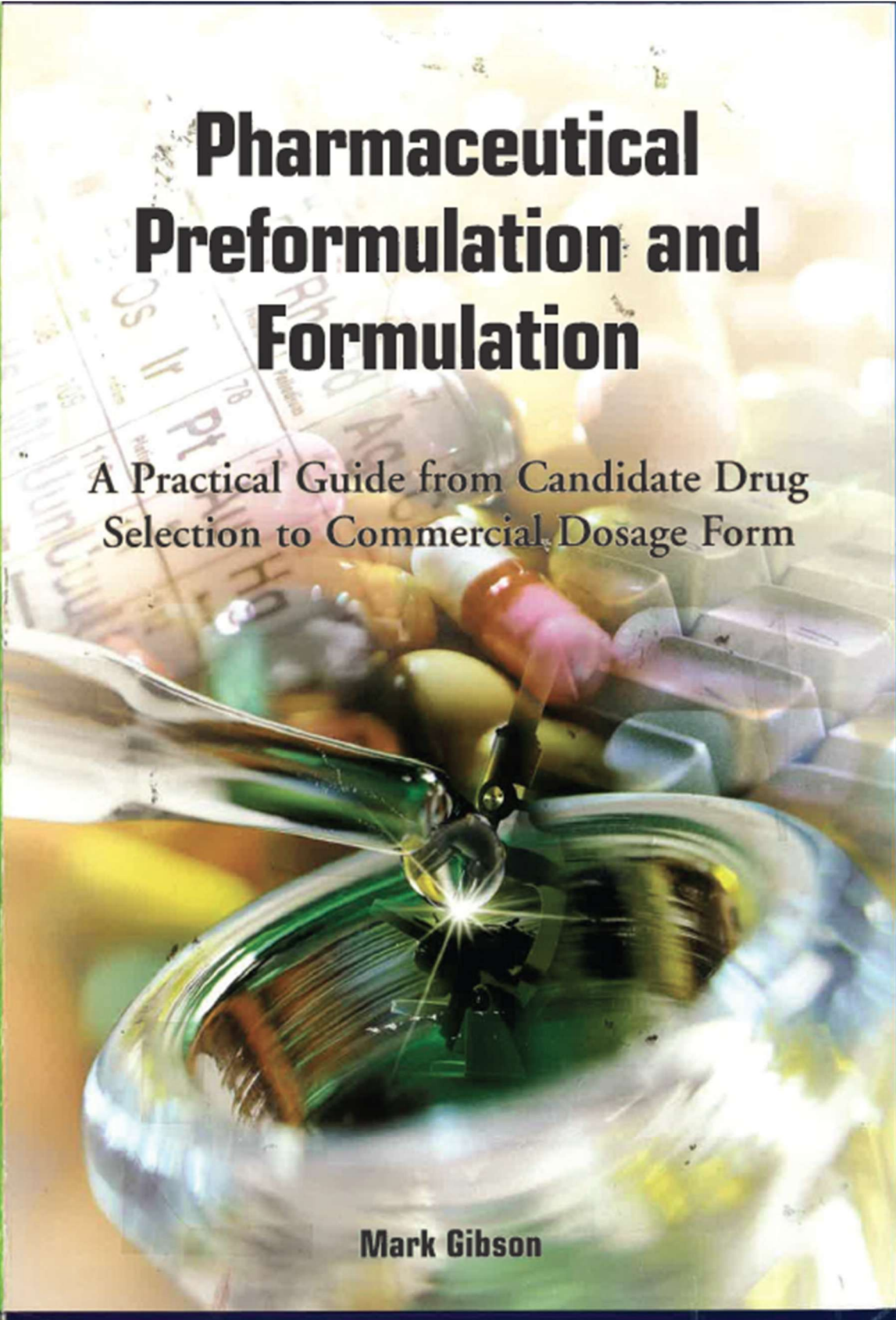




Pharmaceutical Preformulation and Formulation

A Practical Guide from Candidate Drug
Selection to Commercial Dosage Form

Mark Gibson

Pharmaceutical Preformulation and Formulation

A Practical Guide from Candidate Drug Selection to Commercial Dosage Form

RS 200
.P425
2001
COPY 1

PHARMACEUTICAL PREFORMULATION AND FORMULATION

**A Practical Guide from
Candidate Drug Selection to
Commercial Dosage Form**

Mark Gibson

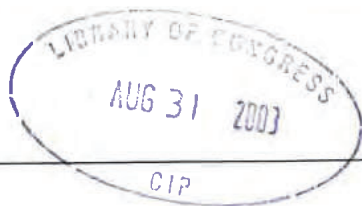
Editor



IHS[®] Health Group

An IHS[®] GROUP Company

Your Enterprise Solution to
Global Healthcare Knowledge



Invitation to Authors



IHS® Health Group publishes books focused upon applied technology and regulatory affairs impacting healthcare manufacturers worldwide. If you are considering writing or contributing to a book applicable to the pharmaceutical, biotechnology, medical device, diagnostic, cosmetic, or veterinary medicine manufacturing industries, please contact our director of publications.

