presentations are essentially glass cylinders that are sealed by an elastomeric closure, or stopper, and both contain a gaseous headspace, or bubble. However, there is one noteworthy difference. A vial's stopper is held in place by a crimp, while a syringe's stopper is designed to move in order to allow injection of the drug product. This freedom of movement, when coupled with a gas bubble (which is not intrinsic to a syringe but is a byproduct of sub-optimal filling processes) can potentially cause significant challenges with regard to package integrity and product sterility, particularly when the syringe is exposed to repeated changes in atmospheric pressure, such as during shipping. Reducing or eliminating the

FIGURE 1



Comparison of a vial and a syringe. Both are essentially glass tubes sealed with an elastomeric closure and contain a gas headspace.

bubble inside the syringe would limit stopper movement, potentially enhancing sterility assurance of the product.[1]

In a preliminary study of the impact of a bubble on stopper movement in a prefilled syringe, three syringes were placed inside a Hypak vacuum chamber. One syringe contained a 2.5-mm bubble, one a 5.0-mm bubble, and yet another contained no bubble at all. Next, a vacuum was pulled at 8 inches of mercury and then again at 15 inches while the syringes were closely monitored for signs of stopper movement. The procedure was then repeated five more times, with a new set of syringes each time, to substantiate the initial findings, which included the following:

- In the syringes containing a bubble, the stopper was seen rising into non-sterile areas of the syringe barrel each time the vacuum was pulled.
- In the syringes containing no gas bubble, however, the stopper was not seen rising at all.
- The size of the bubble inside the syringe made a difference in the amount of stopper movement. The syringes filled with a 2.5-mm bubble experienced less movement than the syringes filled with a 5.0-mm bubble. When the vacuum was released and the pressure returned to original levels, the stoppers in the syringes containing a bubble returned to their original position with no indication that they had moved.

Due to the difficulty of controlling for all of the variables that affect stopper movement in a prefilled syringe, a series of equations were devised to show, on a theoretical level, the relationship between the size of the gas bubble and stopper movement. Using Boyle's Law, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to changes in pressure, and the amount of stopper movement that occurs as a result of that expansion and contraction was calculated.

TABLE 1

Gas Bubble Size	H_{sb} = 6.2 mm Approximate Elevation (1,000s ft)	H_{sb} = 4.3 mm Approximate Elevation (1,000's ft)
0.5 mm	21	19
1.0 mm	16	14
2.5 mm	13	7
5.0 mm	7	<5

Approximate elevation (in feet above sea level) at which a stopper will have moved 1/5 H_{sb}.

Plugging these calculations into a hypothetical situation in which a syringe is shipped multiple times from the manufacturer to the end-user, a rational approach was developed for determining the maximum allowable size of a gas bubble inside a prefilled syringe. Among the factors taken into account were stopper height, the elevations to which a syringe will likely be exposed and the consequent changes in pressure which it will undergo, as well as the number of times a syringe will be subjected to reduced atmospheric pressure.

STERILE BARRIER HEIGHT: H_{SB}

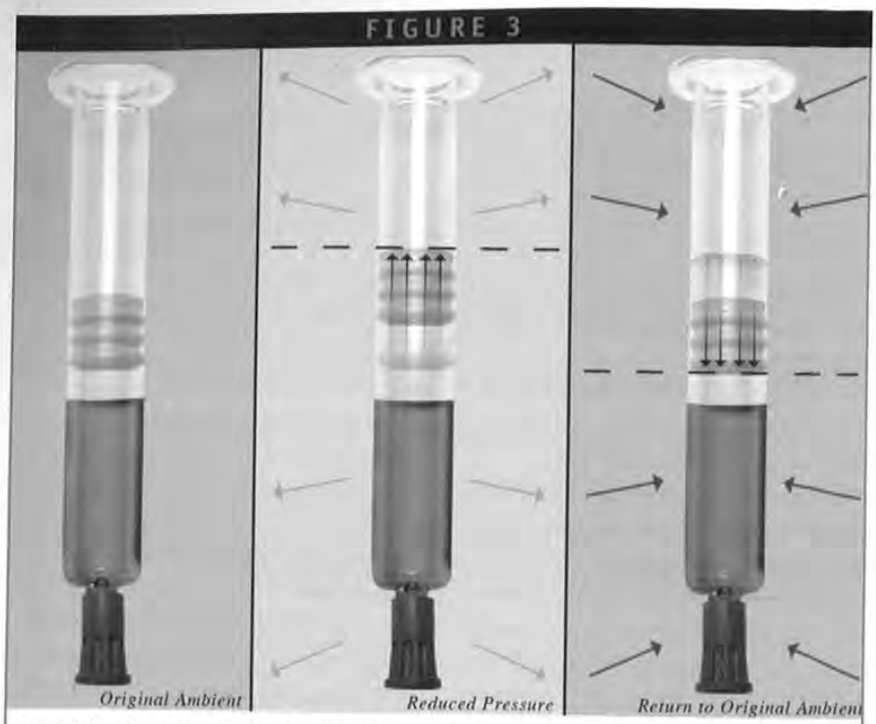
In a prefilled syringe, a sterile barrier is created in which the stopper is in intimate contact with the glass barrel of the syringe, as shown in Figure 2. The sterile barrier height, or H_{sb}, spans the entire distance from the uppermost to the lowermost point of stopper contact and represents the limit of upward stopper movement, which the stopper can undergo before product sterility is potentially compromised.

A gas bubble sealed inside a prefilled syringe acts like a spring, expanding and contracting with changes in temperature or external ambient pressure. If the external ambient temperature increases or pressure decreases, the gas bubble expands, pushing the stopper up until the pressure in the syringe is equivalent to the external pressure. When the external ambient pressure and/or temperature return to their original levels, the gas bubble in the syringe contracts until the pressure in the syringe is equal to the external pressure. This causes the stopper to return to its

FIGURE 2

Syringes and stoppers. The distance from the uppermost to the lowermost point of contact between the stopper and the syringe is known as the sterile barrier height or H_{sb}.

FIGURE 3



A gas bubble will expand or contract under changes in ambient pressure. This expansion/contraction will cause stopper movement in a syringe with no visible evidence that the stopper has moved when external conditions are returned to their original levels.

original position, leaving no visible evidence that the stopper has moved (Figure 3).[2]

If the stopper in a syringe moves more than the distance of H_{sb}, it can pull microorganisms or contaminants from the non-sterile portion of the syringe into the drug product, potentially causing a sterility failure. This same phenomenon could occur when a stopper moves less than the distance of H_{sb} if it moves multiple times and the sum of all stopper movements exceeds H_{sb}, as demonstrated in Figure 4.

PRESSURE & THE VOLUME OF A GAS BUBBLE

The amount of change in the volume of a gas bubble is relatively small over the reasonable temperatures to which a syringe might be exposed (total range of approximately 40ºC); however, the volume change due to pressure changes alone can be significant, as demonstrated in the calculations that appear further on.

Assuming that temperature remains constant, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to pressure changes can be calculated using Boyle's Law (Equation 1).

Equation 1.

$$P_1V_1 = P_2V_2$$

Where P_1 = pressure condition 1, V_1 = volume condition 1, P_2 = pressure condition 2, and V_2 = volume condition 2. The volume (V) of a cylinder, such as a syringe, is given by Equation 2.

Equation 2.

$$V = \pi r^2 h$$

Where r = internal radius of the syringe barrel, and h = height of the gas bubble/air gap (assuming the bubble spans the entire diameter of the syringe). If Equation 2 is substituted for V in Equation 1, and both sides are divided by πr^2, the result is as Equation 3.

Equation 3.

$$P_1h_1 = P_2h_2$$

Where P_1 = pressure condition 1, h_1 = height condition 1, P_2 = pressure condition 2, and h_2 = height condition 2. Thus in Equation 4, the theoretical height of the gas space in the syringe at a given external pressure can be determined based on the initial conditions (condition 1).[2]

Equation 4.

$$h_2 = P_1h_1/P_2$$

The percentage of total stopper movement beyond the initial sterility barrier (H_{sb}) can be calculated by subtracting the initial height (H_1) from the height calculated in Equation 4 (H_2) and dividing the result by Hsb, as shown in Equation 5.

Equation 5.

$$\text{Percent } H_{sb} = 100*(H_2 - H_1)/H_{sb}$$

Figures 5b and 5c show the percentage of H_{sb} that a stopper will move in syringes with an H_{sb} of 6.2 and 4.3 mm, respectively, and initial bubble sizes ranging from 0.5 mm to 5 mm, the most common size range for a bubble. The points on the x axis in Figures 5b and 5c represent feet of elevation rather than absolute pressure to demonstrate the effect that reduced pressure (due to changes in elevation) will have on a syringe. These points were determined using a conversion of 1 inch Hg vacuum equal to 1000 feet of elevation (Figure 5a).

The *y* axis in Figures 5b and 5c represents the percentage of H_{sb}, which the stopper in a syringe will move, while the red line at 100% shows the point at which the stopper will enter a non-sterile area of the syringe, potentially compromising product sterility.

In the example in Figure 5b, in which H_{sb} is 6.2 mm and the initial bubble size is 2.5 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 23,000 feet. When the initial bubble is 5.0 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 20,000 feet.[2]

Because the cargo hold of an airplane is generally maintained at a pressure equal to 8,000 feet of elevation, and ground elevations during shipment do not often exceed 10,000 feet, a stopper is not likely to move more than H_{sb} in a single exposure. However, during shipment, a syringe could possibly be exposed to reduced pressure on several occasions which, taken together, increases the potential for total stopper movement to exceed H_{sb}.

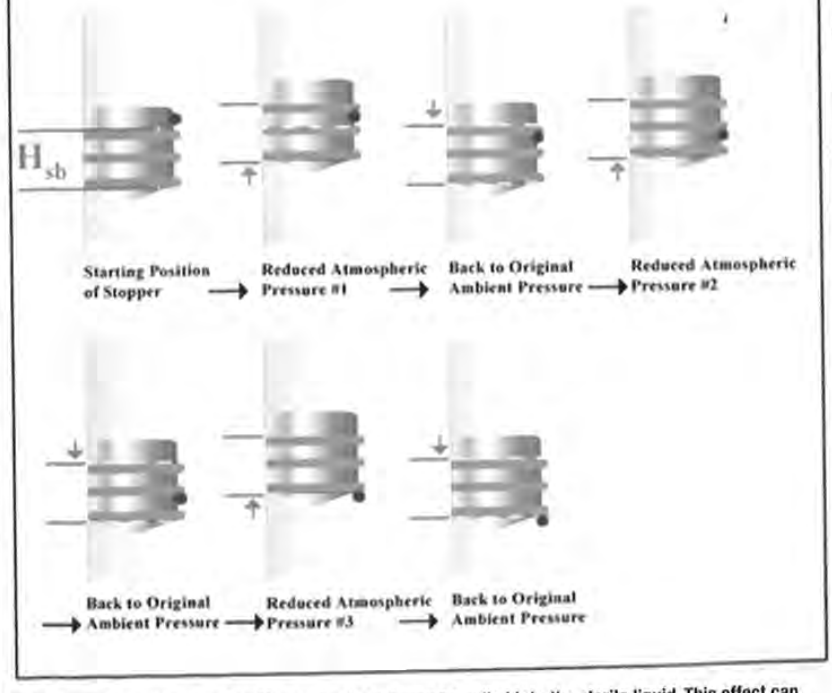
Consider, for example, a syringe that is shipped from a CMO's manufacturing site to the sponsor company's facility to a distribution center and finally to the end-user's site, for a total of three shipments. It is possible that one or more legs of the product's journey could involve more than one flight, creating additional opportunities for the stopper to rise and fall. Under those conditions, it is conceivable that a syringe could be exposed to changes in pressure on five occasions, resulting in five up and down stopper movements. In that case, a stopper would only need to rise 1/5 H_{sb} each time to potentially pull non-sterile material, such as silicon, or other contaminants into the product causing a sterility failure.

Table 1 shows the approximate elevations at which the stopper would exceed 1/5 of H_{sb} given several different sized bubbles. To prevent stopper movement as a result of changes in ambient pressure, syringes should ideally be filled without any gas bubbles. However, in practice, most syringe filling equipment does not have the capability to remove all of the gas in a syringe. When that is the case, the maximum acceptable size of a gas bubble for a given stopper in a prefilled syringe should be determined. This can be done by factoring in the differential pressure changes to which a syringe will likely be exposed, the number of times it will be subjected to reduced pressure, and the height of the sterile barrier.

DETERMINING THE MAXIMUM SIZE OF A GAS BUBBLE

Using the aforementioned equations, the size of the bubble that will lead to a movement of the stopper equal to 1/5 of H_{sb} can be calculated at a number of different elevations. For example, Figure 6 shows the results of calculations performed using elevations of 8,000 and 12,000 feet with a range of H_{sb} from 1 to 15 mm. In situations where H_{sb} is 4.0 and elevation is 8,000 feet, the maximum acceptable size of the gas bubble is approximately 2.0 mm. When the elevation reaches 12,000 feet, however, the maximum acceptable size of the gas bubble decreases to approximately 1.6 mm.[2] The aforementioned analysis is a worst-case scenario and does not take into account frictional forces and break loose forces. Frictional forces caused by the stopper rubbing against the syringe, and the break loose force, which is required to start the stopper moving, should reduce stopper movement. Break loose forces, which increase over the life of the syringe, would improve resistance to stopper movement the longer the product was in transit, requiring greater force to initiate the movement of the stopper. However, it is not unreasonable to assume that a newly filled prefilled glass syringe with silicon has very little break loose force. In fact, we have confirmed in our laboratories that standard, commercially available glass syringes and elastomeric stoppers with silicon show actual stopper movement that is approximately 75% of that which has been theoretically calculated in this article. We did not perform an extensive study of all factors that could affect glide and breakloose forces; therefore, we have used theoretical calculations to demonstrate

FIGURE 4



If the stopper moves more than H_{sb}, contaminants may be pulled into the sterile liquid. This effect can occur with multiple movements if the sum of all stopper movements exceeds H_{sb}.

several worst-case scenarios for stopper movement.

