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Workshop Report

Assuring Quality and Performance of Sustained and Controlled Release Parenterals: AAPS Workshop Report, Co-Sponsored by FDA and USP[1]

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

INTRODUCTION

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

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

This workshop brought together experts from the pharmaceutical industry, the regulatory authorities, and academia to discuss and debate issues pertaining to ensuring the quality and performance of sustained and controlled release parenterals. The workshop was divided into formal presentations in the morning and parallel breakout discussion sessions in the afternoon. The breakout sessions served to identify future directions for regulatory activity and public standards in this rapidly emerging area. At the close of each breakout session, the moderators were asked to prepare a summary of the key points discussed in their session. This report represents a

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compilation of these summaries together with background information explaining the need for regulatory activity in this area. Because many of the same concerns and issues were raised in different parallel sessions, this report is not divided by the breakout sessions, but rather by the key issues discussed.

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

BACKGROUND

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

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

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

Table I. Approved CR Parenteral Products

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

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

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

In Vitro Release Methods

Because the issue of *in vitro* release testing was raised at many of the breakout sessions, attendees generally agreed that an immediate need for guidance in this area exists. This

guidance should focus on regulatory and compendial approaches with respect to acceptable apparatus, media and sampling methods, test intervals, and total percent release. Attendees also requested guidance on the method development process for *in vitro* tests for quality control purposes as well as on how to ensure the *in vivo* relevance of these tests. A need for guidance on accelerated *in vitro* testing for routine quality control purposes was also expressed. The issue of IVIVC was discussed.

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

Apparatus

Current USP apparatus for *in vitro* release testing are designed for oral and transdermal products and may not be optimal for controlled release parenteral products. USP apparatus 1 (basket) and 2 (paddle) were designed for immediate- and modified-release oral formulations. USP apparatus 5 (paddle over disc), 6 (cylinder), and 7 (reciprocating holder) were designed for the transdermal route. USP apparatus 3 (reciprocating cylinder) and 4 (flow through cell) were designed for extended-release oral formulations. These latter two methods may be the most relevant to CR parenterals and may be suitable after appropriate modification. Alternative apparatus, such as small sample vials and vessels, with and without agitation, are currently used for CR parenterals. Problems that may be associated with these alternative apparatus include lack of sink conditions and sample aggregation.

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

Method Development

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

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

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

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

Development of IVIVC for CR Parenterals

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

The use of animals was considered to be acceptable to

prove that an *in vitro* release system is discriminating. However, the use of animal models was considered inappropriate to prove an IVIVC for regulatory purposes. Instead, biorelevance should be developed by using clinical data. Nevertheless, IVIVC modeling using animal data would be suitable for "proof of principle" for initial research purposes. Research in this area should be encouraged, possibly coordinated through Product Quality Research Initiative (PQRI).

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

- Increase the number of dosage units or individuals.
- Accept variability as long as its source can be estimated and a valid IVIVC is obtained.
- Minimize variability if the source and importance of the variability can be determined.

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

Use of Animal Models in Release Testing

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

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

Animal models could potentially be used in pharmaceutical development. For SUPAC-type changes, attendees recommended that an animal-human correlation be established so that animal models can be used (along with *in vitro* specifications) in lieu of extensive postapproval human trials. To achieve this, out of specification batches would be used to test the sensitivity of the animal model. Tests should also examine the sensitivity of the animal model to changes in product performance when the duration of testing is truncated (e.g., 3-month release testing for a 1-year release product).

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

Accelerated in Vitro Release Testing

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

Attendees discussed the initial "burst" release associated with some CR parenterals. When a CR parenteral delivery system produces an initial burst release, accelerated release tests should be augmented by an initial "real-time" study that allows adequate assessment of this burst. Specifications for accelerated-release tests should be tied to safety and to manufacturing experience. For example, significant deviation from the expected result may indicate a manufacturing problem. Attendees expressed the view that mathematic modeling to predict long-term release from accelerated release is useful.