Library of Congress Cataloging-in-Publication Data

Pharmaceutical preformulation and formulation : a practical guide from candidate drug selection to commercial dosage form / Mark Gibson, editor.

p. ; cm.

Includes bibliographic references and index.

ISBN 1-57491-120-1 (hard : alk. paper)

1. Drugs—Dosage forms. I. Gibson, Mark, 1957—

[DNLM: 1. Drug Compounding. 2. Biopharmaceutics—methods. 3. Chemistry, Pharmaceutical—methods. 4. Dosage Forms. 5. Drug Evaluation. QV 778 P53535 2001]

RS200 .P425 2001

615'.14—dc21

2001016816

Commissioned in Europe by Sue Horwood of Medi-Tech. Publications, Storrington, England, on behalf of IHS® Health Group, Denver, Colorado, USA. General Scientific Advisor: Dr. Guy Wingate, UK Quality Manager, Computer Systems Compliance, Secondary Manufacturing, Glaxo Wellcome, Barnard Castle, England.

10 9 8 7 6 5 4 3 2 1

ISBN: 1-57491-120-1

Copyright © 2001 by IHS® Health Group. All rights reserved.

All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Printed in the United States of America.

Where a product trademark, registration mark, or other protected mark is made in the text, ownership of the mark remains with the lawful owner of the mark. No claim, intentional or otherwise, is made by reference to any such marks in this book.

While every effort has been made by IHS® Health Group to ensure the accuracy of the information contained in this book, this organization accepts no responsibility for errors or omissions.

IHS® Health Group
15 Inverness Way East
Englewood, CO 80112-5776, USA

Phone: +1-303-662-9101
Fax: +1-303-754-3953
Orders/on-line catalog:
www.ihshealthgroup.com

CONTENTS

Preface	vii
Contributors	ix
1. Introduction and Perspective	1
<i>Mark Gibson</i>	
Drug Development Drivers, Challenges, Risks and Rewards	2
Current Trends in the Pharmaceutical Industry	6
Lessons Learnt and the Way Forward	8
Scope of the Book	10
References	11
 PART I: Aiding Candidate Drug Selection	
2. Aiding Candidate Drug Selection: Introduction and Objectives	15
<i>Mark Gibson</i>	
Stages of the Drug Discovery and Development Process	15
Summary	20
References	20
 3. Preformulation Predictions from Small Amounts of Compound as an Aid to Candidate Drug Selection	21
<i>Gerry Steele</i>	
Initial Physicochemical Characterization	22
Initial Solubility	28
Initial Stability Investigations	34
Crystallinity	41
Crystal Morphology	46
Hygroscopicity	48
Salt Selection	49
Methods for Evaluating Physicochemical Properties	58
Concluding Remarks	87
Acknowledgements	88
References	88
	iii

4.	Biopharmaceutical Support in Candidate Drug Selection	97
	<i>Anna-Lena Ungell and Bertil Abrahamsson</i>	
	Drug Dissolution and Solubility	100
	Luminal Interactions	111
	Absorption/Uptake over the GI Membranes	117
	Models for Studying the Absorption Potential of Drugs	118
	Permeability Coefficients versus F_a	134
	<i>In Vivo</i> Techniques for Studies in Man	135
	Vehicles for Absorption Studies	139
	Functional Use of Absorption Models	141
	References	143
	PART II: Early Drug Development	
5.	Early Drug Development: Product Design	157
	<i>Mark Gibson</i>	
	The Importance of Product Design	157
	Product Design Considerations	158
	Concluding Remarks	173
	References	173
6.	Preformulation as an Aid to Product Design in Early Drug Development	175
	<i>Gerry Steele</i>	
	Solid Dosage Forms	175
	Solution Formulations	196
	Freeze-Dried Formulations	210
	Suspensions	214
	Topical/Transdermal Formulations	215
	Inhalation Dosage Forms	217
	Compatibility	223
	References	228
7.	Biopharmaceutical Support in Formulation Development	239
	<i>Bertil Abrahamsson and Anna-Lena Ungell</i>	
	<i>In Vitro</i> Dissolution	241
	Bioavailability Studies	257
	<i>In Vitro/In Vivo</i> Correlations	269
	Animal Models	276
	Imaging Studies	279
	References	289
	PART III: From Product Design to Commercial Dosage Form	
8.	Product Optimisation	295
	<i>Mark Gibson</i>	
	Product Optimisation Purpose and Scope	295
	Excipient and Pack Optimisation Considerations	296