The aforementioned analysis is also based on the assumption that pressures are controlled at consistent levels throughout shipment when, in fact, the actual magnitude of reduced/increased pressure to which syringes are exposed is generally not known. Cargo is shipped by a variety of carriers, many of whom may not consistently control, measure, or report changes in pressure. Atmospheric pressure in a cargo hold could rise and fall during flight, and the drug manufacturer would not be aware of it upon inspection at the final destination.

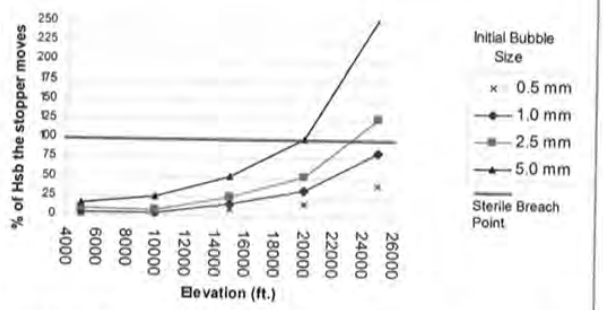
There are alternative means to prevent contamination due to stopper movement other than reducing the size of the gas bubble or increasing H_{sb}. For example, the stopper can be locked in place with a device placed inside the barrel, or the entire syringe can be sealed inside a sterile container (protecting the sterility of the barrel above the stopper), or the syringe can be placed in a holder that secures the plunger rod in place. However, each of these approaches adds cost and requires additional packaging and does not provide the added benefits of a bubble-free syringe.

FIGURE 5A

Elevation	" Hg Vac.	psi	torr
0	0	14.7	760
8,000	8"	10.7	555
10,000	10"	9.8	506
12,000	12"	8.9	455
15,000	15"	7.3	379
18,000	18"	5.9	302
25,000	25"	2.4	125
27,000	27"	1.4	74

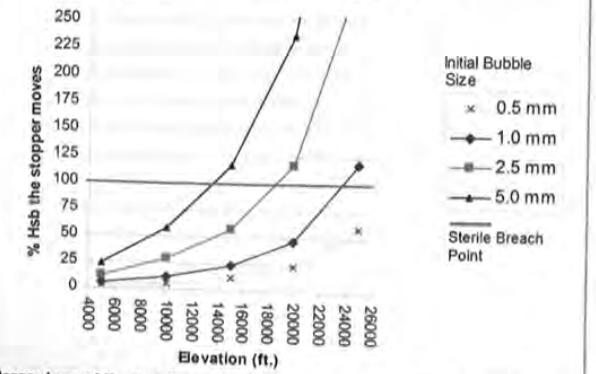
Conversion of 1-inch Hg vacuum equal to 1000 feet of elevation.

FIGURE 5B



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 6.2 mm.

FIGURE 5C



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 4.3 mm.

ELIMINATING PRODUCT LOSS

One added benefit of a bubble-free syringe is the reduction in the amount of product inadvertently lost during use. In a side-by-side analysis, 15 syringes were filled with gas bubbles of varying sizes, while 15 syringes were filled with no bubble. As the tip caps on each set of syringes were removed, the needles were watched for any sign of dripping or product leaks. In the set that were filled with a bubble, product was observed leaking from needle over 75% of the time when the tip cap was removed. Conversely, in the needles that were bubble-free, no product was seen leaking from the needle any time the tip caps were removed (Figure 7).[2]

This is because in a bubble-free syringe, there is no expansion and contraction of the bubble as a result of the small vacuum that is created when the tip cap is removed. Without a drip, there is added assurance that the end-user will receive the entire deliverable dose. There is also less risk that the administrator or end-user will be exposed to cytotoxic or potent compounds, as well as a reduction in product wasted.

CONCLUSION

Although, on the surface, syringes may appear very similar to vials, the freedom of stopper movement in a prefilled syringe, coupled with a gas bubble, will result in challenges to package integrity and product sterility when the syringe is exposed to changes in atmospheric pressure. A gas bubble is not intrinsic to a syringe but is the result of a sub-optimal filling process and therefore, can be reduced or eliminated using alternative filling methods.

Manufacturers go to great lengths to monitor and control the temperature to which products are exposed during shipping. Yet the same attention has not been paid to changes in differential pressures to which a product is exposed. Given that a number of today's parenteral products are shipped several times before reaching the end-user, undergoing several changes in atmospheric pressure and several potential

movements of the stopper, such attention is warranted. Just as exposure to elevated temperatures may impact the shelf-life and efficacy of products, exposure to reduced pressure may potentially impact the sterility and safety of an injectable product in a prefilled syringe if one is not aware of the importance of reduced bubble size and stopper design.

In this discussion, we have proposed one way to determine the maximum acceptable size of a gas bubble that can be left inside a syringe based on stopper height as well as other variables. There are alternative ways to protect prefilled syringes from contamination due to stopper movement, but these require additional packaging and do not offer the added benefits of a bubble-free syringe, such as enhanced dosing accuracy and safety as well as reduced waste due to the elimination of a product drip at the needle when the tip cap is removed.[3]

As prefilled syringes continue to find favor as an alternative to vials for many of today's parenteral products, reduced gas bubble filling should likewise become increasingly popular as an alternative to traditional filling methods and may one day become the industry standard.

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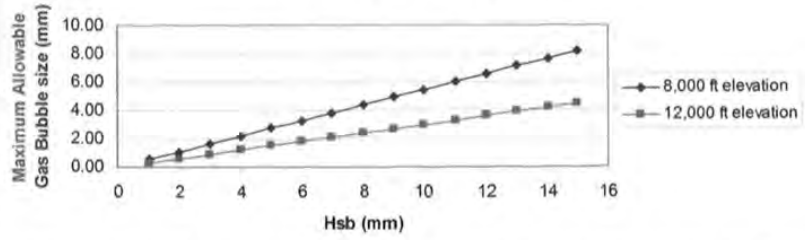
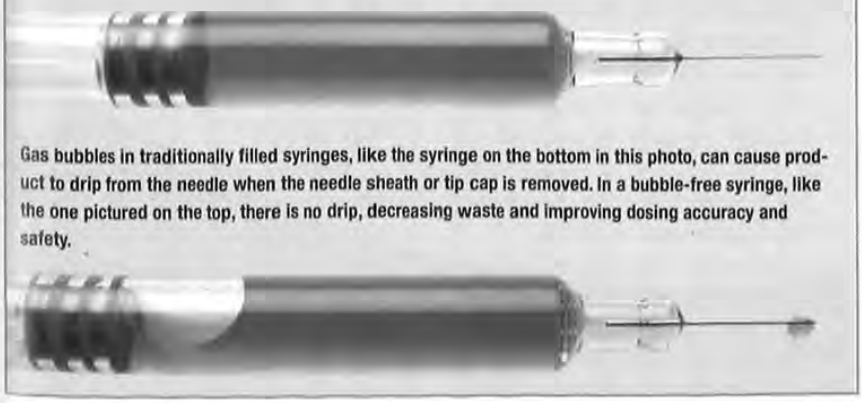
3. Kinney SD. Innovative Solutions Seminar. New Brunswick, NJ, October 30, 2007.

FIGURE 6



The data demonstrates that smaller gas bubbles and stoppers with larger H_{sb} reduce the risk of stopper movement exceeding 1/5 H_{sb}.

FIGURE 7



Gas bubbles in traditionally filled syringes, like the syringe on the bottom in this photo, can cause product to drip from the needle when the needle sheath or tip cap is removed. In a bubble-free syringe, like the one pictured on the top, there is no drip, decreasing waste and improving dosing accuracy and safety.

BIOGRAPHIES

Dr. Shawn D. Kinney, President of Hyaluron Contract Manufacturing (HCM), founded HCM in 1999 to provide aseptic manufacturing and filling services to the pharmaceutical, biotech, and medical device industries. Dr. Kinney earned his PhD in Chemistry from the University of Massachusetts at Amherst, a Masters in Medicinal Chemistry from Northeastern University, and a BS in Chemistry from the University of Massachusetts at North Dartmouth. Dr. Kinney has worked at Anika Therapeutics, Wyeth-Ayerst, and Millipore and has more than 20 years of experience in the pharmaceutical industry. He has extensive experience in the development of sterile formulation and filling processes, including viscous and difficult-to-fill products. Prior to founding HCM, he was responsible for the sterile formulation and filling of hyaluronate into prefilled syringes in his role as VP of Operations at Anika Therapeutics. Recently, Dr. Kinney has pioneered a new technology in online vacuum filling and stoppering (Bubble-Free Filling®) and has been granted a patent. He continues to oversee HCM's expansion and leadership in the aseptic contract manufacturing industry. He can be reached at shawn@hyaluron.com or (781) 270-7900, ext. 218.

Dr. Andrea Wagner is the Vice President of Business Development at HCM, a position she has held for 7 years. Prior to joining HCM, she was employed by the New Jersey Institute of Technology in the capacity of Senior Scientist in a national training program. Simultaneously, she worked as a Manager at Thermo Fisher Scientific as a Manager in business development of pharmaceutical applications for their XRF Analyzers. After earning her PhD in Toxicology, she managed a center devoted to innovative testing technologies in the Chemistry Department at Tufts University in Massachusetts. Dr. Wagner also earned her a MS in Analytical Chemistry and her BS in Chemistry. She can be reached at andrea@hyaluron.com or (781) 270-7900, ext. 106.

Christian W. Phillips is the Director of Process Engineering, at HCM. Mr. Phillips has 14 years of experience in R&D, Process Development, Tech Transfer, and Manufacturing environments suited for the introduction of novel biotherapeutics and generics, including fill/finish applications. Prior to HCM, Mr. Phillips was employed by Transkaryotic Therapies (now Shire HGS). Mr. Phillips earned his a BS in Biology from St. Michael's College and is the co-inventor with Shawn Kinney of HCM's Bubble-Free Filling® technology. He can be reached at cphillips@hyaluron.com or (781) 270-7900, ext. 181.

ATTACHMENT B-3

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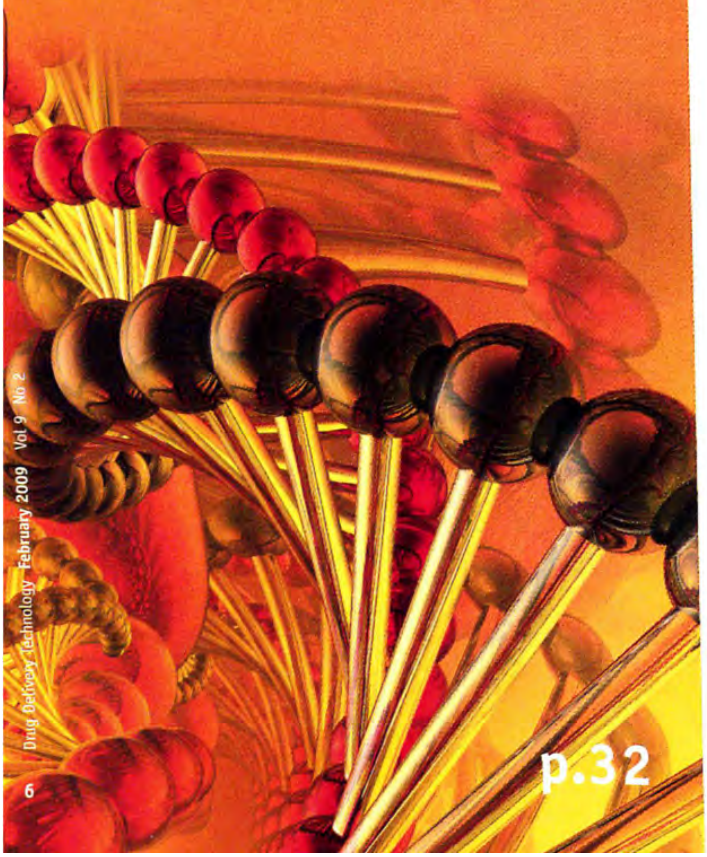
Therapeutic siRNA

"Compared to the local siRNA deliveries that were used in many early siRNA clinical trials, systemic siRNA delivery faces more challenges and hurdles that have slowed down the expansion of siRNA therapeutics. With increasing efforts dedicated to the development of more efficient systemic siRNA delivery technologies, it is conceivable the key delivery hurdles could be overcome and the potential of RNAi-based therapeutics may be realized in a not too distant future."



