

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

Submitted: February 6, 2004; Accepted: February 6, 2004; Published: March 22, 2004

Diane J. Burgess,¹ Daan J.A. Crommelin,² Ajaz S. Hussain,³ and Mei-Ling Chen³

¹Department of Pharmaceutics, University of Connecticut, 372 Fairfield Road, Storrs, CT 06269, USA

²Faculty of Pharmaceutical Sciences, Utrecht University, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands

³Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, 5515 Security Lane, HFD-3, Rockville, MD 20852, USA

*This report may contain statements of opinion that are those of the author(s) and do not necessarily reflect the opinions of EUFEPS or its members, AAPS or its members, the European Agency for the Evaluation of Medicinal Products, the European Pharmacopoeia the Food and Drug Administration or the United States Pharmacopoeia.

PLANNING COMMITTEE

Diane J. Burgess (Co-Chair), Storrs, CT, USA

Daan J.A. Crommelin (Co-Chair), Utrecht, NL

Agnès Artiges, Strasbourg, FR

Ole J. Bjerrum, Copenhagen, DK

Mei-Ling Chen, Rockville, MD, USA

Hendrik de Jong, Courbevoie, FR

Leo G.J. de Leede, Leiden, NL

Paul R. Gellert, Macclesfield, UK

Henning Gjelstrup Kristensen, Copenhagen, DK

Christina Graffner, Uppsala, SE

Brian Henry, Sandwich, UK

Ajaz S. Hussain, Rockville, MD, USA

Claus-Michael Lehr, Saarbrücken, DE

Hans H. Lindén, Stockholm, SE

Philippe Maincent, Nancy, FR

Michael Morris, Dublin, IE

Rainer Müller, Berlin, DE

Jean-Louis Robert, Luxembourg, LU

Roger Williams, Rockville, MD, USA

SPEAKERS AND DISCUSSION LEADERS

Diane J. Burgess, PhD, University of Connecticut, Storrs, CT, USA

Daan J.A. Crommelin, PhD, Utrecht University, Utrecht, NL

Jean-Pierre Benoit, PhD, INSERM ERIT-M, Angers, FR

James C. Boylan, PhD, United States Pharmacopoeia, Rockville, MD, USA

Corresponding Author: Diane J. Burgess, Department of Pharmaceutics, University of Connecticut, 372 Fairfield Road, Storrs, CT 06269, USA. Tel: 860-486-3760. Fax: 860-486-4998. Email: diane.burgess@uconn.edu.

Mei-Ling Chen, PhD, Food and Drug Administration, Rockville, MD, USA

Brian C. Clark PhD, AstraZeneca, Macclesfield, UK

Paul A. Dickinson, PhD, AstraZeneca, Macclesfield, UK

Sven Frokjaer, PhD, Royal Danish School of Pharmacy, Copenhagen, DK

Hendrik De Jong, PhD, I.R.I.S., Courbevoie, FR

Thomas Kissel, PhD, Philipps-University Marburg, Marburg, DE

Christina Graffner, PhD, Medical Products Agency, Uppsala, SE

Paul R. Gellert, D.Phil., AstraZeneca, Macclesfield, UK

Simon R. Hartas, PhD, AstraZeneca, Macclesfield, UK

Henning Gjelstrup Kristensen, PhD, Royal Danish School of Pharmacy, Copenhagen, DK

Lotte Langkjaer, PhD, Novo Nordisk, Bagsvaerd, DK

Leo G.J. De Leede, PhD, OctoPlus Technologies BV, Leiden, NL

Claus-Michael Lehr, PhD, Saarland University, Saarbrücken, DE

Philippe Maincent, PhD, Laboratoire de Pharmacie Galénique, Nancy, FR

Frank Martin, PhD, ALZA Corporation, Mountain View, CA, USA

Arthur B. Shaw, PhD, Food and Drug Administration, Rockville, MD, USA

David Young, Pharm.D., PhD, GloboMax, Hanover, MD, USA

Liang Zhou, PhD, Food and Drug Administration, Rockville, MD, USA

ABSTRACT

This is a summary report of the workshop, organized by the European Federation of Pharmaceutical Scientists in association with the American Association of Pharma-

ceutical Scientists, the European Agency for the Evaluation of Medicinal Products, the European Pharmacopoeia, the US Food and Drug Administration and the United States Pharmacopoeia, on “Assuring Quality and Performance of Sustained and Controlled Release Parenterals” held in Basel, Switzerland, February 2003. Experts from the pharmaceutical industry, 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. This workshop was a follow-up workshop to a previous workshop on Assuring Quality and Performance of Sustained and Controlled Release Parenterals that was held in Washington, DC in April 2001. This report reflects the outcome of the Basel 2003 meeting and the advances in the field since the Washington, DC meeting in 2001. As necessary, the reader is referred to the report on the 2001 meeting. Areas were identified at the 2003 Basel meeting where research is needed in order to understand the performance of these drug delivery systems and to assist in the development of appropriate testing procedures. Recommendations were made for future workshops and meetings.