Labeling Requirements for Release Rates

Attendees were concerned about products that displayed an initial rapid-burst release followed by a second slower-release rate. Total drug content and *in vivo* release rate are label requirements for CR products. Agreement was reached

that inclusion of the initial burst release on the label should be handled on a case-by-case basis. Provided the initial burst rate is supported by clinical safety/efficacy data and is covered by specifications, it may not need to be included. However, if there are safety implications, this rate must be included. Given that regulatory guidance is not available on how much burst release is acceptable, attendees note that this performance factor should also be assessed on a case-by-case basis, depending on the drug and the safety/efficacy implications. Attendees discussed eliminating burst release from products where it did not provide a clinical benefit, but they agreed that this might be prohibitively expensive.

Stability

Attendees considered both shelf life and *in vivo* stability for CR parenterals. In addition to drug stability, attendees noted the importance of "inactive" ingredient stability and product stability for CR parenterals.

Shelf Life Stability

The initial shelf life stability of entrapped drug is a concern because manufacturing conditions for some CR parenterals (e.g., some microsphere products) may be harsh. In protein drugs, documentation of lack of chemical breakdown only is insufficient because conformational changes that can affect activity may have occurred. Therefore, activity must be demonstrated as part of the stability testing using a pharmacodynamic method. Stability testing of many of these products requires extraction of the drug. The method of extraction (e.g., solvent system) should be selected to avoid any potential alteration in drug stability. Shelf life stability should be conducted at room temperature as occurs for other products.

In Vivo Drug Stability

In vivo drug stability is an issue for controlled release parenterals, especially those intended for long-term extended release. In large implants, drug stability could be determined by analyzing the drug remaining in explanted systems. This method could only be feasible for dispersed system CR parenterals by using an appropriate animal model where tissue samples could be excised. An alternative approach that might be acceptable would be an *in vitro* test that simulated *in vivo* conditions (e.g., 37°C and ~100% humidity). Attendees agreed that some *in vivo* drug degradation might be acceptable for extended-release products, provided that the product was demonstrated to be safe and effective. A typical *in vivo* degradation profile should be established together with safety and efficacy data. Immunologic response may require assessment, because protein degradation may occur with prolonged *in vivo* residence time.

In Vivo Product Stability

Attendees agreed that *in vivo* product stability is equally as important as drug stability because degradation/alteration of the product as a whole or unwanted tissue response to the product may affect performance and bioavailabilty. For example, fibrous encapsulation of an implant or microsphere product will reduce/eliminate blood flow and, consequently, affect drug release and bioavailability. Attendees recommended that *in vivo* evaluation of CR parenterals include evaluation of product stability and tissue response to the product as well as drug stability. This is another area where animal models may be useful. Further discussion of this issue is required and/or a research project should be initiated to determine appropriate animal models.

In Vivo Integrity of Targeted Products

Another *in vivo* stability issue is the integrity of products that are intended to remain stable without significant drug release until uptake at the target site. An example of this type of product is "stealth-type" liposomes. There was no consensus as to how to determine *in vivo* integrity of such products. Attendees discussed a proposal to conduct a single-dose study over a sufficient time period, with measurement of both encapsulated and unencapsulated drug. However, there was no prevailing opinion as to what percentage/ratio of unencapsulated to encapsulated drug should remain in the circulation for a liposomal drug product to be considered stable.

Particle Size

Attendees requested guidance/clarification on particle size specifications for dispersed system CR parenterals. Particle size may affect release rates of extended release products, such as microspheres. It may also affect targeting ability and reticuloendothelial system (RES) uptake of liposome products. Acceptable particle size ranges may vary for different CR parenteral systems. For example, a liposome system intended for targeted release, where targeting is particle size-dependent, may require more stringent particle size specifications than some other dispersed systems. Attendees noted the importance of a specification for particle size range as well as average particle size because a few large particles may have a significant effect on product performance as well as safety. Larger particles can cause capillary blockage when injected intravenously. Particle size may also affect syringability of the product. Attendees requested guidance on particle sizing instrumentation and techniques, particularly when more than one instrument is necessary to measure the entire size range. Concluding, attendees generally agreed that a workshop to address particle size issues would be useful.

Sterilization, Sterility Ensurance, and Foreign Particulate Matter

Sterilization and Sterility Assurance

CR parenterals are complex products usually containing polymers and/or lipids with glass transition temperatures below the temperature required for heat sterilization. Consequently, these products would break down if subjected to heat sterilization. For this reason, these products are typically manufactured by using aseptic processing. However, terminal heat sterilization may be appropriate for a few CR parenteral products and is being used in an ongoing drug suspension development project. To reduce drug crystal growth (which could affect performance and bioavailability) during heat sterilization, a cloud point modifier can be introduced.