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PREFILLED SYRINGES

A Rational Approach to Determining the Maximum Allowable Gas Bubble Inside a Prefilled Syringe to Minimize Stopper Movement & Protect Product Sterility

By: Shawn Kinney, PhD; Andrea Wagner, PhD; and Christian W. Phillips

ABSTRACT

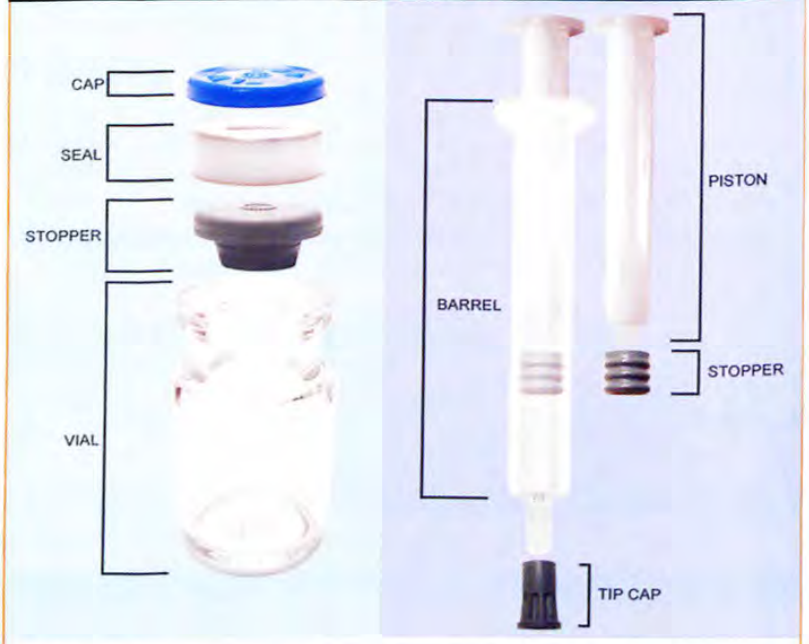
Prefilled syringes are a fast-growing alternative to vials in the parenteral product market due to the many advantages they offer relative to vials. These include reduced overfill requirements, ease of use, more accurate dosing, decreased waste, and enhanced product differentiation.

Conventional syringe-filling processes typically leave a large air bubble in a syringe that can negatively impact product sterility and package integrity. Using a series of equations and hypothetical scenarios, this article will demonstrate the potential impact of a bubble on stopper movement during periods of reduced atmospheric pressure. It will also propose a rational approach for determining the maximum allowable size of a gas bubble inside a prefilled syringe taking into account several critical factors. After weighing some of the alternatives for limiting stopper movement during shipping as well as one additional benefit of bubble-free filling, this article will make the case that reducing or eliminating the bubble inside a prefilled syringe is a preferred means for ensuring product sterility while enhancing the benefits of a prefilled syringe.

INTRODUCTION

The internal environments of a glass vial and a glass syringe have a number of features in common, as shown in Figure 1. Both presentations are essentially glass cylinders that are sealed by an elastomeric closure, or stopper, and both contain a gaseous headspace, or bubble. However, there is one noteworthy difference. A vial's stopper is held in place by a crimp, while a syringe's stopper is designed to move in order to allow injection of the drug product. This freedom of movement, when coupled with a gas bubble (which is not intrinsic to a syringe but is a byproduct of sub-optimal filling processes) can potentially cause significant challenges with regard to package integrity and product sterility, particularly when the syringe is exposed to repeated changes in atmospheric pressure, such as during shipping. Reducing or eliminating the

FIGURE 1



Comparison of a vial and a syringe. Both are essentially glass tubes sealed with an elastomeric closure and contain a gas headspace.

bubble inside the syringe would limit stopper movement, potentially enhancing sterility assurance of the product.[1]

In a preliminary study of the impact of a bubble on stopper movement in a prefilled syringe, three syringes were placed inside a Hypak vacuum chamber. One syringe contained a 2.5-mm bubble, one a 5.0-mm bubble, and yet another contained no bubble at all. Next, a vacuum was pulled at 8 inches of mercury and then again at 15 inches while the syringes were closely monitored for signs of stopper movement. The procedure was then repeated five more times, with a new set of syringes each time, to substantiate the initial findings, which included the following:

- In the syringes containing a bubble, the stopper was seen rising into non-sterile areas of the syringe barrel each time the vacuum was pulled.
- In the syringes containing no gas bubble, however, the stopper was not seen rising at all.
- The size of the bubble inside the syringe made a difference in the amount of stopper movement. The syringes filled with a 2.5-mm bubble experienced less movement than the syringes filled with a 5.0-mm bubble. When the vacuum was released and the pressure returned to original levels, the stoppers in the syringes containing a bubble returned to their original position with no indication that they had moved.

Due to the difficulty of controlling for all of the variables that affect stopper movement in a prefilled syringe, a series of equations were devised to show, on a theoretical level, the relationship between the size of the gas bubble and stopper movement. Using Boyle's Law, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to changes in pressure, and the amount of stopper movement that occurs as a result of that expansion and contraction was calculated.

TABLE 1

Gas Bubble Size	H_{sb} = 6.2 mm Approximate Elevation (1,000s ft)	H_{sb} = 4.3 mm Approximate Elevation (1,000's ft)
0.5 mm	21	19
1.0 mm	16	14
2.5 mm	13	7
5.0 mm	7	<5

Approximate elevation (in feet above sea level) at which a stopper will have moved 1/5 H_{sb}.

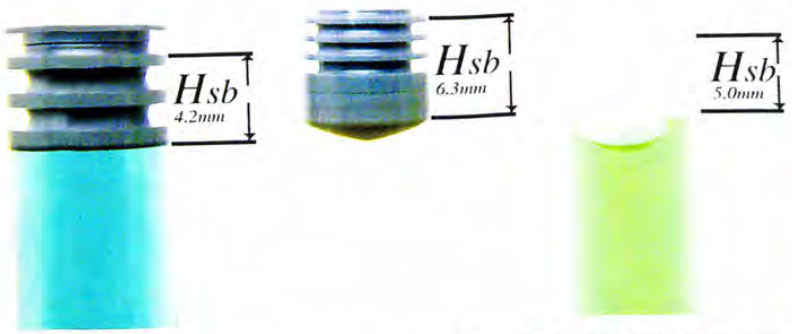
Plugging these calculations into a hypothetical situation in which a syringe is shipped multiple times from the manufacturer to the end-user, a rational approach was developed for determining the maximum allowable size of a gas bubble inside a prefilled syringe. Among the factors taken into account were stopper height, the elevations to which a syringe will likely be exposed and the consequent changes in pressure which it will undergo, as well as the number of times a syringe will be subjected to reduced atmospheric pressure.

STERILE BARRIER HEIGHT: H_{SB}

In a prefilled syringe, a sterile barrier is created in which the stopper is in intimate contact with the glass barrel of the syringe, as shown in Figure 2. The sterile barrier height, or H_{sb}, spans the entire distance from the uppermost to the lowermost point of stopper contact and represents the limit of upward stopper movement, which the stopper can undergo before product sterility is potentially compromised.

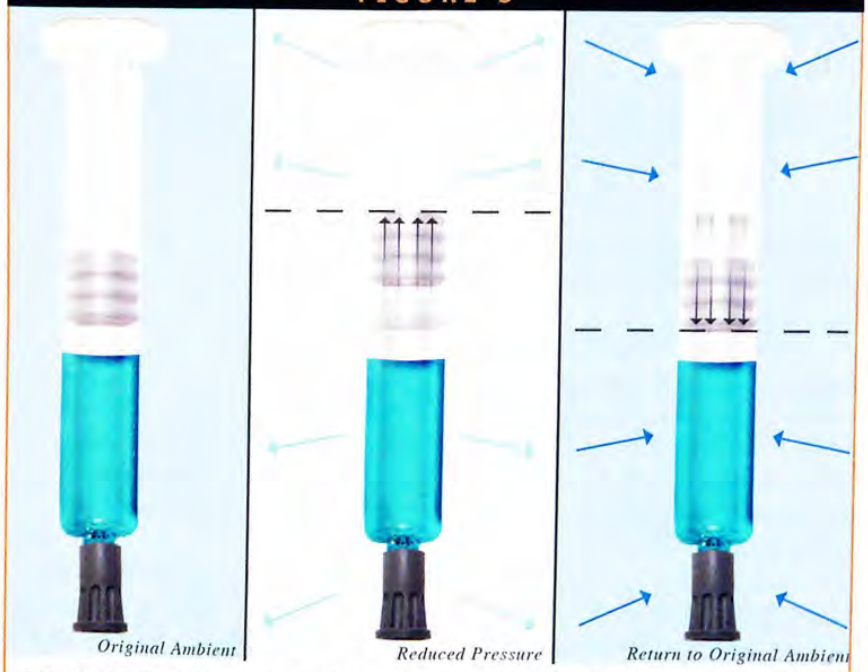
A gas bubble sealed inside a prefilled syringe acts like a spring, expanding and contracting with changes in temperature or external ambient pressure. If the external ambient temperature increases or pressure decreases, the gas bubble expands, pushing the stopper up until the pressure in the syringe is equivalent to the external pressure. When the external ambient pressure and/or temperature return to their original levels, the gas bubble in the syringe contracts until the pressure in the syringe is equal to the external pressure. This causes the stopper to return to its

FIGURE 2



Syringes and stoppers. The distance from the uppermost to the lowermost point of contact between the stopper and the syringe is known as the sterile barrier height or H_{sb}.

FIGURE 3



A gas bubble will expand or contract under changes in ambient pressure. This expansion/contraction will cause stopper movement in a syringe with no visible evidence that the stopper has moved when external conditions are returned to their original levels.

original position, leaving no visible evidence that the stopper has moved (Figure 3).[2]

If the stopper in a syringe moves more than the distance of H_{sb}, it can pull microorganisms or contaminants from the non-sterile portion of the syringe into the drug product, potentially causing a sterility failure. This same phenomenon could occur when a stopper moves less than the distance of H_{sb} if it moves multiple times and the sum of all stopper movements exceeds H_{sb}, as demonstrated in Figure 4.

PRESSURE & THE VOLUME OF A GAS BUBBLE

The amount of change in the volume of a gas bubble is relatively small over the reasonable temperatures to which a syringe might be exposed (total range of approximately 40°C); however, the volume change due to pressure changes alone can be significant, as demonstrated in the calculations that appear further on.

Assuming that temperature remains constant, the amount of expansion or contraction a gas bubble inside a prefilled syringe undergoes due to pressure changes can be calculated using Boyle's Law (Equation 1).

Equation 1.

$$P_1V_1 = P_2V_2$$

Where P_1 = pressure condition 1, V_1 = volume condition 1, P_2 = pressure condition 2, and V_2 = volume condition 2. The volume (V) of a cylinder, such as a syringe, is given by Equation 2.

Equation 2.

$$V = \pi r^2 h$$

Where r = internal radius of the syringe barrel, and h = height of the gas bubble/air gap (assuming the bubble spans the entire diameter of the syringe). If Equation 2 is substituted for V in Equation 1, and both sides are divided by πr^2, the result is as Equation 3.

Equation 3.

$$P_1h_1 = P_2h_2$$

Where P_1 = pressure condition 1, h_1 = height condition 1, P_2 = pressure condition 2, and h_2 = height condition 2. Thus in Equation 4, the theoretical height of the gas space in the syringe at a given external pressure can be determined based on the initial conditions (condition 1).[2]

Equation 4.

$$h_2 = P_1h_1/P_2$$

The percentage of total stopper movement beyond the initial sterility barrier (H_{sb}) can be calculated by subtracting the initial height (H_1) from the height calculated in Equation 4 (H_2) and dividing the result by Hsb, as shown in Equation 5.

Equation 5.

$$\text{Percent } H_{sb} = 100*(H_2 - H_1)/H_{sb}$$

Figures 5b and 5c show the percentage of H_{sb} that a stopper will move in syringes with an H_{sb} of 6.2 and 4.3 mm, respectively, and initial bubble sizes ranging from 0.5 mm to 5 mm, the most common size range for a bubble. The points on the x axis in Figures 5b and 5c represent feet of elevation rather than absolute pressure to demonstrate the effect that reduced pressure (due to changes in elevation) will have on a syringe. These points were determined using a conversion of 1 inch Hg vacuum equal to 1000 feet of elevation (Figure 5a).

The *y* axis in Figures 5b and 5c represents the percentage of H_{sb}, which the stopper in a syringe will move, while the red line at 100% shows the point at which the stopper will enter a non-sterile area of the syringe, potentially compromising product sterility.

In the example in Figure 5b, in which H_{sb} is 6.2 mm and the initial bubble size is 2.5 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 23,000 feet. When the initial bubble is 5.0 mm, the stopper travels in excess of one stopper height in a single exposure to an elevation of approximately 20,000 feet.[2]

Because the cargo hold of an airplane is generally maintained at a pressure equal to 8,000 feet of elevation, and ground elevations during shipment do not often exceed 10,000 feet, a stopper is not likely to move more than H_{sb} in a single exposure. However, during shipment, a syringe could possibly be exposed to reduced pressure on several occasions which, taken together, increases the potential for total stopper movement to exceed H_{sb}.