INTRODUCTION

This report summarizes the outcome of the workshop on “Assuring Quality and Performance of Sustained and Controlled Release Parenterals”, which was held in February 2003 in Basel, Switzerland. This workshop was sponsored by the European Federation of Pharmaceutical Scientists (EUFEPS), in association with the American Association of Pharmaceutical Scientists (AAPS), the European Agency for the Evaluation of Medicinal Products (EMA), the European Pharmacopoeia (EP), the US Food and Drug Administration (FDA) and the US United States Pharmacopoeia (USP).

In April 2001, AAPS, FDA and USP co-sponsored a workshop on Assuring Quality and Performance of Sustained and Controlled Release Parenterals in Washington, DC. This very successful workshop brought together scientists from industry, academia and the regulatory authorities to review, discuss and debate formulation, processing and manufacture of sustained and controlled release parenterals, and to identify critical process parameters and their control. Areas were identified where research is needed in order to understand the performance of these drug delivery systems and to assist in the development of appropriate testing procedures. Recommendations were made for future workshops, meetings and working groups in this area. A full report of the

US workshop is available in the referenced *AAPS PharmSci* article.¹

The European Workshop reported here followed on from the US workshop and specifically brought the European regulatory viewpoint as well as focusing on some of the areas identified in the US workshop that required further debate and discussion (such as, particle size analysis, stability, sterility and new excipients). This workshop report covers dispersed systems (microspheres, liposomes, gels and suspensions) as well as implants of small molecule and protein/peptide therapeutics for human and animal use. The goals of the European Workshop were

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

The European workshop was divided into formal presentations and parallel breakout discussion sessions. The breakout sessions served to identify hot topics as well as future directions for regulatory activity and public standards. At the close of each breakout session, the moderators were asked to prepare a summary of the key points discussed in their session. This report represents a compilation of these summaries together with background information explaining the need for regulatory activity in this area. For further background information and in the case of issues where no substantive advances or changes in opinion had occurred since the 2001 US workshop report, the reader is referred to that report.¹ Since concerns and issues that were raised in different parallel sessions overlapped to a certain extent, this report is not divided by the breakout sessions, but rather by key issues.

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, manufac-

turing, and control issues and were divided by product (liposomes, microspheres/implants, gels/oil suspensions/emulsions, stability/sterility and new excipients). The second day centered on biopharmaceutic issues, including physiology of the parenteral routes, bioavailability and bioequivalence, in vitro release testing and the possibility of in vitro-in vivo correlation. The breakout sessions on the second day covered in vitro release issues, pharmacokinetic issues/animal models, and particle size and analytical approaches.

BACKGROUND

Controlled and sustained release parenteral drug delivery systems include liposomes, microspheres, suspensions, gels, emulsions, and implants. They are generally used to improve the therapeutic response by providing appropriate dosing strategies (this may be constant or pulsatile release). Such systems can be considered safer than conventional parenteral dosage forms since less drug is required and since the drug may be targeted to the in vivo site, avoiding high systemic levels. Due to the lower dosing frequency and simpler dosage regimes, patient compliance can be improved with these dosage forms. For example, microspheres and larger implantable devices can be used to modify release over periods of months to years. Liposomes may achieve targeted delivery both by passive and active means following intravenous administration and are utilized to target toxic drugs, such as anti-cancer agents, to avoid systemic side effects.

A controlled release parenteral dosage form is usually selected when there are problems associated with oral delivery (eg, gastric irritation, first pass effects or poor absorption) and a need for extended release and/or targeted delivery (eg, rapid clearance, toxic side effects). The CR dosage form selected may be dependent on the desired effect (eg, long term localized release) as well as compatibility of the drug with the manufacturing process. Examples of applications for CR parenteral delivery include: fertility treatment, hormone therapy, protein therapy, infection treatments (antibiotics and antifungals), cancer therapy, orthopedic surgery and post-operative pain treatment, chronic pain treatment, vaccination/immunization, treatment of CNS disorders, and immunosuppression.

CR parenterals are often complex formulations and therefore present significant challenges to the development of regulations and standards. Attendees at this con-

ference repeatedly expressed the urgent need for regulatory standards for these products. Of particular concern was the need for standards for in vitro release methods and for guidance on in vivo release testing and in vitro - in vivo correlation/prediction. Other key issues identified at this workshop include: stability, sterility and particle size analysis and excipients (in particular the need for new polymers).

Approved CR parenteral products are listed in Table 1.

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

IN VITRO RELEASE METHODS

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

Research was encouraged to ensure a scientific basis for the development of different tests, procedures (including apparatus) and acceptance criteria. It was agreed that general approaches to in vitro testing could be modified, as appropriate, for specific products. For example, a given product may have specific requirements with respect to media, sampling interval, apparatus or temperature.

Discussants agreed that the choice of dissolution testing method and media needs to be justified and should take into account in vivo release and absorption in order to allow for correlation/prediction between in vitro and in vivo results. Dissolution methods must discriminate between batches with respect to manufacturing variables that can impact on bioavailability. The method must show batch-to-batch consistency/variability, be able to monitor product stability with time, evaluate the effect of process changes, and demonstrate acceptability for use. The need for accelerated testing was discussed.