Because CR parenterals are not liquids, terminal filtration is not an option. Attendees discussed the possibility of using gamma irradiation as an alternative method of terminal

sterilization. Because product breakdown (e.g., via polymer degradation) is a potential problem with gamma irradiation, continuing product integrity would have to be demonstrated after gamma radiation. This could be demonstrated by maintenance of polymer weight before and after irradiation. Low-energy gamma radiation may be effective in sterilizing without damaging the product and may be an acceptable method of terminal sterilization for some CR parenterals, provided that the long-term quality of the product is not compromised.

CR parenterals typically involve complex manufacturing that may complicate aseptic processing. Attendees noted the importance of aseptic drug crystallization to ensure that no bacteria are entrapped inside the drug crystals. Attendees agreed that both internal and external sterility of CR parenterals should be tested, given that organisms may become entrapped within these products during manufacture. Internal sterility may be demonstrated via a modified dissolution test. Methods development for internal stability need to be addressed, and this is an area where research is required.

Foreign Particulate Requirements

Attendees requested guidance related to foreign particulate requirements. For example, would the parenteral suspension require adhering to small-volume parenterals (SVP) and large-volume parenterals (LVP) guidances? Some attendees pointed out that an ongoing practice is to dissolve drug suspension products with suitable organic solvent systems and then count the amount of foreign particulate. Other methods such as that used for lyophilized products are also used. Attendees questioned whether the 100% inspection requirement for parenteral products is required for parenteral drug suspensions. Attendees concluded that sterility issues associated with CR parenterals is a special topic that warrants further discussion in the form of workshop or other meeting.

Qualification of New Biopolymers

Many discussants noted a significant concern about the need for new biopolymers and that a process be established on how to qualify any new biopolymers or other excipients. In this regard, the appropriate animal models should be identified. Attendees also expressed concern that failure to address this issue would significantly limit the types of CR products that could be developed. Concluding, attendees agreed that a workshop or other type of meeting be held to discuss this important topic and that an agencywide guidance on studies needed for qualifying inactive ingredients, such as biopolymers that are incorporated in CR parenterals, would be useful.

Residual Solvents

Attendees expressed a need for clarification of the International Conference on Harmonization (ICH) guidelines on residual solvents in controlled-release parenterals. For example, is the total amount of residual solvent important or is the amount released *in vivo* on a daily basis important? This issue may require research, with resulting data supplied to FDA to support optimal regulatory approaches.

Reconstitution at the Time of Use

Attendees discussed some of the technical issues and challenges in maintaining quality and sterility of drug products designed for reconstitution at the time of use. This is particularly important for some liposome and suspensions products. Many noted that regulatory guidance in this area would be helpful. Unit to unit reproducibility of the drug product is a main concern, because particle size distribution, crystallinity, morphology, and other physical and chemical parameters may vary with slight changes in the reconstitution procedure(s). Attendees noted that reconstitution at the time of use may be appropriate for some single-dose unit products. However, because of the more significant challenges associated with multidose drug products, reconstitution at the time of use may not be applicable for these products. The current requirements and practices for lyophilized products may be used as a reference. It was recommended that well-defined reconstitution procedures/methodologies be included in label inserts to ensure the quality, dosage accuracy, and sterility of the products.

Syringeability and Injectability

Attendees discussed a number of issues for this important topic, including Newtonian vs. non-Newtonian viscosity of the product, syringe size, needle size, particle size, and morphology of the suspension. Most of the discussion concentrated on the test method. Attendees generally agreed that an appropriate method needs to be established and submitted to FDA for review. The method should be suitable at zero time as well as throughout the shelf life of the product. A major problem is clogging of needles.

Resuspendability

Attendees suggested that resuspendability approaches should achieve a homogenous formulation through well-defined methods, by manual or mechanical shaking. To test the homogeneity of a resuspended formulation, a statistically significant amount of sample should be subjected to assay for drug active.