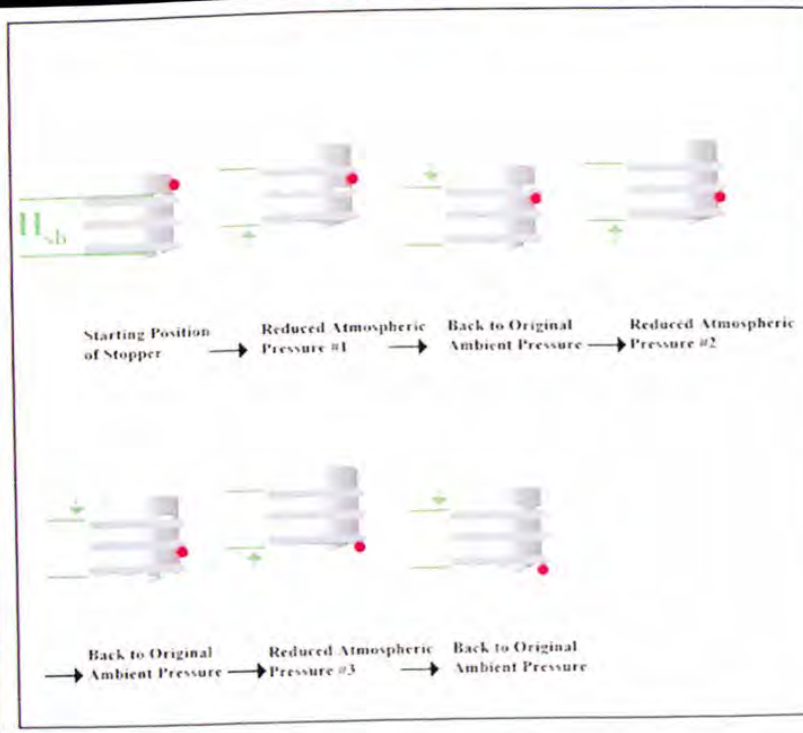
Consider, for example, a syringe that is shipped from a CMO's manufacturing site to the sponsor company's facility to a distribution center and finally to the end-user's site, for a total of three shipments. It is possible that one or more legs of the product's journey could involve more than one flight, creating additional opportunities for the stopper to rise and fall. Under those conditions, it is conceivable that a syringe could be exposed to changes in pressure on five occasions, resulting in five up and down stopper movements. In that case, a stopper would only need to rise 1/5 H_{sb} each time to potentially pull non-sterile material, such as silicon, or other contaminants into the product causing a sterility failure.

Table 1 shows the approximate elevations at which the stopper would exceed 1/5 of H_{sb} given several different sized bubbles. To prevent stopper movement as a result of changes in ambient pressure, syringes should ideally be filled without any gas bubbles. However, in practice, most syringe filling equipment does not have the capability to remove all of the gas in a syringe. When that is the case, the maximum acceptable size of a gas bubble for a given stopper in a prefilled syringe should be determined. This can be done by factoring in the differential pressure changes to which a syringe will likely be exposed, the number of times it will be subjected to reduced pressure, and the height of the sterile barrier.

DETERMINING THE MAXIMUM SIZE OF A GAS BUBBLE

Using the aforementioned equations, the size of the bubble that will lead to a movement of the stopper equal to 1/5 of H_{sb} can be calculated at a number of different elevations. For example, Figure 6 shows the results of calculations performed using elevations of 8,000 and 12,000 feet with a range of H_{sb} from 1 to 15 mm. In situations where H_{sb} is 4.0 and elevation is 8,000 feet, the maximum acceptable size of the gas bubble is approximately 2.0 mm. When the elevation reaches 12,000 feet, however, the maximum acceptable size of the gas bubble decreases to approximately 1.6 mm.[2] The aforementioned analysis is a worst-case scenario and does not take into account frictional forces and break loose forces. Frictional forces caused by the stopper rubbing against the syringe, and the break loose force, which is required to start the stopper moving, should reduce stopper movement. Break loose forces, which increase over the life of the syringe, would improve resistance to stopper movement the longer the product was in transit, requiring greater force to initiate the movement of the stopper. However, it is not unreasonable to assume that a newly filled prefilled glass syringe with silicon has very little break loose force. In fact, we have confirmed in our laboratories that standard, commercially available glass syringes and elastomeric stoppers with silicon show actual stopper movement that is approximately 75% of that which has been theoretically calculated in this article. We did not perform an extensive study of all factors that could affect glide and breakloose forces; therefore, we have used theoretical calculations to demonstrate

FIGURE 4



If the stopper moves more than H_{sb}, contaminants may be pulled into the sterile liquid. This effect can occur with multiple movements if the sum of all stopper movements exceeds H_{sb}.

several worst-case scenarios for stopper movement.

The aforementioned analysis is also based on the assumption that pressures are controlled at consistent levels throughout shipment when, in fact, the actual magnitude of reduced/increased pressure to which syringes are exposed is generally not known. Cargo is shipped by a variety of carriers, many of whom may not consistently control, measure, or report changes in pressure. Atmospheric pressure in a cargo hold could rise and fall during flight, and the drug manufacturer would not be aware of it upon inspection at the final destination.

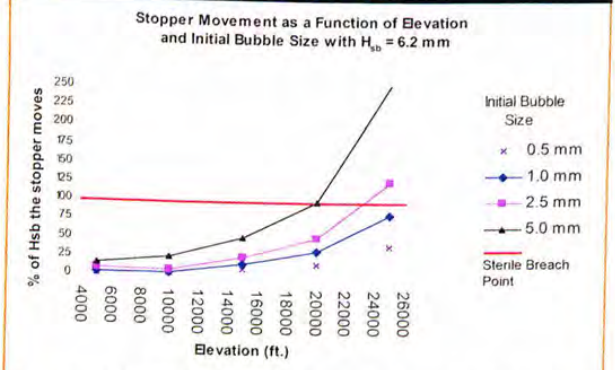
There are alternative means to prevent contamination due to stopper movement other than reducing the size of the gas bubble or increasing H_{sb}. For example, the stopper can be locked in place with a device placed inside the barrel, or the entire syringe can be sealed inside a sterile container (protecting the sterility of the barrel above the stopper), or the syringe can be placed in a holder that secures the plunger rod in place. However, each of these approaches adds cost and requires additional packaging and does not provide the added benefits of a bubble-free syringe.

FIGURE 5A

Elevation	" Hg Vac.	psi	torr
0	0	14.7	760
8,000	8"	10.7	555
10,000	10"	9.8	506
12,000	12"	8.9	455
15,000	15"	7.3	379
18,000	18"	5.9	302
25,000	25"	2.4	125
27,000	27"	1.4	74

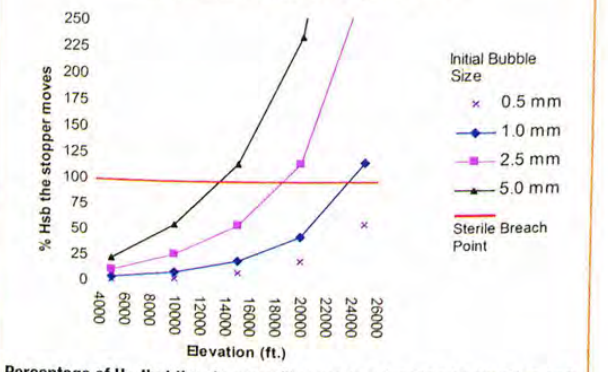
Conversion of 1-inch Hg vacuum equal to 1000 feet of elevation.

FIGURE 5B



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 6.2 mm.

FIGURE 5C



Percentage of H_{sb} that the stopper will move as a function of elevation and initial bubble size when H_{sb} is 4.3 mm.

ELIMINATING PRODUCT LOSS

One added benefit of a bubble-free syringe is the reduction in the amount of product inadvertently lost during use. In a side-by-side analysis, 15 syringes were filled with gas bubbles of varying sizes, while 15 syringes were filled with no bubble. As the tip caps on each set of syringes were removed, the needles were watched for any sign of dripping or product leaks. In the set that were filled with a bubble, product was observed leaking from needle over 75% of the time when the tip cap was removed. Conversely, in the needles that were bubble-free, no product was seen leaking from the needle any time the tip caps were removed (Figure 7).[2]

This is because in a bubble-free syringe, there is no expansion and contraction of the bubble as a result of the small vacuum that is created when the tip cap is removed. Without a drip, there is added assurance that the end-user will receive the entire deliverable dose. There is also less risk that the administrator or end-user will be exposed to cytotoxic or potent compounds, as well as a reduction in product wasted.

CONCLUSION

Although, on the surface, syringes may appear very similar to vials, the freedom of stopper movement in a prefilled syringe, coupled with a gas bubble, will result in challenges to package integrity and product sterility when the syringe is exposed to changes in atmospheric pressure. A gas bubble is not intrinsic to a syringe but is the result of a sub-optimal filling process and therefore, can be reduced or eliminated using alternative filling methods.

Manufacturers go to great lengths to monitor and control the temperature to which products are exposed during shipping. Yet the same attention has not been paid to changes in differential pressures to which a product is exposed. Given that a number of today's parenteral products are shipped several times before reaching the end-user, undergoing several changes in atmospheric pressure and several potential

movements of the stopper, such attention is warranted. Just as exposure to elevated temperatures may impact the shelf-life and efficacy of products, exposure to reduced pressure may potentially impact the sterility and safety of an injectable product in a prefilled syringe if one is not aware of the importance of reduced bubble size and stopper design.

In this discussion, we have proposed one way to determine the maximum acceptable size of a gas bubble that can be left inside a syringe based on stopper height as well as other variables. There are alternative ways to protect prefilled syringes from contamination due to stopper movement, but these require additional packaging and do not offer the added benefits of a bubble-free syringe, such as enhanced dosing accuracy and safety as well as reduced waste due to the elimination of a product drip at the needle when the tip cap is removed.[3]

As prefilled syringes continue to find favor as an alternative to vials for many of today's parenteral products, reduced gas bubble filling should likewise become increasingly popular as an alternative to traditional filling methods and may one day become the industry standard.

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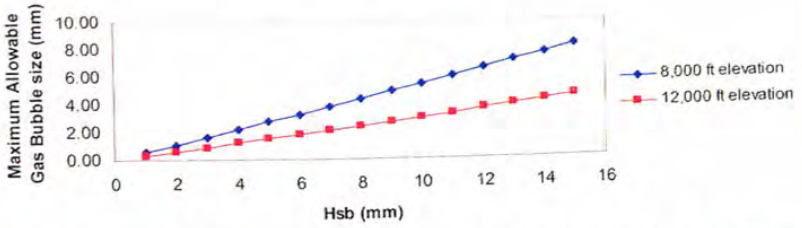
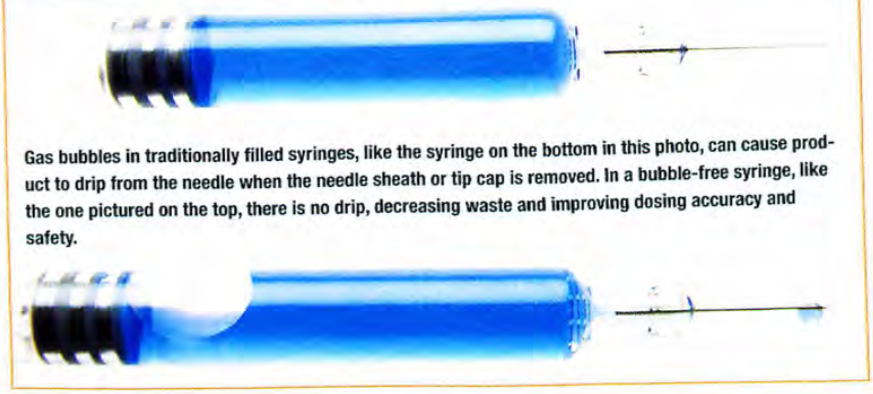
3. Kinney SD. Innovative Solutions Seminar. New Brunswick, NJ, October 30, 2007.

FIGURE 6



The data demonstrates that smaller gas bubbles and stoppers with larger H_{sb} reduce the risk of stopper movement exceeding 1/5 H_{sb}.

FIGURE 7



Gas bubbles in traditionally filled syringes, like the syringe on the bottom in this photo, can cause product to drip from the needle when the needle sheath or tip cap is removed. In a bubble-free syringe, like the one pictured on the top, there is no drip, decreasing waste and improving dosing accuracy and safety.

BIOGRAPHIES

Dr. Shawn D. Kinney, President of Hyaluron Contract Manufacturing (HCM), founded HCM in 1999 to provide aseptic manufacturing and filling services to the pharmaceutical, biotech, and medical device industries. Dr. Kinney earned his PhD in Chemistry from the University of Massachusetts at Amherst, a Masters in Medicinal Chemistry from Northeastern University, and a BS in Chemistry from the University of Massachusetts at North Dartmouth. Dr. Kinney has worked at Anika Therapeutics, Wyeth-Ayerst, and Millipore and has more than 20 years of experience in the pharmaceutical industry. He has extensive experience in the development of sterile formulation and filling processes, including viscous and difficult-to-fill products. Prior to founding HCM, he was responsible for the sterile formulation and filling of hyaluronate into prefilled syringes in his role as VP of Operations at Anika Therapeutics. Recently, Dr. Kinney has pioneered a new technology in online vacuum filling and stoppering (Bubble-Free Filling℠) and has been granted a patent. He continues to oversee HCM's expansion and leadership in the aseptic contract manufacturing industry. He can be reached at shawn@hyaluron.com or (781) 270-7900, ext. 218.

Dr. Andrea Wagner is the Vice President of Business Development at HCM, a position she has held for 7 years. Prior to joining HCM, she was employed by the New Jersey Institute of Technology in the capacity of Senior Scientist in a national training program. Simultaneously, she worked as a Manager at Thermo Fisher Scientific as a Manager in business development of pharmaceutical applications for their XRF Analyzers. After earning her PhD in Toxicology, she managed a center devoted to innovative testing technologies in the Chemistry Department at Tufts University in Massachusetts. Dr. Wagner also earned her a MS in Analytical Chemistry and her BS in Chemistry. She can be reached at andrea@hyaluron.com or (781) 270-7900, ext. 106.

Christian W. Phillips is the Director of Process Engineering, at HCM. Mr. Phillips has 14 years of experience in R&D, Process Development, Tech Transfer, and Manufacturing environments suited for the introduction of novel biotherapeutics and generics, including fill/finish applications. Prior to HCM, Mr. Phillips was employed by Transkaryotic Therapies (now Shire HGS). Mr. Phillips earned his a BS in Biology from St. Michael's College and is the co-inventor with Shawn Kinney of HCM's Bubble-Free Filling℠ technology. He can be reached at cphillips@hyaluron.com or (781) 270-7900, ext. 181.