Sources of Information	304
Expert Systems	305
Experimental Design	309
Stability Testing	313
Developing Specifications	316
Process Design, Process Optimisation and Scale-Up	319
Validation and Launch	323
Acknowledgements	327
References	327
 9. Parenteral Dosage Forms	 331
<i>Joanne Broadhead</i>	
Guiding Principles for Simple Parenteral Solutions	332
Choice of Excipients	334
Sterility Considerations	336
Strategies for Formulating Poorly Soluble Drugs	336
Strategies for Formulating Unstable Molecules	340
Strategies for the Formulation of Macromolecules	342
Liposomal Delivery Systems	343
Sustained-Release Parenteral Formulations	343
<i>In Vitro</i> and <i>In Vivo</i> Testing Methods	346
Packaging of Parenteral Products	347
Manufacturing of Parenteral Products	348
Administration of Parenteral Products	350
Parenteral Products and the Regulatory Environment	351
References	353
 10. Inhalation Dosage Forms	 355
<i>Paul Wright</i>	
Lung Deposition	356
Particle Sizing	357
Dry Powder Inhalers	361
Metered Dose Inhalers	364
Nebulisers	372
Standards	374
Future	375
References	376
Bibliography	378
 11. Oral Solid Dosage Forms	 379
<i>Peter Davies</i>	
Powder Technology	381
Powder Flow	382
Mixing	388
Compaction	390
Solid Dosage Forms	403
Tablets	403
Hard Gelatin Capsules	441

Soft Gelatin Capsules	453
Summary	455
References	456
12. Ophthalmic Dosage Forms	459
<i>Mark Gibson</i>	
Ocular Topical Drug Delivery Issues and Challenges	460
Drug Candidate Selection	464
Product Design Considerations	465
Product Optimisation Considerations	473
Processing Considerations	482
Concluding Remarks	486
References	488
13. Aqueous Nasal Dosage Forms	491
<i>Nigel Day</i>	
Nasal Anatomy and Physiology	494
Formulation Selection Considerations	496
Device Selection Considerations	499
Regulatory Aspects	506
Special Considerations for Peptide Nasal Delivery	508
References	511
Additional Reading	513
14. Topical and Transdermal Delivery	515
<i>Kenneth A. Walters and Keith R. Brain</i>	
The Skin and Percutaneous Absorption	516
Drug Candidate Selection and Preformulation	534
Formulation	543
Concluding Remarks	567
Bibliography	567
References	569
Index	581

9

Parenteral Dosage Forms

Joanne Broadhead

AstraZeneca R&D Charnwood
Loughborough, United Kingdom

The dictionary definition of parenteral is non-enteral or non-oral and, therefore, strictly speaking, the term *parenteral* includes all products administered other than by the oral route. The pharmaceutical convention, however, is to use the term parenteral to describe medicines administered by means of an injection. The most common routes of parenteral administration are intravenous (IV), subcutaneous and intramuscular, but there are a variety of lesser used routes, such as intra-arterial. In addition, products such as subcutaneous implants are usually classed as parenterals.

There are, arguably, a greater variety of formulations administered by the parenteral route than by any other. These include emulsions, suspensions, liposomes, particulate systems and solid implants as well as the ubiquitous simple solution. What sets parenteral products apart from most other dosage forms, (with the exception of ocular products), is the absolute requirement for sterility, regardless of the formulation type. This requirement must be uppermost in the pharmaceutical scientist's mind from the first stages of formulation conception, so that the formulation and manufacturing process can be developed in tandem to produce an optimised sterile product.