Nomenclature

Attendees requested a resolution to "name" confusion that exists with current products. It was suggested that the drug name, the delivery system and the type of delivery system should be included in the product name to avoid prescriber and patient confusion between immediate-release and targeted/controlled-release parenteral products, given that the same drug can have very different *in vivo* behavior, depending on the type of CR parenteral approach. For example, attendees agreed that liposome products could be named as follows: "Liposome + Name of active ingredient + Type X" (X referring to descriptive classes of liposomes with similar physical/chemical and/or biologic properties). Attendees agreed that a working group of experts consider the task of devising suitable nomenclature for CR parenteral products.

Classification of Micelle and Microemulsion Formulation

Some discussants noted that there are ongoing efforts to formulate water-insoluble drugs into microemulsions for parenteral applications. A point of further discussion is the classification of micelle and microemulsion formulations. Some attendees proposed that these may be classified as immediate-

release (IR), sustained-release (SR), or CR emulsions, depending on the biologic behavior of the individual product.

How Are Release Specifications Set

Attendees requested guidance on how specifications should be set for individual CR parenteral products, noting the ICH definition of a specification as a list of tests, procedures, and acceptance criteria for a substance, an excipient, a product, a package, or other component using in manufacturing. The following example is a general guideline for liposome products.

Example Specifications for Liposome "Controlled-Release Products"

1. Identify critical parameters during development
   - Extensive physical/chemical characterization
   - Impact of formulation variants
     In vitro (stability, drug release)
     In vivo (PK, safety, efficacy)
2. Set specifications based on experience—three categories
   - "Standard" for IV systems
   - Liposome-specific/unique
   - Drug product-specific

There was general agreement that procedures in specifications for liposomal products fall into three categories:

1. Standard
   - Appearance
   - pH
   - Osmolarity
   - Residual solvent
   - Sterility (USP)
   - Pyrogen (USP)
   - Drug potency
   - Drug-related substances
2. Liposome-specific
   - Particle size
   - Percent "free" vs. encapsulated
3. Product-specific
   - Lipid assay(s)
   - Lamellarity
   - Peroxidation measure
   - % Lyso lipid
   - Zeta potential
   - Phase transition

Validated methods and acceptance criteria for each of these tests would have to be developed to support a regulatory application, unless a compendial approach (as noted) is available.

Bioavailability, Bioequivalence, and Pharmaceutical Equivalence

The bioavailability (BA) and bioequivalence (BE) requirements for innovator as well as generic products attracted a great deal of discussion. In this context, attendees also considered IVIVC.

Conceptual Definitions of Bioavailability (BA) and Bioequivalence (BE) for CR Parenterals

Attendees generally agreed that the definitions of BA and BE as stated in the current U.S. regulations apply to controlled-release parenterals.

For BE demonstration of injectable products such as liposomes, some attendees questioned whether both active and inactive ingredients should be qualitatively (Q1) and quantitatively (Q2) the same between the test and reference products. According to the U.S. regulations, the "sameness" in active and inactive ingredients is part of the requirements for allowing a waiver of *in vivo* BE studies (biowaiver) for parenteral solutions. The general opinion was that biowaivers might not be applicable to liposome drug products because these products are not true solutions. Because demonstration of BE for liposome drug products has to be established by *in vivo* studies, a requirement for sameness in inactive ingredients between the test and reference products may not be needed. Discussants focused on how to define pharmaceutical equivalence and how to measure BA and BE.

Pharmaceutical equivalents are defined in U.S. regulations as drug products that contain identical amounts of the active drug ingredient in the same dosage form. They do not necessarily contain the same inactive ingredients but do meet compendial or other standards of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. Pharmaceutically equivalent products may not be bioequivalent, whereas pharmaceutical alternatives may. If the same approach is followed for CR parenterals as is now followed for nonparenteral extended-release dosage forms, the type of ingredient used to control rate of release will not be a factor in determining pharmaceutical equivalence, nor will it appear in the product name. Attendees agreed that further discussion of this complex issue is needed.

In Vivo Measurement of BE

Some attendees expressed a view that plasma levels may not be the best measure of BE for CR parenterals intended for targeted and/or localized delivery. Instead, measurement of rate and extent of release of active drug at the site of action would be ideal. However, such measurements may not be practical clinically. Because of the lack of a clear understanding of the way liposomes and other CR parenteral products and their contents are handled in the body, attendees could not reach consensus regarding the appropriate approaches to assess BE of these drug products. With the understanding that further investigation is needed, the following approaches were discussed.