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Investigating Liquid Leak from Pre-Filled Syringes upon Needle Shield Removal: Effect of Air Bubble Pressure

Edwin Chan, Yuh-Fun Maa, David Overcashier, et al.

PDA J Pharm Sci and Tech **2011**, *65* 363-371
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Investigating Liquid Leak from Pre-Filled Syringes upon Needle Shield Removal: Effect of Air Bubble Pressure

EDWIN CHAN[a], YUH-FUN MAA[a], DAVID OVERCASHIER[b], and CHUNG C. HSU[a]

[a]*Pharmaceutical Processing and Technology Development and* [b]*Device Development, Genentech*

ABSTRACT: This study is to investigate the effect of headspace air pressure in pre-filled syringes on liquid leak (dripping) from the syringe needle upon needle shield removal. *Drip tests* to measure drip quantity were performed on syringes manually filled with 0.5 or 1.0 mL of various aqueous solutions. Parameters assessed included temperature (filling and test), bulk storage conditions (tank pressure and the type of the pressurized gas), solution composition (pure water, 0.9% sodium chloride, and a monoclonal antibody formulation), and testing procedures. A headspace pressure analyzer was used to verify the drip test method. Results suggested that leakage is indeed caused by headspace pressure increase, and the temperature effect (ideal gas expansion) is a major, but not the only, factor. The dissolved gases in the liquid bulk prior to or during filling may contribute to leakage, as these gases could be released into the headspace due to solubility changes (in response to test temperature and pressure conditions) and cause pressure increase. Needle shield removal procedures were found to cause dripping, but liquid composition played little role. Overall, paying attention to the processing history (pressure and temperature) of the liquid bulk is the key to minimize leakage. The headspace pressure could be reduced by decreasing liquid bulk storage pressure, filling at a higher temperature, or employing lower solubility gas (e.g., helium) for bulk transfer and storage. Leakage could also be mitigated by simply holding the syringe needle pointing upward during needle shield removal.

KEYWORDS: Prefilled syringe, Headspace pressure, Drip test, Gas solubility, Ideal gas, Syringe fill

LAY ABSTRACT: Substantial advances in pre-filled syringe technology development, particularly in syringe filling accuracy, have been made. However, there are factors, as subtle as how the needle shield (or tip cap) is removed, that may affect dosing accuracy. We recently found that upon removal of the tip cap from a syringe held vertically with needle pointed downwards, a small amount of solution, up to 3–4% of the 1 mL filled volume or higher for filled volume of <1 mL, leaked out from the needle. This paper identified the root causes of this problem and offered solutions from the perspectives of the syringe fill process and the end user procedure. The readers will benefit from this paper by understanding how each process step prior to and during syringe filling may affect delivery performance of the pre-filled syringe device.

Introduction

Large molecules like monoclonal antibodies, proteins, and peptides need to be delivered via the parenteral route. Pre-filled syringes are now the primary container of choice for most parenteral drug delivery systems mainly for reasons that they are safe and user friendly (1). In recent years substantial advances in pre-filled syringe technology development have been made, particularly in syringe filling accuracy (2). However, there are factors, as subtle as how the needle shield (or tip cap) is removed, that may affect dosing accuracy. We recently found that upon removal of the tip cap from a syringe held vertically with needle pointed downwards, a small amount of solution (up to 3–4% of the 1 mL filled volume) leaked out from the needle. Although holding the syringe tip downwards during needle shield removal is not recommended, this remains a significant issue affecting the overall delivery dose, especially with small fill volumes.

The same observation was previously reported by Kinney and co-workers who attributed such leakage to bubble expansion as the result of small vacuum created during tip cap removal (3). We agree that the root cause of leakage is the air bubble (or headspace) and

Correspondence author: Yuh-Fun Maa, 1 DNA Way South San Francisco, CA 94080; tel: 650-225-3499; fax: 650-742-1504; e-mail: maay@gene.com

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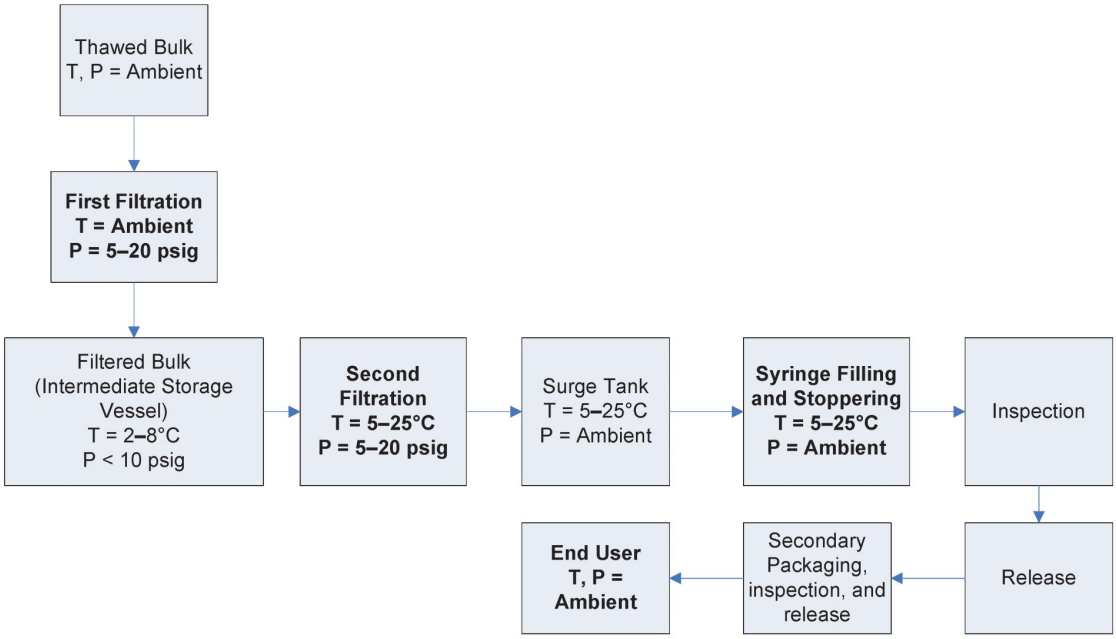


Figure 1

Process flow diagram of syringe filling.

that the vacuum created by tip cap removal can cause bubble expansion, thereby resulting in liquid dripping. This phenomenon, however, may be more complex. Actually, any factors capable of causing air bubble expansion may be able to induce leakage. Certainly, temperature increase (e.g., from refrigeration to an ambient environment) could cause bubble expansion simply following the Ideal Gas Law (described below). Yet, this study would go far beyond to investigate upstream process effects. Prior to filling, thawed liquid bulks are filtered (under a trans-membrane pressure) and stored in a tank pressurized under nitrogen blank for some time before second filtration (under a trans-membrane pressure) (Figure 1). Certainly, all these steps up to liquid fill can be performed under a controlled temperature and/or pressure. Thus, this study investigates whether and how the temperature and pressure history of the liquid may eventually affect headspace expansion/pressure. Furthermore, procedures of needle shield removal were assessed to better understand the leakage phenomenon. Three aqueous solutions, pure water, 0.9% NaCl, and an anti-IgE monoclonal antibody formulation, were tested in this study to understand the effect of formulation on leakage.

Materials and Methods

All experiments in this study employed 1.0 mL long 26G ½ inch staked needle syringes filled with 1.0 mL or 0.5 mL volume of pure water, 0.9% NaCl aqueous solution, or an anti-IgE monoclonal antibody aqueous solution. All solutions were 0.22 μm–filtered and stored at 2–8 °C under a pre-determined pressure. All pre-filled syringes were manufactured and manually filled in the laboratory. Two different lots of syringe barrel (pre-assembled with needle shields) were used to demonstrate reproducibility. Samples were analyzed by measuring gross weight change using an analytical balance before and after removal of the rigid needle shield. Equipment and materials used in this study are tabulated in Table I.

The following describes the processing and test procedures for pre-filled syringes manufactured for this study.

Components Sterilization

Empty syringes with 26G ½ inch staked needle (previously washed and siliconized by an external contract manufacturer), W4023/FLT stoppers, and stopper in-

TABLE I
Equipment and Materials Used in the Study

Equipment	Supplier/Model
Autoclave	Steris (Mentor, OH)/Amsco Century
Balance	Mettler Toledo AG 204 (Columbus, OH)/ AG135
Digital thermometer; with Type K thermocouple	John Fluke Mfg., Inc. (Everett, WA)/Fluke 52
Pressure gauge (0 psi–30 psi) with 1-inch sanitary fitting	Anderson (Fultonville, NY)/EB029
Pressure vessel, 5 liter, stainless steel storage tank	Alloy Products Corp. (Waukesha, WI) Custom made
Stoppering tool	Becton Dickinson (Frankilin Lake, NJ)/Custom made
Materials	
1 mL-long syringe with 26G × ½" staked needle	Becton Dickinson (Swedesboro, NJ)/1 Ml long
Rigid needle shield (RNS)	Helvoet Pharma (Pennsauken, NJ)/FM27
Plunger stopper stopper (Flurotec coated on product-contact surface)	Becton Dickinson (Swedesboro, NJ)/W4023/ FLT
Helium	Praxair (Danbury, CT), 5.0 Ultra High Purity Grade
Nitrogen	Praxair (Danbury, CT), 5.0 Ultra High Purity Grade
Vent filter, pore size: 0.2 μm, membrane: PTFE	Pall Corporation (Ann Arbor, MI)/ACRO® 50
Monoclonal antibody formulation (150 mg/mL anti-IgE, 200 mM arginine-HCl, 20 mM histidine/histidine-HCl, 0.04% polysorbate 20, pH 6.0)	Genentech (South San Francisco, CA)
Sodium chloride	J. T. Baker (Phillipsburg, NJ)
Water, distilled	Genentech (South San Francisco, CA)

sertion tools were autoclaved using a conservative ramp cycle (ramps at 1 psi/min, 30 min exposure at 121.1 °C, and 30 min drying at 2 psia) during pressurization and evacuation to minimize the chance of needle shield movement during the sterilizing process. After the cycle was complete, each syringe was visually inspected for loose needle shield.

Liquid Bulk Storage under Pressurization

A 5 L stainless steel pressure tank was assembled with a calibrated pressure gauge, a valve connected with a vent filter, and a pressure regulator connected to a gas source. Each filtered solution was individually loaded into the pressure tank and pressurized to a desired pressure (0, 10, or 20 psig) and held at 2–8 °C (cold room) for 24 h. The pressure gauge was checked periodically to ensure constant pressure was maintained.

Manual Syringe Filling and Stopper Insertion

The pressure tank was depressurized in the cold room to 0 psig by closing the gas source and opening the vent filter valve. A liquid volume of 1.0 mL or 0.5 mL was withdrawn from the pressure tank using a repeater pipette and filled into 1 mL long syringes. W4023/FLT plunger stoppers were manually inserted using a Becton Dickinson (BD) stopper insertion tool as illustrated in Appendix I. The depth of the stopper (measured from the back of the syringe flange to the back of the stopper) was positioned at 8 mm for 1 mL syringes and 24 mm for 0.5 mL syringes. This resulted in headspace height of approximately 8 mm for both configurations.

Although the majority of the syringes were filled in the cold room at 2–8 °C, some were filled at higher temperatures (15 °C and 21.5 °C) using a circulation bath

to control the liquid temperature. In that case a digital thermometer was submerged directly in the solution to monitor the actual fill temperature. All samples were stored at 2–8 °C after filling for at least 24 h to allow the headspace pressure to equilibrate.

Drip/Leakage Test

Unless otherwise specified, all filled syringes were equilibrated to ambient temperature (measured and recorded) for at least 30 min before testing. The initial syringe weight, $W_{initial}$, was measured. Syringes were held vertically with the needle pointing downward—except for samples tested for different rigid needle shield (RNS) removal methods—and the needle shield was then removed to allow for solution dripping from the tip of the needle on water-absorbent material (e.g., paper tissue). When the needle stopped dripping, the syringe and the needle shield were weighed together to obtain the leakage amount by taking the difference in weight before and after the drip. Finally, to determine the liquid extractable volume in each syringe, a plunger rod was inserted to eject all liquid content from the syringe. Empty syringe weight (including the needle shield), W_{empty}, was then determined, and the gross weight of the dripped solution could be calculated accordingly.

Headspace Pressure Measurement

An optical-based, non-destructive gas analyzer (Model FMS-1400P, Lighthouse Instruments) was employed to determine the headspace pressure inside sealed prefilled syringes. Briefly, light from a near-infrared laser is tuned to match an internal absorption frequency of the water molecule and passes through a container in the headspace above the product. The amount of laser light absorbed is proportional to the water vapor concentration in the headspace, while the width of the absorption signal is related to the headspace pressure (4).