Table 1. Approved CR Parenteral Products (not intended to be complete)

| Trade Name | Active Ingredient | Approval Date* |
|--------------------------------|--------------------------|-----------------------|
| <i>Suspension Products:</i> | | |
| Depo-Medrol | Methylprednisolone | pre-1982 |
| Depo-Provera | Medoxyprogesterone | pre-1982 |
| Celestone Soluspan | Betamethasone | pre-1982 |
| Insulin | Lente Unltralente NPH | pre-1962 |
| Plenaxis | Abarelix | 2003 |
| <i>Microsphere Products:</i> | | |
| Lupron Depot | Leuprolide | 1989 |
| Sandostatin LAR | Octreotide | 1998 |
| Nutropin Depot | Somatropin | 1999 |
| Trelstar Depot | Triptorelin | 2000 |
| Plenaxis | Abarelix | 2003 |
| <i>Liposome Products:</i> | | |
| Doxil | Doxorubicin | 1995 |
| Daunoxome | Daunorubicin | 1996 |
| Ambisome | Amphotericin B | 1997 |
| Depocyt | Cytarabine | 1999 |
| <i>Lipid Complex Products:</i> | | |
| Ambelcet | Amphotericin B | 1995 |
| Amphotec | Amphotericin B | 1997 |
| <i>Implant Products:</i> | | |
| Norplant | Levonorgestrel | 1990 |
| Gliadel | Carmustine | 1996 |
| Zoladex | Goserelin | 1989 |
| Viadur | Leuprolide | 2000 |

*Approval dates refer to the date of approval by US FDA.

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 1 and 2 suffer from problems with sample containment and although this can be overcome by use of a sinker for monolithic depots and dialysis tubing to contain dispersed systems (such as, microspheres), these solutions in themselves create additional problems. For example, microsphere aggregation due to confinement in the dialysis tubing, and uneven dissolution from the sides of monolithic depots associated with the sinker device. Violation of sink conditions may also result from confinement within dialysis tubing. Another concern is the large volume required with apparatus 1 and 2, which may not be relevant for small volume parenterals injected subcutaneously (sc) or intramuscularly (im).

USP apparatus 5 (paddle over disc), 6 (cylinder) and 7 (reciprocating holder) were designed for the transdermal route and do not offer any advantages for parenteral delivery systems. USP apparatus 3 (reciprocating cylinder) and 4 (flow through cell) were designed for extended-release oral formulations. These latter two methods may be the most relevant to CR parenterals and may be suitable following appropriate modification. Some researchers have noted evaporation problems with apparatus 3. Alternative apparatus, such as small sample vials and vessels, with and without agitation, are currently used for CR parenterals. However, problems are associated with these alternative apparatus, including lack of sink conditions and sample aggregation.

Participants agreed that USP apparatus 4 was the most suitable of the currently available USP apparatus for controlled and sustained release parenterals. This apparatus allows flexibility in volume, sample cell, flow rate and can be modified for specific product applications (such as the avoidance of aggregation problems and of potential violation of sink conditions). However, some

users noted problems with the USP 4 apparatus in terms of robustness under extreme conditions applied for accelerated testing. Examples of robustness problems were O-ring failure and filter blockage leading to variable flow rates, as well as polymer migration resulting in valve problems. These problems were product-specific and it appeared that they could be overcome by suitable method alteration (eg, solvent change) and apparatus modification with parts that could withstand the desired operating conditions (such as high temperature).

Method Development

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

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

Sink Conditions: Attendees 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. It was generally agreed 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.

Extent of In Vitro Release: In general, it was considered that in vitro release of over 80% is desirable, from both an economical and a safety standpoint. When it is meant that 80% of the declared content of over 80% is desirable, this is not the case for products that can be removed. In this case it is merely an economical standpoint and not a safety standpoint. It was stressed that in vitro release methods should allow determination of mass balance. Poor mass balance as well as variability in release data is often a problem with protein formulations (eg, human growth hormone in poly(lactic-co-glycolic) PLGA microsphere products). This can be due to acid degradation of the protein as a consequence of PLGA breakdown into acidic byproducts (lactic and glycolic acid). Protein degradation may also be a result of exposure in the test media with time due to the long-term release profiles of these products (weeks to months). Degradation in the release media can also be a problem for other relatively unstable drugs. This can be overcome by frequent media change or by measurement of the concentration of drug remaining within the product rather than the concentration in the release medium. It was stressed that for protein formulations, in vitro release methods should account for mass balance with respect to bioactivity. It was agreed that to overcome problems associated with acid degradation of proteins in PLGA formulations, alternative polymers and/or PLGA formulations with buffering capacity are required. In addition, attendees raised serious concerns over delayed immune reactions with degradation of controlled release protein formulations.

Attendees noted that microbial degradation could occur during real time test despite the presence of sodium azide. This can be overcome by periodically removing and replacing the release media.

“Burst Release”: Attendees agreed that the term “burst release” must be defined as it is being used extensively to describe different situations. The duration of the burst should be noted and the efficacy and safety window must be stated to determine significance for a particular drug product. The relationship between in vitro and in vivo burst effects should be described. One of the participants described a case where no burst was observed in vitro, but a significant burst was found in vivo. Discussants suggested that scientific rationale for such observations should be sought.