Liposome drug products may be classified into two general categories based on how they are handled in the body: mononuclear phagocyte system (MPS)-uptake and MPS-avoiding products. For MPS-uptake products, systemic exposure measures (e.g., AUC and Cmax based on plasma concentrations) may be used to determine BA and BE of the products using single-dose studies. The need for multiple-dose studies for either BA or BE assessment should be determined on a case-by-case basis. For instance, if accumulation is a concern for safety, multiple-dose studies may be conducted to assess BA. For MPS-avoiding products, which

are preferentially taken up at specific sites, the relevance of systemic exposure measures is uncertain. In this setting, measurement of biomarkers over time (e.g., a pharmacodynamic study) or a small confirmatory clinical study may be useful. Further discussions are needed on what are the appropriate biomarkers and what constitutes a small confirmatory clinical study. When systemic exposure studies are useful, sensitive and specific analytical methods are needed to distinguish between encapsulated and unencapsulated drug.

Burst Release

Attendees agreed that the clinical significance of any initial burst of drug from CR parenteral products in safety and/or efficacy implications should be assessed, with safety and/or efficacy implications addressed in the sponsor's original application. If the initial burst release is important clinically, different types of systemic exposure measures (e.g., early exposure) may be needed.

The general opinion of the participants was that the recommendations provided in the FDA Guidance on "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Consideration" should be applicable to microsphere formulations.

BE for Implants with Long Duration of Action

For implants that are intended for short duration of application, the regular method of assessing BE should be adequate. However, for implants that are intended for long duration of application, participants generally agreed that a parallel study should be used. There was discussion on how long these studies should be conducted. A suggestion was made that the studies should be evaluated for sufficient time to reflect steady-state conditions. Alteration in physiologic conditions during a long duration of action should be considered in evaluating the BA and BE for implants. The release characteristics should be adequately characterized.

In Vitro Release Test for Batch Release That Would Document "Likely" BA and BE

Attendees generally agreed that *in vitro* release tests would be useful for batch release as a quality control tool. Some debated whether an IVIVC can be used to reduce the number of BE studies. For CR parenteral products, especially liposome drug products, development of *in vitro* release tests that correlate with product bioavailability may be difficult. As indicated in previous sections of this report (under *In Vitro* Release Testing and IVIVC), *in vitro* release tests should be designed with as much biorelevance as possible for future application to IVIVC. If an IVIVC can be established, the agency may allow waiver of some *in vivo* BA/BE studies. Successful approaches in this regard might also allow application of approaches in the SUPAC guidances to CR parenteral products.

SUMMARY

Attendees recommended:

1. Workshops or other meetings be organized to further discuss:
   - Particle size analysis
   - Regulatory pathway for new biopolymers
   - Sterility assurance and testing
2. A working group of experts be formed to resolve issues with respect to the nomenclature of CR parenteral products
3. Research be initiated in the following areas, possibly coordinated through PQRI
   - Identification of most appropriate animal models for parenteral products
   - Development of apparatus and methodologies for *in vitro* release testing of CR parenterals
   - Accelerated *in vitro* release tests and mathematical modeling to predict long-term release
   - Investigation of the possibility of IVIVC of CR parenterals
   - Investigation of *in vivo* product stability and tissue response and the impact on bioavailability and release rates using appropriate animal models
   - Method development for internal sterility testing of CR parenterals
4. Agencywide working groups be established to provide guidance in the following areas:
   - *In vitro* release testing for acceptable apparatus, acceptable media, and acceptable sampling methods, testing intervals, and total percent release
   - Clarification of the ICH guidelines on residual solvents in controlled-release parenterals
   - Foreign particulate requirements
5. USP general chapters be revised as follows:
   - USP ⟨1151⟩ to include new drug delivery systems such as Doxil and Viadur
   - USP ⟨88⟩ biologic reactivity test to include implantation test for polymeric delivery matrix
   - USP ⟨711⟩ to include new apparatus used with controlled-released parenterals
   - USP ⟨1074⟩ to include excipients used in controlled-released parenterals to evaluate polymeric excipients
   - USP ⟨1088⟩ IVIVC to include controlled-released parenterals and to address interspecies correlations (ISC)