Pressure and Temperature of Gas Bubble Calculation (Ideal Gas Law)

Based on the Ideal Gas Law (eq 1), when syringes were filled at 5 °C (T_1) under ambient pressure (P_1) and then relocated to an ambient environment at use (P_2 and T_2) for drip test, the air bubble would experience volume and/or pressure increase. After the needle shield was removed, the open system allowed the volume of the air bubble to expand until the bubble

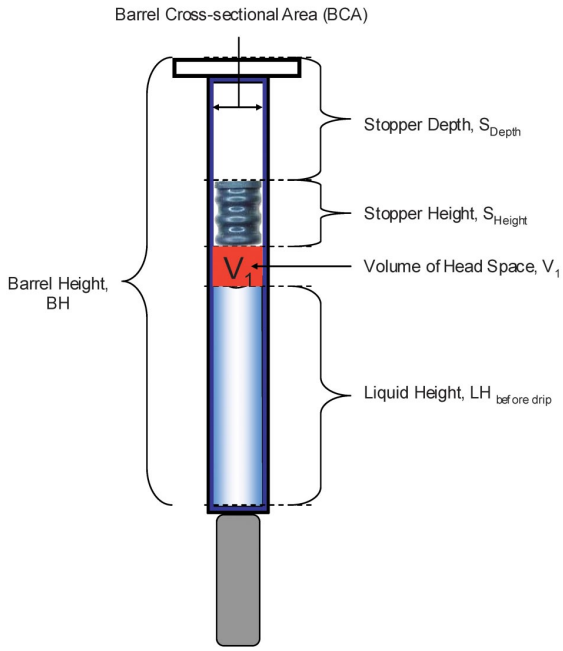


Figure 2

Graphic representation of syringe and its physical dimensional parameters used in eq 3.

pressure equilibrated with the ambient pressure ($P_1 = P_2$). Bubble expansion (V_2) displaced some solution as leakage and the expanded volume ($V_2 - V_1$) could be theoretically calculated by eq 2.

$$\frac{P_1V_1}{nRT_1} = \frac{P_2V_2}{nRT_2} \quad (1)$$

$$V_2 - V_1 = V_1 \times \left(\frac{T_2}{T_1} - 1\right) \quad (2)$$

where T_1 and T_2 are known values, initial and final temperatures, respectively; and V_1 is a constant that can be calculated from known syringe physical parameters (eq 3 and Figure 2).

$$V_1 = (BH - LH_{Before\ Drip} - S_{Height} - S_{Depth}) \times BCA \quad (3)$$

where BH is the barrel height, $LH_{Before\ Drip}$ is the liquid height before removal of the needle shield, S_{Height} is the stopper total height, S_{Depth} is the stopper position measured from the back of the syringe flange to the back of the stopper, and BCA is the barrel cross-sectional area.

TABLE II
Physical Dimensions of Syringe, Components, and Liquid Fill

Parameters	1.0 mL	0.5 mL
Fill volume (mL)*	1.00	0.50
Barrel diameter (mm)	6.35	6.35
Stopper depth, S_{Depth} (mm)*	8.00	24.00
Stopper height, S_{Height} (mm)	7.85	7.85
Neck volume offset (mL)	0.04	0.04
Barrel length (mm)	54.00	54.00
Liquid height (mm)*	30.00	14.34

* Average fill volumes and stopper depths were measured for each experiment, therefore these values may vary.

Conversion of Drip Test Results into Pressure Units (Torr)

Before and after the drip test, the headspace conditions in the filled syringe are (T_1, P'_1, V_1) and (T_2, P'_2, V_2), respectively. P'_1 represents the internal pressure of the syringe headspace before the drip test, and P'_2 represents ambient pressure or is 1 atm.; V_1 and V_2 can be calculated using eqs 3 and 4 and physical dimensions (Table II):

$$V_2 = (\text{Barrel Height} - (\text{Liquid Height}_{\text{After Drip}}) - S_{Height} - S_{Depth}) \times \text{BCA}. \quad (4)$$

Once V_1 and V_2 are calculated, assuming $T_1 = T_2$, the Ideal Gas Law (eq 1) can be used to derive eq 5 and solve for P_1:

$$P_1 = P_2 \times \frac{V_2}{V_1}. \quad (5)$$

Results and Discussion

Effect of Pressure and Temperature during Bulk Storage and Filling

Leakage was first tested on syringes manually filled with the anti-IgE antibody formulation that had been stored under N_2 blank at three different pressures: 0, 10, and 20 psig. The results are summarized in Figure 3. The ideal gas expansion of inert nitrogen, calculated using eq 2 with the temperature change from filling at 5 °C to testing at 21.5 °C, was 17 mg (the horizontal line in Figure 3) based on density of 1.06 g/L. Both 0.5 mL and 1.0 mL syringes leaked more than the dripping contributed by ideal gas expansion. In addition, the amount of leakage increased with increasing storage pressure, approximately 0.3 mg/psig. The 1.0 mL syringes appeared to expel more liquid, 25–33 mg (6–8 drips or 2.4–2.8% of the overall dose) than the 0.5 mL syringes, 23–29 mg (5–7 drips or 4.6–5.0% of the overall dose) over the whole pressure range. These observations could be attributed to increased gas solubility. When the storage pressure increased, it dissolved more nitrogen molecules into the solution. Some of dissolved N_2 would escape to the headspace created during filling under ambient pressure, thereby enhancing the headspace pressure. Because 1.0 mL filled syringes contained twice the liquid volume, more dissolved gas diffused from the liquid to the gaseous phase, which resulted in slightly higher headspace pressure than the 0.5 mL filled counterpart.

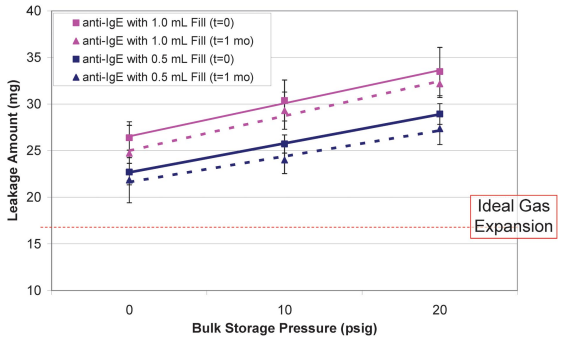


Figure 3

Effect of liquid bulk storage pressure (0, 10, and 20 psig) on leakage from syringes filled with 1-mL or 0.5-mL of anti-IgE antibody liquid formulation. Syringes tested at t=0 and t=1month are represented by square and triangle symbols, respectively. The two fill volumes of 1.0 mL and 0.5 mL are illustrated by pink and blue color, respectively.

It is worth noting that the storage pressure effect could not explain the 0 psig storage condition where the leakage was still higher than that predicted by ideal gas expansion. Again, it is a gas solubility phenomenon and could be interpreted by the temperature-solubility relationship. Gas solubility in water generally decreases with increasing temperature. Nitrogen solubility can be predicted as a function of temperature as illustrated in Appendix II (5–8), showing that nitrogen solubility decreases from 1.7×10^{-5} (mole fraction) at 5 °C (278 °K) to 1.25×10^{-5} (mole fraction) at

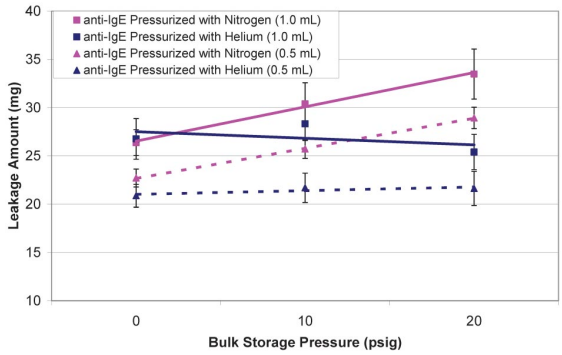


Figure 4

Effect of gas species (nitrogen vs argon) on leakage from syringes filled with 1 mL or 0.5 mL of anti-IgE antibody liquid formulation. Syringes with fill volumes of 1.0 mL and 0.5 mL are represented by square and triangle symbols, respectively. The two inert gases, nitrogen and helium, are illustrated by pink and blue colors, respectively.

21.5 °C (294.5 °K). Thus, during the leakage test at ambient temperature, some nitrogen and oxygen molecules originally dissolved in the liquid during filling at 2–8 °C became insoluble and would diffuse to the headspace, which caused higher pressure and additional leakage. Note that oxygen is even more soluble than nitrogen (Appendix II).

Some pre-filled syringes were stored at 2–8 °C for 1 month as part of a stability study and tested for leakage. The results (Figure 3) were similar to the T = 0 condition, suggesting the additional storage time has little effect on leakage, which was primarily determined by the temperature and pressure of liquid storage, filling, and leakage test.

Effects of Gas Species

Because a soluble gas like N_2 contributed to headspace pressure increase, a less soluble gas might alleviate such an effect. As shown in Appendix II, helium is less soluble than N_2, $\sim 0.7 \times 10^{-5}$ mole fraction, and is independent of temperature changes. Drip tests were performed on syringes filled with liquid bulks previously stored under helium at three different pressures: 0, 10, and 20 psig. It is apparent that helium caused less leakage than N_2, and both 0.5 mL and 1.0 mL filled syringes showed little changes in leakage amount with pressure (Figure 4). Again, the 0 psig result exceeds what is predicted by the Ideal Gas Law

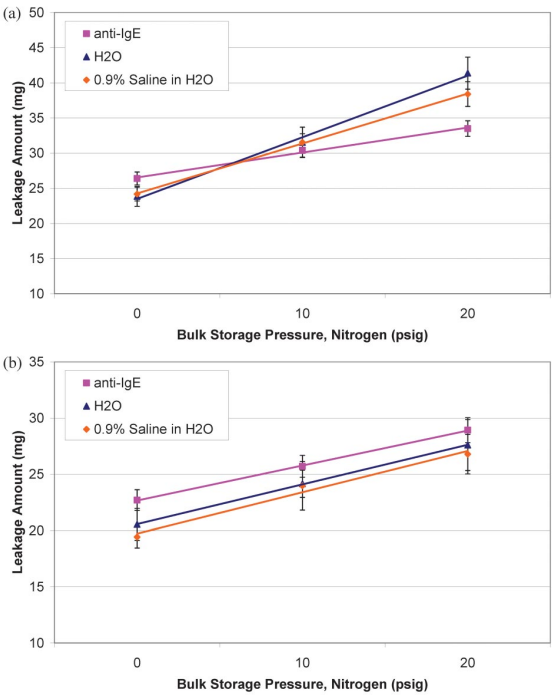


Figure 5

Effect of liquid bulk composition (anti-IgE antibody formulation [pink square], pure water [blue triangle], and 0.9% NaCl aqueous solution [orange diamond]) on leakage from syringes filled with 1.0 mL liquid (a) or 0.5 mL liquid (b).

and can be attributed to soluble gases (oxygen and nitrogen) that already dissolved in the liquid during storage and filling (2–8 °C). The dissolved gases could have diffused into the headspace during the leakage test at the higher ambient temperature.

Effects of Liquid Composition

Liquid salinity may influence gas solubility; higher salinity in the solution may have a tendency to reduce gas solubility (6). The anti-IgE antibody formulation contains arginine HCl, which makes the formulation slightly higher in salinity than water. In addition, a 0.9% NaCl solution was evaluated. The leakage results on these three liquids showed no clear trend of salinity effects (Figure 5a for 1.0 mL filled syringes and Figure 5b for 0.5 mL filled syringes) when all three storage pressures (0, 10, and 20 psig) were compared. This leakage phenomenon appeared to be insensitive to formulation changes given the test conditions.

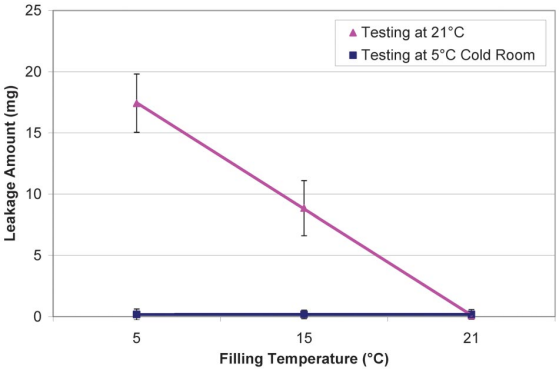


Figure 6

Effect of filling temperature (5° C, 15° C, and 21.5° C) and drip test temperature (5 °C [blue square] and 21.5 °C [pink triangle]) on leakage from syringes filled with 1.0 mL of pure water.

Effect of Liquid Fill and Drip Test Temperature

Temperature is certainly one of the most important factors influencing the amount of leakage, particularly the temperature during liquid fill and drip test. The former represents the final equilibration condition that the liquid experiences before being sealed in the syringe. Assuming the liquid is filled and tested under the same ambient pressure, higher test temperature/lower fill temperature would result in bubble expansion and liquid leakage, but lower test temperature/higher fill temperature would cause bubble contraction and no liquid leakage. Theoretically there should be little or no leakage if fill temperature and test temperature are identical. This temperature effect takes both ideal gas expansion/contraction and gas solubility into consideration.

Syringes were manually filled with 1 mL of pure water at three temperatures, 5, 15, and 21.5 °C and tested for leakage at 5 and 21.5 °C at ambient pressure (0 psig). The results (Figure 6) confirmed that leakage can be minimized or completely avoided if the liquid fill temperature is equal to or higher than the drip test temperature, particularly filling at 21.5 °C resulting in almost no leakage. Thus, performing liquid fill at higher temperatures (if protein stability allows) is one of the most effective approaches to mitigate leakage when the needle shield is removed.

Effect of Needle Shield Removal Methods

Kinney and co-workers reported that needle shield removal creates vacuum at the tip of the needle

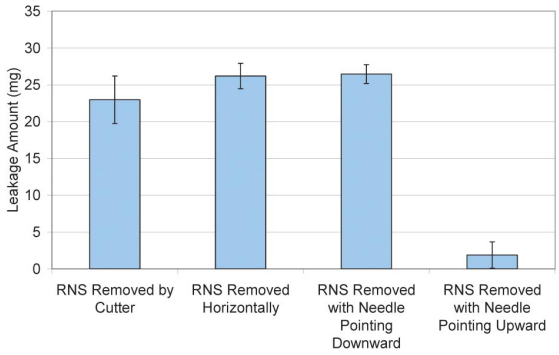


Figure 7

Effect of rigid needle shield removal methods on leakage from syringes containing 1.0 mL of pure water filled at 5 °C and 0 psig.

which promotes leakage (3). This vacuum effect is probably inevitable. Therefore, this part of the study was to evaluate some needle shield removal procedures and identify the one having the least effect on leakage.