Development of IVIVC for CR Parenterals

Attendees agreed that IVIVC was very important in the development process of CR parenterals (eg, to assist in formulation development and setting dissolution specifications) as well as for consideration of biowaivers in the presence of scale-up and post-approval changes (SUPAC). At the 2001 US workshop the possibility of IVIVC for controlled release parenterals was discussed, but there were no reports of successful IVIVC at that time. However, at the 2003 European meeting several researchers reported successful IVIVC for a range of controlled release parenteral products. This is an indication of the high level of activity in this area in the past two years. 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 versus extended release products). Similarly, in vitro release methods and media are likely to vary depending on the product and should be developed based on in vivo relevance. Discussants stressed that both in vitro and in vivo measurements must be justified scientifically. Examples were discussed where time shifting and/or scaling was used to establish IVIVC using linear as well as non-linear correlations.

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 requesting biowaivers in the regulatory setting. Instead, bio-relevance should be developed using human data. Nevertheless, IVIVC modeling using animal data was considered suitable for "proof of principle" for initial research purposes and establishment of in vitro release specifications.

IVIVC must be validated by estimating the magnitude of error in predicting in vivo bioavailability. The percent prediction error (%PE) is calculated for predicted versus observed C_{max} and AUC (obtained from the IVIVC model and dissolution profiles for various formulations). The %PE must be less than or equal to 10% for the mean absolute prediction error, and must be less than or equal to 15% for all formulations.

What Is Needed to Support Changes?

Attendees discussed what is needed to support changes. It was suggested that for changes such as manufacturing site changes, along with sterility tests, in vitro characterization may be sufficient with a well defined IVIVC. For an excipient change the situation is more complex. The role of the excipient in the formulation is critical as

is its effect on release and there is also the possibility of tissue incompatibility. The rationale of what is needed to support changes must be determined primarily by science.

Use of Animal Models in Release Testing

Readers are referred to 'use of animal models in release testing' section in the 2001 workshop report,¹ as this issue was not discussed in length at the European workshop.

Accelerated In Vitro Release Testing

While real time in vitro release tests are necessary to gain a mechanistic understanding of drug release and to help in formulation design, accelerated tests for controlled release parenterals are essential for quality control purposes since real time release tests are of the order of weeks to months (product specific). Accelerated tests should be predictive of real time tests and they should be designed as early as possible in the development process in order to accrue sufficient data to underline the relationship between real time and accelerated tests. It was agreed that as much as possible, accelerated tests as well as real time tests should be bio-relevant. Parameters that can be altered to achieve accelerated release include: temperature, solvent, ionic strength, pH, enzymes, surfactants and agitation rate. It was suggested that specifications for accelerated release should include an early time, the mid-point and > 80% release (when it is meant >80% of the cumulative amount released I agree, when it means >80% of the declared content I do not agree. In this case it is only correct when the product actually releases more than 80% of the declared content during its lifetime) with a tolerance in the order of $\pm 10\%$ (also the tolerance should be bio-relevant without restricting to numbers). A depending test was suggested such as particle size determination. For prediction between accelerated and real time release, it was suggested to use the time to plateau of release at approximately 100% and determine whether a relationship can be established for products with different real time release rates (eg, products where release plateaus at approximately 100% in real time at 1, 3 and 6 months). It was also suggested to investigate whether a relationship exists between in vitro accelerated release and in vivo release.

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.

Attendees discussed the initial “burst” release associated with some CR parenterals and how to account for this in accelerated testing. When a CR parenteral delivery system produces an initial burst release, accelerated release tests may need to be augmented by an initial “real time” study that allows adequate assessment of this burst.

STABILITY

In addition to drug stability, attendees noted the importance of both “inactive” ingredient stability and product stability for controlled and sustained release parenterals. The reader is advised to refer to this section in the 2001 US workshop report.¹

PARTICLE SIZE

Particle size and size distribution are important specifications for dispersed system controlled release parenteral products (such as emulsions, microspheres, liposomes and other suspensions) as size and size distribution can affect release rates, bioavailability, targeting, syringability, suspension properties and therefore content uniformity. Attendees requested guidance on particle size specifications for these products as well as on particle sizing instrumentation and techniques.

Participants agreed that there was a great need for fast, reliable/validated analytical methods for particle sizing of dispersed system CR parenterals for use in research and development as well as in manufacturing quality control. There are many methods available for particle sizing [such as, centrifugation, sedimentation, analytical ultracentrifugation, electrical conductivity, microscopy (light and electron), dynamic light scattering, static light scattering, laser diffraction, light obscuration, electrical zone sensing, permeability, field flow fractionation, small angle x-ray and neutron scattering, and sieving]. However, the inherent differences in what is being measured and the requirements of most instruments for data modeling result in inconsistencies between instruments in reported mean particle size and size distributions for a given sample. Different instruments report data as number, weight and/or Z-average, resulting in large differences in reported mean size. For example, dynamic light scattering measures diffusion rather than size for polydisperse samples producing a sum of exponentials weighted according to frequency and scattering intensity. These data are very sensitive to large particles and contamination such as dust and bubbles. Other sources of error in dynamic light scattering include:

temperature fluctuations, measurement duration, rheological properties, concentration range and particle shape.