Syringes manually filled with 1.0 mL of pure water (under 0 psig bulk storage pressure) were tested by holding the syringe either vertically (needle tip pointing up and down) or horizontally and by carefully cutting the needle shield open (lengthwise into halves) to avoid or minimize any vacuum that may be created from pulling on the rubber part of the needle shield. As shown in Figure 7, the vertical (needle tip pointing downwards) and horizontal removal methods showed no observable differences and the amount of leakage remained high (25–27 mg). The cutting removal methods had a mild effect in reducing leakage (20–25 mg), suggesting leakage contributed by vacuum from removing the needle shield is minor. Vertically removing the needle shield with needle pointing upwards was most effective and caused almost no leakage. With the needle pointing upwards, the air bubble flowed to the top of the syringe, allowing air to vent for pressure reduction. This is the simplest solution to this leakage issue if users follow this recommendation.

Headspace Pressure Measurement

An optical gas analyzer (Model FMS-1400P, Lighthouse Instruments) was employed to directly measure headspace pressure in syringes filled with 1.0 mL of pure water that have been stored under a pressure of 0

TABLE III
Comparison of Headspace Pressure Measured Using an Optical Gas Analyzer and Derived from Drip Test (n = 5) in Syringes Filled with 1.0 mL of Pure Water

Bulk Storage	Headspace Pressure (Torr)	
	Gas Analyzer	Derived from Drip Test
0 psig	815	817 ± 4
20 psig	879	851 ± 4

psig or 20 psig prior to fill. In the meanwhile, the amount of leakage (in weight) measured by the drip test could be converted to pressure (Torr) using eqs 4 and 5 along with the physical dimensions in Table II. The results are summarized in Table III. The measured headspace pressure agreed well with what is derived from the drip test, suggesting that the drip test is a good tool for headspace pressure measurement and that headspace pressure increase is indeed the root cause of leakage.

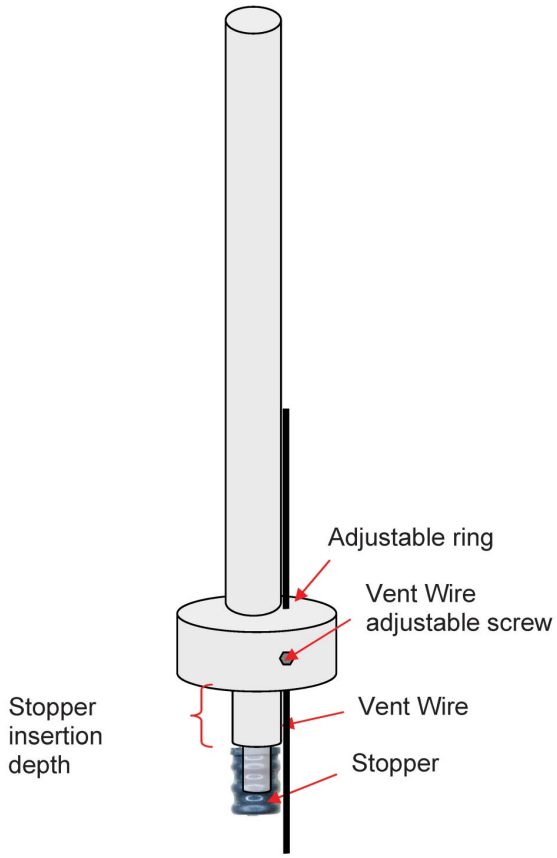
Conclusions

Liquid leakage from the pre-filled syringe after needle shield removal is a phenomenon universal to all aqueous liquids. Other than the vacuum created during needle shield removal, we demonstrated that the root cause of leakage is an increase in headspace pressure dictated by multiple parameters, mainly the temperature and pressure history of the liquid bulk during the filling manufacturing process. Headspace pressure increase was primarily caused by ideal gas expansion and soluble gas re-equilibration between the liquid and the gas phases. We determined that performing liquid fill at a temperature close to a standard ambient temperature (~20 °C) or removing the needle shield while pointing the needle upward is most effective in minimizing leakage. Lowering liquid bulk storage/filtration pressure or using a low solubility gas (e.g., helium) for storage/filtration is also useful in alleviating headspace pressure/leakage.

Conflict of Interest Declaration

The author(s) declare that they have no competing interests.

Appendix I. Stopper Insertion Tool (not drawn to scale)



Appendix II. Solubility Profile of Different Gases in Water at 1 atm

According to Reference 7, the mole fraction solubility X_1 of the gas can be derived from the smoothing equation at each temperature:

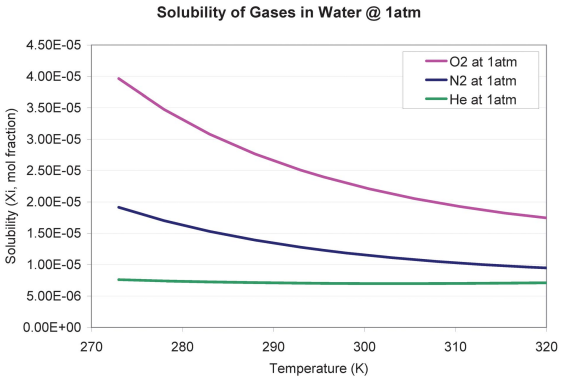
$$\ln X_1 = A + \frac{B}{T^*} + C \ln T^*$$

where

$$T^* = \frac{T}{100\ K}.$$

Plugging in all the constants from the table below, a solubility profile can be plotted from 273K to 328K.

Equation Constants	He	N_2	O_2
A	−41.4611	−67.3877	−66.7354
B	42.5962	86.3213	87.4755
C	14.0094	24.7981	24.4526



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APPENDIX A

JAMES L. MULLINS, PhD

Prior Art Documentation Librarian Services, LLC

205 Saint Cuthbert, Williamsburg, VA 23188

jlmullins@priorartdoclib.com

ph. 765 479 4956

Prior Art Documentation Librarian Services, LLC. (PADLS). Founded January 2018. As of April, 2022, 98 declarations have been completed for 35 law firms; four depositions scheduled, three cancelled a few days prior, and one was held, and was successful for my client.

Library Experience:

2018-present	**Dean Emeritus of Libraries and Esther Ellis Norton Professor Emeritus**
2011 - 2017	**Dean of Libraries & Esther Ellis Norton Professor**
2004 - 2011	**Dean of Libraries & Professor, Purdue University, West Lafayette, IN**
2000-2004	**Assistant/Associate Director for Administration, MIT Libraries, Massachusetts Institute of Technology, Cambridge, MA.**
1996-2000	**University Librarian & Director, Falvey Memorial Library. Villanova University, Villanova, PA.**
1978-1996	**Director of Library Services, Indiana University South Bend.**
1974-1978	**Associate Librarian, Indiana University Bloomington, School of Law.**
1973-1974	**Instructor/Catalog Librarian. Georgia Southern College (now University).**

Teaching Experience:

1977-1996	**Associate Professor (part-time), School of Library and Information Science, Indiana University. Subjects taught: Cataloging, Management, and Academic Librarianship.**

Education:

The University of Iowa. Honors Bachelor of Arts in History, Religion and Political Science.

The University of Iowa. Master of Arts in Library Science.

Indiana University. Doctor of Philosophy. Concentration: Academic Library Administration. Emphasis: Law Librarianship.

Awards and Recognition:

2017 Wilmeth Active Learning Center/Library of Engineering and Science, Grand Reading Room, was announced by President Mitch Daniels, Purdue University, that it would be re-named the James L. Mullins Reading Room to honor his leadership and reputation in the academic library profession. September 2017. Portrait unveiled December 2017.

2017 Distinguished Alumnus Award by the School of Informatics and Computing, Indiana University, Bloomington. Given June 25, 2017.

2016 Hugh C. Atkinson Memorial Award, jointly sponsored by the four divisions of the American Library Association (ALA), June 27, 2016.

2015 ACRL Excellence in University Libraries Award, April 23, 2015.

Named Esther Ellis Norton Professor of Library Science by Purdue Trustees, December 11, 2011.

International Review Panel to evaluate the University of Pretoria Library, February 20 – 24, 2011. Pretoria, South Africa.

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Presentation at University of Cape Town, Cape Town, South Africa, August 20, 2015.

"The Challenge of Discovering Science and Technology Information," Moderator, International Federation of Library Associations (IFLA) Science and Technological Libraries Section Program, Cape Town, South Africa, August 18, 2015.

"An Odyssey in Data Management: Purdue University," International Federation of Library Associations (IFLA) Research Data Management: Finding Our Role – A program of the Research Data Alliance, Cape Town, South Africa, August 17, 2015.

Presentation at University of Pretoria, Pretoria, South Africa, August 11, 2015.

Co-Convener with Sarah Thomas, Harvard University, at the Harvard Purdue Symposium on Data Management, Harvard University, Cambridge, MA, June 15-18, 2015.

"Strategic Communication," panel discussion on the Director's role and perspective on library communications at Committee on Institutional Cooperation (CIC) Center for Library Initiatives (CLI) Annual Conference, University of Illinois Urbana-Champaign, May 20, 2015.

"Issues in Data Management," panel discussion moderated by Catherine Woteki, United States Undersecretary for Research, Education & Economics at 20th Agriculture Network Information Collaborative (AgNIC) Annual Meeting in the National Agricultural Library, Beltsville, MD, May 6, 2015.

"Active learning/IMPACT & the Active Learning Center at Purdue University," Florida Institute of Technology, Melbourne, FL, February 11, 2015.

"Science+art=creativity: libraries and the new collaborative thinking," panel moderator, International Federation of Library Associations (IFLA) 80th General Conference and Assembly, Lyon, France, August 19, 2014.

"Purdue University The Active Learning Center—A new concept for a library," Association of University Architects 59th Annual National Conference, University of Notre Dame, South Bend, IN, June 23, 2014.

"Big Data & Implications for Academic Libraries," keynote speaker, Greater Western Library Alliance (GWLA) Cyber-infrastructure Conference, Kansas City, MO, May 28, 2014.

"Research Infrastructure," panel moderator, Association of Research Libraries (ARL) 164th Membership Meeting, Ohio State University, Columbus, OH, May 7, 2014.

"An Eight Year Odyssey in Data Management: Purdue University," International Association of Scientific and Technological University Libraries (IATUL) 2013 Workshop Research Data Management: Finding Our Role, University of Oxford, UK, December 2013.

"Purdue University Libraries & Press: from collaboration to integration," Ithaka Sustainable Scholarship, The Evolving Digital Landscape: New Roles and Responsibilities in Higher Education, libraries as publishers, New York, New York, October 2013.

"Tsinghua and Purdue: Research Libraries for the 21st Century," Tsinghua University, Tsinghua, China, August 2013.

"Purdue Publishing Experience in the Libraries Publishing Coalition," Association of American University Presses Annual Meeting, Press-Library Coalition Panel, Boston, Massachusetts, June 21, 2013.

"Indiana University Librarians Day: Purdue University Libraries Ready for the 21st Century," Indiana University Purdue University Indianapolis (IUPUI), June 7, 2013.

"Purdue University Libraries and Open Access; CNI Project Update," Coalition for Networked Information, San Antonio, TX, April 5, 2013.

Memorial Resolution, honoring Joseph Brannon, to the Board of the Association of College & Research Libraries, Seattle, WA, January 2013.

"An overview of sustaining e-Science collaboration in an Academic Research Library—the Purdue experience," Duraspace e-Science Institute webcast, October 17, 2012.

"The Role of Libraries in Data Curation, Access, and Preservation: an International Perspective, " Panel Moderator, 78th General Conference and Assembly, International Federation of Library Associations, Helsinki, Finland, August 15, 2012.

"21st Century Libraries," moderator of First Plenary Session, International Association of Technological University Libraries 33rd Annual Conference, Singapore, June 4, 2012.

"Planning for New Buildings on Campus," panel presenter, University of Calgary Building Symposium on Designing Libraries for the 21st Century, Calgary, Alberta, Canada, May 17, 2012.

"Data Management and e-Science, the Purdue Response." Wiley-Blackwell Executive Seminar-2012, Washington, DC, March 23, 2012.

"An overview of Sustaining e-Science Collaboration in Academic Research Libraries and the Purdue Experience." Leadership & Career Development Program Institute, Association of Research Libraries (ARL). Houston, TX, March 21, 2012.

"An overview of Data Activities at Purdue University in response to Data Management Requirements." Coalition for Academic Scientific Computation (CASC). Arlington, VA, September 8, 2011.

"Getting on Track with Tenure," Association of College and Research Libraries (ACRL) Research Program Committee. Washington, DC, June 26, 2011.

"Integration of the Press and Libraries Collaboration to Promote Scholarly Communication," Association of Library Collections & Technical Services (ALCTS) Scholarly Communication Interest Group – American Library Association, New Orleans, Louisiana, June 25, 2011.

"Cooperation for improving access to scholarly communication," with N. Lossau (Germany), C. Mazurek (Poland), J. Stokker (Australia), panel moderator and presenter, Second Plenary Session, International Association of Scientific and Technological University Libraries (IATUL) 32nd Conference 2011, Warsaw, Poland. May 29-June 2, 2011.

"Riding the Wave of Data," STM Annual Spring Conference 2011. Trailblazing & transforming scholarly publishing **2011**. Washington, D.C., April 28, 2011.

"Confronting old assumptions to assume new roles: physical and operational integration of the Press and Libraries at Purdue University," keynote speaker, 2011 BioOne Publishers & Partners Meeting. Washington, D. C., April 22, 2011.

"Are MLS Graduates Being Prepared for the Changing and Emerging Roles that Librarians must now assume within Research Libraries?" University of Oklahoma Libraries Seminar, March 4, 2011, Oklahoma City, Oklahoma.

"The Future Role of University Librarians," the University of Cape Town, South Africa, February 25, 2011.

"New Roles for Librarians: the Application of Library Science to Scientific/Technical Research – Purdue University – a case study. International Council for Science and Technology (ICSTI); Ottawa, Canada. June 9, 2009.

"Reinventing Science Librarianship: Models for the Future," Association of Research Libraries / Coalition for Networked Information. October 16-17th, 2008, Arlington, VA. Moderator and convener of Data Curation: Issues and Challenges.

"Practical Implementation and Opportunities Created at Purdue University," African Digital Curation Conference, Pretoria, South Africa, (live video transmission), February 12, 2008.

Keynote speaker. "*Scholarly Communication & Academe: The Winter of Our Discontent,"* XXVII Charleston Conference on Issues in Book and Serial Acquisition, Charleston, South Carolina. November 8, 2007.

Keynote speaker. "*Enabling Access to Scientific & Technical Data-sets in e-Science: a role for Library and Archival Sciences,"* Greater Western Library Alliance (GWLA), Tucson, Arizona. September 17, 2007. A meeting of library directors and vice presidents for research of member institutions.

"*The Challenge of e-Science Data-set Management to Domain Sciences and Engineering: a Role for Academic Libraries and Librarians,"* KIT (Kanazawa Institute of Technology)/CLIR (Council of

Library and Information Resources) International Roundtable for Library and Information Science, July 5-6, 2007. Invited to participate by the Deputy Librarian of Congress.

International Association of Technological University Libraries (IATUL), Stockholm, Sweden. June 8, 2007**.** Invited paper**,** *Enabling International Access to Scientific Data-sets: creation of the Distributed Data Curation Center (D2C2).*

"A New Collaboration for Librarians: The Principles of Library and Archival Sciences Applied to the Curation of Datasets," Symposium of the Libraries and the College of Engineering, University of Louisville, April 6, 2007.

"Purdue University Libraries: Through Pre-eminent Innovation and Creativity, Meeting the Challenges of the Information Age," Board of Trustees, Purdue University, February 15, 2007.

ARL Workshop on New Collaborative Relationships: The Role of Academic Libraries in the Digital Data Universe, September 26-27, 2006, Arlington, VA. Invited participant.

NARA and SDSC: A partnership. A panel before the National Science Foundation, June 27, 2006. Arlington, VA. Invited participant.

"Kaleidoscope of Scientific Literacy: fusing new connections," with Diane Rein, American Library Association, Association of College and Research Libraries, Science & Technology Section, Annual Conference, New Orleans, June 26th, 2006.

"Leadership for Learning: Building a Culture of Teaching in Academic Libraries – an administrative perspective," American Library Association, Association of College and Research Libraries, Instruction Section, Annual Conference, New Orleans, June 25th, 2006.

"Building an interdisciplinary research program in an academic library:
how the Libraries'associate dean for research makes a difference at Purdue University," International Association of Technological University Libraries (IATUL), Porto, Portugal, May 23rd, 2006.

"Enabling Interaction and Quality in a Distributed Data DRIS," *Enabling Interaction and Quality: Beyond the Hanseatic League*. 8th International Conference on Current Research Information Systems, with D. Scott Brandt and Michael Witt. Promoted by euro CRIS, Bergen, Norway, May 12th, 2006, Brandt, and Witt presented in person

"Interdisciplinary Research," with D. Scott Brandt, Coalition for Networked Information (CNI) Spring Meeting: Project Briefing, Washington, D.C., April 3rd, 2006.

"An Interview with Purdue's James Mullins," a podcast submitted by Matt Pasiewicz, on *Educause Connect,* http://connect.educause.edu/James_L_Mullins_Interview_CNI_2005

"Managing Long-Lived Digital Data-sets and their Curation: Interdisciplinary Policy Issues," Managing Digital Assets Forum, Association of Research Libraries (ARL), Washington, D.C., October 28th, 2005.

"The Odyssey of a Librarian." Indiana Library Federation (ILF), District 2 Meeting, South Bend, Indiana. October 4th, 2005.

"New College Library Standards," Standards Committee Presentation, ALA, Chicago, July 7, 2000.

SUNY Library Directors, Lake George, New York. "*The College Library Standards: a Tool for Assessment."* April 5, 2000.

Tri-State College Library Association, *Finding You Have Talents You Never Knew You Had,* Penn State Great Valley, March 25, 2000.

Using Web Statistics, American Library Association, New Orleans, June 24, 1999.

Keynote speaker at the JSTOR Workshop, January 29, 30, 1999. University of Pennsylvania, Philadelphia, PA.

"The New Standards for Electronic Resources Statistics," Society of Scholarly Publishers, Washington, D.C., September 17, 1998.

"Evaluating Online Resources: Now that you've got them what do you do?," joint presenter with Chuck Hamaker, LSU, at the NASIG Conference, Boulder, Colorado. June 1998.

"What Employers Are Looking for in New Librarians?" Pennsylvania Library Association, Philadelphia. September 26, 1997.

"The Theory of Matrix Management" panel presentation of the Comparative Library Organization Committee of the Library Organization and Management Section of the Library Administration and Management Association, a division of the American Library Association, Annual Meeting, Chicago, June 24, 1990.

Professional Involvement: (summary of recent emphasis)

The focus for my professional involvement and research has moved recently toward managing massive data-sets. This has resulted in working with faculty in the sciences and technology to determine how librarians can collaborate in managing, curating, and preserving data-sets for future access and documentation. This has included various speaking opportunities as well as participation in planning with the National Science Foundation (NSF) on ways in which librarians can be integrated more completely into the funded research process. Participation in the Kanazawa Institute of Technology/Council of Library Resources Roundtable was particularly rewarding and provided new opportunities to share with international colleagues the issues surrounding data-set management. I was

the champion for the creation of the Distributed Data Curation Center (D2C2) at Purdue University (http://d2c2.lib.purdue.edu/)

Throughout my career, beginning with my dissertation, I have been actively involved with assessing and evaluating libraries. In the fall of 1999, I contacted twenty-two academic library directors to determine whether the need was also felt by others. The response was overwhelmingly affirmative. This resulted in a meeting at ALA Midwinter, January 2000. A formal meeting followed at Villanova University in April 2000. As convener, I helped to form the University Libraries Group (ULG), modeled after the Oberlin Group for college libraries. The ULG is made up of university libraries that support diverse wide-ranging programs through doctoral level and have a level of support that places them in the top tier of academic institutions. A few of the member libraries, along with Villanova, are William and Mary, Wake Forest, Lehigh, Carnegie-Mellon, Tufts, Marquette, Miami of Ohio, and Southern Methodist.

In 1994 appointed to the Standards Committee, College Section, Association of College and Research Libraries. During the next six years, the Committee concentrated on changing the focus of the standards from quantitative analysis of input and output factors to emphasis on assessment of the outcome. Culmination of the work was a re-issue of the *Standards for College Libraries* in 2000. The knowledge gained through my work experience enabled me to formulate the changes needed in the standards. This work allowed for close collaboration with accrediting agencies, both professional and regional.

During this same time another focus emerged, the impact of digital resources. Through my work on the JSTOR Statistics Task Force, standards were developed on the collection of use of electronic databases. This Standard was later adopted in 1998 by the International Consortium of Library Consortia (ICOLC).

In 2002, the American Library Association appointed me to serve as the liaison to the Marketing and Management Section of the International Federation of Library Associations (IFLA).

Professional Service: (representative list)

Nominations Committee, Association of Research Libraries (ARL), 2016.

Steering Committee, Scholarly Publishing and Academic Resources Coalition (SPARC), 2016 – 2017.

"Excellence in Library Services," Chair, Review Team, University of Hong Kong, Hong Kong, August 24-27, 2015.

Chair, Management Advisory Board, 2015-2017; Member, Scientific Advisory Board, arXiv, Cornell University, 1/1/2013 – present.

Advisory Board for the Wayne State University School of Library and Information Science, July 2012 – present.

Advisory Board for Microsoft Academic Search, 2012 – 2015. Redmond, WA.

Transforming Research Libraries, a Strategic Direction Steering Committee of the Association of Research Libraries (ARL), 2012-2015.

Science and Technology section, representing ARL, International Federation of Library Associations (IFLA), Chair, 2013 – 2017; Member, 2011 to present.

Member of University of Pretoria, South Africa, Library Review Committee. August 2013.

Co-chair, Local Arrangements Planning Committee for 2013 Conference, Association of College and Research Libraries (ACRL), a division of the American Library Association (ALA).

Association of Research Libraries Leadership & Career Development Program Mentor, 2011-2017.

e-Science Task Force, Association of Research Libraries. July 2006 – present. Chair, October 2011 – October 2012.

Board of Directors, International Association of Technological University Libraries (IATUL). January 2008 – December 2014.

Midwest Collaborative for Library Services (MCLS); Board Member, October 2010 – December 2012.

Chair, Library Directors, Committee on Institutional Cooperation (CIC), July 2010 – June 2012.

Board of Directors, Association of Research Libraries (ARL); October 2008 – October 2011.

Scholarly Communication Steering Committee, Association of Research Libraries (ARL) 2008-2011.

Editorial Board, *College and Research Libraries,* Association of College and Research Libraries, American Library Association. January 2008 – December 2014.

Chair, Organizing Committee for IATUL Conference 2010, June 21-24, 2010, Purdue University, West Lafayette, Indiana/Chicago, Illinois.

Conference Planning Committee for National Conference of the Association of College and Research Libraries, 2009, Seattle, Washington.

Research Committee, Association of College and Research Libraries, ACRL, division of ALA. 2002-2007, chair, 2005-2007.

Association of Research Libraries, Search and Screen Committee, Executive Director. March – January 2008.

Center for Research Libraries, Board of Directors. April 2006 – April 2012.

Academic Libraries of Indiana, Board of Directors, 2004 – present. Vice-president, 2005-2007. President, 2007- 2009.

ALA Representative to the International Federation of Library Associations (IFLA), Marketing and Management (M&M) Section, initial term 2003-2007, re-appointed for second term, 2007-2011.
Invited to represent Research Libraries at the ACRL/3M Wonewok Retreat to assess Marketing of Academic Libraries, October 2002.
Hugh A. Atkinson Award Committee, LAMA Representative, ALA, 2001-2005.
Program Committee, Library Administrators and Management Association (LAMA), a division of ALA. 1996-2001.
ACRL, Standards and Accreditation Committee, a division of ALA. Liaison to RBMS Section of ACRL. 1997-2002.
Elected to the Executive Committee of LAMA, LOMS, a division of the American Library Association, 1998-2000. Nominated as Chair/Elect for 2003 – 2005.
Columbia University Press Advisory Committee. 1996 - 2000.
LITA/LAMA Conference Evaluation Committee, Pittsburgh, Pennsylvania, October 1996.
"New Learning Communities," Coalition for Networked Information, Indianapolis. November 19-21, 1995. Facilitator for invitational, national conference committed to developing collaborative learning and teaching techniques, involving librarians.
Planning Committee-Evaluation. LITA/LAMA 1996 Conference, Pittsburgh. This first conference, to be held jointly between two divisions of ALA, will focus on new technologies within libraries.
Indiana Cooperative Library Services Authority (InCoLSA), elected to Executive Committee, April 1991, served as President in 1993-94. InCoLSA is a statewide network of academic, public, school, and special libraries that supports library cooperation for cataloging, interlibrary loan, collection development and application of new technologies.
Governor’s Conference on Libraries and Information Services. Served on Planning Committee, Academic Libraries Representative, appointed by the Governor to represent academic libraries in Indiana, Chair, Finance Committee, April 1989-July 1991.
Indiana Library Endowment Foundation Board, 1984-92. Charter Member, 1984, President, 1988-1992. 2004-2005.

University Service: (Summary)

Served on search and screen committees for senior positions including chancellor, dean, and directors; most recently I have been asked to serve on the search committee for the provost of Purdue University. At MIT service included the Library Council & appointment to the Administrative Council by President

Vest, 2001-2003 & Member of the Faculty Committee on the Library System. At Purdue appointed by the President to the Search Committee for the Provost, October 2007 to May 2008; member of the Capital Projects Committee, and IT Operational Oversight Committee as senior academic dean, 2008-2014.

Global Council, Global Policy Institute, 2012 – 2016.

Academic Program Excellence and Rankings (APER) project team, 2014.

Representative of the Academic Deans on the Re-engineering Business Operations, Purdue University, 2016 –

Academic Deans Council chaired by Provost – 2004 – 2017.

University Promotion and Tenure Committee – 2006 – 2017.

"Outstanding Team Award, Electronic Reserve Project," served as Chair, recognition awarded by the President of Villanova University to one team who made an outstanding contribution to the operations of the University, selected by a committee of administrators, faculty, and staff. Awarded September 9, 1999.

Nominated for the IUSB Lundquist Award, 1995 & 1996. The Lundquist award is given to faculty who have "exhibited excellence in teaching, scholarly or artistic achievement, and diversified relevant service..."