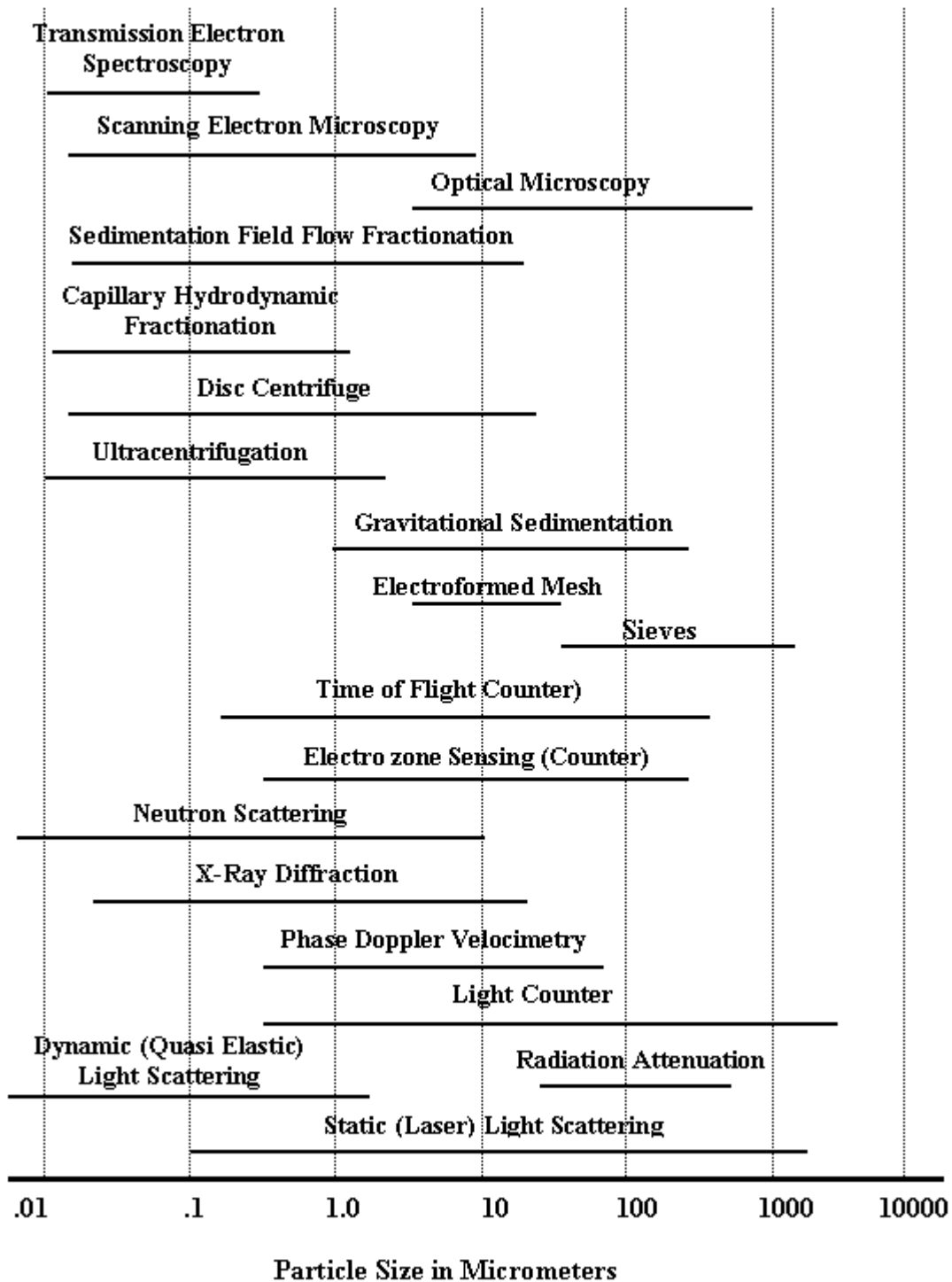
The same instrument and the same standard operating procedure must be used for quality control testing of a given product. This limitation can result in problems in scale up and in manufacturing site changes. Each of the different methods of size analysis have different limitations and different associated problems. For example, in freeze fracture microscopy different cut locations on the particle will result in different measured sizes.

Another problem is that the different instruments, with the exception of (electron) microscopy, do not cover the entire size range of dispersed delivery systems, which is from a few nanometers for micellar systems to 100 micrometers for large microspheres. (Table 2) This is of particular importance for systems with wide size distributions, where often more than one technique may be required to cover the entire size range mentioned above. Although microscopical analysis could be used for such products, this is a cumbersome method and validation is not trivial, particularly for electron microscopy. The use of more than one sizing technique is not only burdensome but results in problems in terms of inconsistencies in sizing between different techniques making validation difficult. Particle size distributions in the size range of roughly 500 to 1000 nm are best measured by microscopy as this range falls outside the measuring range of other techniques such as light scattering, electrical conductivity and light obscuration. Below and above this size range methods such as, light scattering, light obscuration and sedimentation can provide relatively reliable, cheap and fast alternatives to the microscope. However, for wide particle size distributions, and bimodal or multimodal size distributions analysis using scattering techniques has reduced reliability and therefore systems that measure signals of individual particles are more valuable.

Processing Issues Related to Particle Size

It is important to understand particle size and size distribution of CR parenterals with respect to processing. For example, the size distribution of microspheres for the final product should be the same as that used for clinical batches. In addition, QC controls with appropriate validation are needed to determine whether segregation occurs during processing and if so methods to avoid/overcome this problem must be developed. It is also important to make an early decision with respect to the final presentation since this can affect specifications for particle size distribution. For example, a pre-filled

Table 2. Comparison of Particle Size Ranges



syringe may aid reproducibility with respect to products with the potential to segregate during storage.

STERILIZATION, STERILITY ASSURANCE AND FOREIGN PARTICULATE MATTER

Sterilization and Sterility Assurance

Although a large battery of sterilization options exists including: traditional (moist and dry heat, radiosteriliza-

tion, filtration, and irradiation), as well as emerging methods (plasma treatment and supercritical fluid treatment), the choice is often limited for CR parenterals and the method is usually selected on a case-by-case basis. CR parenterals are complex products often involving complex manufacturing processes that preclude traditional methods of sterilization. The group agreed that heat sterilization is the preferred sterilization method for CR parenteral products; however, both dry and moist heat often cause degradation and/or hydrolysis of the excipients/polymer materials used in controlled release parenterals. The glass transition temperatures (T_g) of polymers and/or lipids used are often below the temperature required for heat sterilization. Consequently, these products would breakdown if subjected to heat sterilization. However, a participant reported that autoclaving may be possible on a case-by-case basis. Whether this means that there are new excipients coming into the market or there are improvements in the technique online was not explained. In addition to excipient instability, many of the drugs used in CR parenteral products are heat sensitive.

Another conventional sterilization technique is irradiation. However, this method is risky as it can cause changes in the properties of excipients used in CR parenterals. Gamma-irradiation is being tested at present for some products, but participants were hesitant about this approach since product breakdown (eg, via polymer degradation) is a potential problem. It should be noted that this is highly product dependent. A general consensus was reached that post-irradiation characterization was needed. Product integrity must be demonstrated (eg, maintenance of polymer weight pre- and post-irradiation). Since polymer degradation can affect both polymer molecular weight and glass transition temperature (T_g) and these, in turn, can affect drug release characteristics (both immediately and on storage), it was proposed that release changes must be documented both immediately following gamma irradiation and during storage. Furthermore, the use of an overkill cycle of gamma-irradiation to produce material for preclinical toxicology studies was proposed.

CR parenterals typically involve complex manufacturing processes that may complicate aseptic processing. However, due to the problems, noted above, that can be associated with sterilization techniques these products are most often produced by aseptic processing. This procedure means that sterility is systematically built into a product. The formulation components, the container, and the closure are subjected to sterilization processes separately and are then brought together. In the case of liposomes, when possible, the liquid formulation is passed

through a sterilizing filter. This is of course restricted to liposomes of small size and to dispersions of low viscosity. When these properties are not met, the whole production process has to be carried out under aseptic conditions. A very important factor during aseptic processing is the reduction and control of bioburden of the excipients used. Another very important factor is that the environment during the whole production chain is maintained at extremely high quality.

Foreign Particulate Requirements

The reader is referred to the 2001 US report.¹

QUALIFICATION OF NEW BIOPOLYMERS

The use of new excipients and in particular, new polymers was discussed. Discussants were concerned about the need for new biopolymers and it was suggested that a process be established on how to qualify new biopolymers and other excipients. Current guidances were reviewed and researchers are advised to consult the published guidelines and guidances. IPEC, the International Pharmaceutical Excipients Council, an industry association made up of manufacturers and consumers of excipients has developed and published guidelines for safety testing (see <http://www.ipec.org>). Recently the US FDA has published for comment a guidance for preclinical safety testing of excipients (see <http://www.fda.gov>). Full development of an ingredient (intended for chronic use in patients) is a long (5-6 years) and costly (20-30 M£) operation, whereas the development of new grades of materials is a quicker and far less risky operation.

Although only medicinal products as a whole (and not excipients alone) are accepted for assessment and eventual approval by the regulatory authorities, a Drug Master File (DMF) system (at present being updated) exists in the USA, which allows submission of a data package to the FDA. A new drug application (NDA) file can make reference to relevant DMFs. In the European Union (EU), DMFs only exist for active pharmaceutical ingredients, and there is currently no possibility of establishing this system for excipients. Japan is working towards a DMF system, allowing submission of quality (chemistry, manufacturing, and controls) and safety data for actives, excipients and products. At this time, the EU and Japan only allow for submission of data on a new excipient or new use of an excipient in the framework of a new drug product file.

In the field of sustained/controlled release parenterals a number of PLA-GA polymer ingredients have been accepted and are in use for registered medicinal products

in combination with various active ingredients. This track record affords a “safety comfort level” for subsequent product development with the polymer that limits chances for failure in regulatory acceptability. However, no comprehensive safety data package exists for each individual polymer. This translates into similar requirements regarding a known or a new polymer in combination with an active ingredient.

Discussants suggested some strategic approaches to help bring new excipients into use in pharmaceutical field. These may include: targeting a “high need” therapeutic area; developing a base package of (short term) safety data sufficient for clinical trial purposes; creating interest in the new ingredient to open up the possibility for “full scale” development; and in the area of polymers it was suggested to consider developing a “family” concept, whereby based on experimental design some matrix type safety testing could be envisaged in order to obtain a general acceptance. For example, one could envision polymers having the same bio-degradation pathways leading to identical metabolites. Final approval of an individual pharmaceutical product will of course have to cover the specific ingredient used (composition, grade, etc).

The following general strategy was proposed for a product containing a new excipient: 1) build a development plan based on available data and guidance, 2) seek scientific advice from the regulators, and 3) look for business alliances. Once regulatory approval of a product containing a new excipient is achieved, then it would be wise to expand the field of application. In certain cases a consortium approach can be highly efficient (cost and risk sharing, as well as joining expertise).

Participants discussed quality requirements for excipients used for controlling drug release from parenterals, such as those that are given in the general monograph of the European Pharmacopeia “substances for pharmaceutical use”. When different grades of an excipient exist with, for example, functionality-related characteristics, the requirements of the monograph will apply to all. The specified requirements in the monograph have to be met by the excipient throughout its shelf-life. It was agreed that a novel excipient should be regarded in the same way as a new active substance and the specifications covering storage conditions and shelf-life have to be based on scientific data established by the manufacturer.

Attendees agreed that a reproducible quality of all the starting materials, including release-controlling excipients/polymers, must be achieved. However, it is important to understand that the functioning of an excipient may be dependent on both manufacturing processes and formulation. Therefore, during the development of CR

parenterals it is essential to explore whether standardization of the excipient/polymer is enough or whether there are other factors (eg, processing parameters) that influence excipient functionality. The stability of the excipients in a product must be optimized during product development and thereafter it should be followed indirectly by functionality-related tests both *in vitro* and *in vivo*.

Attendees discussed the need for monographs on polymer excipients. No conclusion was reached. However, attendees agreed that PLGA and other polymers need to be standardized. The excipient used in the beginning may be well characterized but this may be replaced later with a PLGA from a different source or from the same source with different characteristics. It is important to know the molecular weight range of the original PLGA and understand how critical this is to product performance.

RESIDUAL SOLVENTS

The reader is referred to the 2001 US report.¹

RECONSTITUTION AT THE TIME OF USE

The reader is referred to the 2001 US report.¹

SYRINGEABILITY AND INJECTABILITY

The reader is referred to the 2001 US report.¹

The need for more research on injectability was discussed. Needle depth, force, volume, sedimentation of suspensions, and tissue compatibility are all critical issues that require investigation to establish their significance. Attendees agreed that with respect to tissue compatibility, animal histology studies rather than cell culture studies are needed.

RE-SUSPENDABILITY

The reader is referred to the 2001 US report.¹

NOMENCLATURE

The reader is referred to the 2001 US report.¹

HOW ARE SPECIFICATIONS SET?

The reader is referred to the 2001 US report.¹

DOSAGE FORM SPECIFIC ISSUES

Gels, Oil-Suspension and Emulsion

It was generally agreed, that gels, oil-suspensions and emulsions in sustained and controlled release parenterals, although sometimes considered old-fashioned, do have an important role to play as pharmaceutical dosage forms. Compared to more advanced formulations they have the advantage of relative ease of processing using well established technology.

The basic parameters for quality assessment of gels, oil-suspensions and emulsion formulations were discussed. These include: 1) drug oil/water partition coefficient; 2) affinity constant for any polymer/drug interaction; 3) particle size/particle size distribution; 4) release characteristics; and 5) spreading at the site of administration (sc and im).

Discussants agreed that it was important to determine the significance of the precision of administration. For example, what difference does it make if an injection is given inter-muscularly rather than intra-muscularly? Is the bioavailability of the drug affected if the injection is into fatty tissue rather than into a lean tissue?

Attendees agreed that the effect of thin needles on formulation stability should be investigated. With the trend towards thinner needles to improve patient compliance, this requires less viscous formulations and reduced particle size for dispersed systems. A special concern is the characteristics of the interior of the needle, the surface structure of which may be damaging to the formulation.

Liposomes

The possibility of generic liposome products was discussed. Due to the complexity of these products, it was not clear how therapeutic equivalence could be shown other than by clinical efficacy trials. This is an area that requires research as well as further discussion.

Discussants raised concern over liposome "kits" that require loading drug into empty liposomes in the pharmacy setting (mixing, heating, incubations). Although the use of these kits circumvents problems related to leakage of drug during storage, it is not an ideal practice as mistakes might happen. These kits require extensive validation in the settings where the drug will be used (hospital pharmacies, group practices) as well as a fail-safe assay to confirm proper drug loading prior to the administration to patients.

Discussants raised concern over the multi-faceted issue of liposome stability. Liposome stability encompasses: changes in colloidal character such as aggregation; the

potential for release of hydrophilic drugs into the medium; and chemical degradation (such as peroxidation and hydrolysis) of the lipids. Some participants pointed out the importance of factors such as storage temperature and pH on liposome stability.

Microspheres

Attendees agreed that it is important to evaluate microsphere injection sites for possible histological changes using animal models. Acute and chronic inflammatory responses, fibrous encapsulation, the presence of foreign body giant cells as well as tissue necrosis should be evaluated. Attendees noted that injection volume and the amount of microspheres can affect the tissue response.

BIOAVAILABILITY, BIOEQUIVALENCE AND PHARMACEUTICAL EQUIVALENCE

Participants discussed the approach of using pharmacokinetic studies to determine bioavailability and/or establish bioequivalence of sustained and controlled release parenteral products. For assessment of bioavailability and bioequivalence, regulatory recommendations from the US FDA have primarily relied on the pharmacokinetic approach whenever feasible. The prime factors for choosing one approach over another are accuracy, sensitivity and reproducibility of the measures. Accordingly, in descending order of preference, the following approaches have been used for determining the bioavailability and bioequivalence of a drug product: 1) pharmacokinetic studies in humans; 2) acute pharmacological effects in humans; 3) well-controlled clinical trials; and 4) in vitro tests that ensure in vivo bioavailability.

To qualify the pharmacokinetic approach, it must be possible to measure drug concentrations in an accessible fluid (eg, blood/plasma). There must be a known relationship between drug levels in the measurable fluid and those at the site of action. A specific, sensitive and reproducible analytical method must be available. In addition, it is essential to assess the rate and extent of drug availability as determined by systemic exposure using concentration-time profiles. C_{max} only denotes the maximum concentration of the profile and does not provide rate of input, but it has clinical significance in terms of safety and/or efficacy of the drug product.

Attendees discussed the difficulties of demonstrating pharmaceutical equivalence for certain sustained or controlled release parenteral products, in particular, therapeutic proteins and liposomes. Proteins are complicated since the currently available physicochemical tests may not be able to determine their structures and biological

assays lack sensitivity in detecting small changes and often do not measure the intended mechanism of action (clinical activity). Furthermore, proteins suffer from inherent microheterogeneity, containing multiple isoforms and impurities. As for liposomes, these drug products are unique compared to other drug products in that physicochemical characterization tests are currently required for the drug product (in addition to the drug substance) to ensure batch-to-batch product quality.

Based on regulatory definitions, there are two important factors that need to be considered when assessing bioavailability and/or bioequivalence of a drug product; namely, the release of the active ingredient from the drug product; and the availability of the drug at the site of action. In this context, the participants expressed concern regarding the use of blood measurement for determination of bioavailability and/or bioequivalence of a liposome drug product. There is much uncertainty as to when and where the encapsulated drug is released from controlled release parenteral systems, such as liposomes, *in vivo*, as well as whether the drug concentrations in the blood can predict the levels at the site of action. This is dependent on the nature of the liposome as described below.

The attendees discussed the classification scheme for liposomes according to their uptake by the mononuclear phagocytic system (MPS) or the reticuloendothelial system (RES) in the body. In theory, assessment of bioavailability/bioequivalence may be based on the type of liposomes if this classification scheme is feasible. For a liposome product designed to be taken up by MPS, the drug will be accumulated in the MPS shortly after injection and the MPS may act as the depot site for the drug to release back to the systemic circulation. Under such conditions, it is postulated that the drug concentrations measured in the blood may be used for determination of bioavailability and bioequivalence. In contrast, for liposomes that are designed to avoid MPS uptake, the encapsulated drug will be circulating in the bloodstream for a long time. Although these liposomes may eventually extravasate into the tissue and release the drug at specific sites, it is not clear if all of the drug will be delivered to the site of action. Under such circumstances, measurement of drug concentrations in the blood/plasma, albeit feasible, may not be an effective means to forecast the drug concentrations in the tissue at any time. Yet, in most cases, a liposome drug product may not be classified in either category based on the above classification scheme.

As for microsphere and implant dosage forms, it is recognized that there is no problem of using blood measurement for assessment of bioavailability and bioequiva-

lence since the drug is readily available in the systemic circulation from these drug products. Participants discussed the clinical relevance of initial bursts that were often observed from these dosage forms. The initial burst of the drug may be a result of loss of surface-associated drug. Attendees indicated that the general practice is to minimize the initial burst to reduce associated drug wastage and more especially adverse reactions. The development of new polymers and improvements in manufacturing processes may help to remove/reduce initial burst release of a drug. However, in some cases high initial drug levels achieved from burst release may be essential to the therapeutic effect. In conclusion initial burst release must be determined and judged with respect to safety and therapeutic effect on a case-by-case basis.

The use of animal models is considered appropriate for exploring possible *in vitro-in vivo* correlations during drug development. However, animal models are not used for demonstration of bioavailability or bioequivalence in the regulatory setting.

SUMMARY

Attendees recommended that workshops or other meetings be organized to further discuss:

1. Particle size analysis (meeting was held in Washington, DC April 2003 and is planned to be held in Europe)
2. Regulatory pathway for new bio-polymers
3. Sterility assurance and testing (a meeting is planned for Washington DC December 2003)

There was a general consensus among discussants that the following issues needed more focus:

- Identification of product characteristics that are critical for the therapeutic effect
- IVIVC
- *In vitro* methods for testing drug release and spreading characteristics
- Accelerated stability tests that can be used to predict storage effects under non-accelerating conditions.
- Formulation design and stability with respect to injectability

REFERENCES

1. Burgess DJ, Hussain AS, Ingallinera TS, Chen M. Assuring quality and performance of sustained and controlled release parenterals. *AAPS PharmSci* 2002; 4(2): article 7. Available at: <http://www.aapspharmsci.org/view.asp?art=ps040207>.