This chapter aims to provide a practical guide to the development of parenteral products, initially reviewing the basic principles of formulating a straightforward parenteral solution. Subsequent sections will examine the formulation options available when a more sophisticated formulation is warranted, for example when the candidate drug exhibits poor aqueous solubility, is a macromolecule or requires a more sophisticated delivery system. *In vitro* and *in vivo* testing methods for parenteral products will be touched on and the chapter concludes with a discussion of the manufacturing and regulatory issues unique to parenteral products. While, of necessity, the individual topics will be covered only briefly, the objective is to

provide the reader with the basic information necessary to evaluate the formulation options available and to provide appropriate references to sources of further and more detailed information.

GUIDING PRINCIPLES FOR SIMPLE PARENTERAL SOLUTIONS

This section summarises the principles which should be followed when developing simple solution formulations; these, after all, comprise the majority of marketed parenteral products. The information presented has been gleaned from standard textbooks and references, but where appropriate an attempt has been made to summarise the industry “norms”. For further detailed information on the concepts discussed in this section, the reader is referred to Avis et al. (1992).

Selection of Injection Volume

Pharmacopoeias classify injectables into small-volume parenterals (SVPs) and large-volume parenterals (LVPs). The U.S. Pharmacopeia (USP) defines SVPs as containing less than 100 mL and LVPs as containing more than 100 mL. Many regulatory standards, for example, those for subvisible particulates, have first been developed for LVPs prior to their later application to all parenterals. SVPs can be given rapidly in a small volume; this type of injection is known as a bolus. They may also be added to LVPs, such as 5 percent dextrose and 0.9 percent sodium chloride infusion/injection, for administration by IV infusion. Some antibiotics are sold as LVPs, which eliminates the need for the extemporaneous addition of the drug to the infusion fluid prior to administration. The selection of bolus or infusion will depend on the pharmacokinetics of the drug and the distinction can be somewhat blurred. Infusions can be as brief as 15 minutes or may continue for several days. Generally speaking, if a medicament is to be administered by infusion, the simplest approach is to formulate it as a concentrate which will subsequently be diluted by the practitioner or pharmacist prior to administration.

Intramuscular or subcutaneous injections are almost always administered a bolus. Typically, the injection volume is less than 1–1.5 mL by the subcutaneous route and usually no more than 2 mL by the intramuscular route, although higher volumes (up to 4 mL) can be administered if essential (Ford 1988). Jorgensen et al. (1996) have shown a correlation between pain and the volume of a subcutaneous injection with volumes of 1–1.5 mL causing significantly more pain than volumes of 0.5 mL or less. Clearly, it is preferable to minimize injection volume wherever possible, particularly if chronic administration is anticipated. When the total volume to be administered cannot be reduced to an acceptable level, two or more injections at multiple sites may be required.

One of the first steps in the formulation of a solution product is, therefore, to select the administration volume and concentration. This may be dictated primarily by physiological considerations, such as maximum injection volume as discussed above, or by pharmaceutical considerations. For example, if solubility is low, a larger volume/lower concentration formulation may be required, whereas if stability is improved at higher concentrations, then the converse would be true.

pH and Tonicity Requirements

pH Considerations

Clearly, a parenteral product should be formulated with a pH close to physiological, unless stability or solubility considerations preclude this. Often, the pH selected for the product is a compromise between the pH of maximum stability, solubility and physiological acceptability.

The first step in selecting a suitable formulation pH will be the generation of pH/stability and pH/solubility profiles. This type of information is often available in the preformulation data package. The target pH for maximum physiological acceptability is approximately pH 7.4. In practice, however, a reasonably wide pH range can be tolerated, particularly when dosing is via the IV route, and dilution with blood is rapid. In these circumstances pHs ranging from 2 to 12 can be tolerated (although formulations at the extremes of this range are not recommended). The dilution rate is slower when administration is via the intramuscular route and decreases further when the subcutaneous route is used. For this reason, pH ranges of 3 to 11 and 3 to 6, respectively, are recommended for these routes (Strickley 1999). Many products are formulated at a slightly acidic pH because of solubility or stability considerations, and the vast majority of licensed products have a pH between 3 and 9. A pH outside this range should be avoided if possible, since a pH of greater than 9 can cause tissue necrosis, whereas a pH of less than 3 may cause pain and phlebitis (DeLuc and Boylan 1992). Nevertheless, products with extreme pH values are encountered; Dilantin Injection (phenytoin sodium) is formulated at pH 12, whereas Robinul Injectable (glycopyrrolate) is formulated at pH 2–3. Both products are for intramuscular administration. When a pH at the extreme of the acceptable ranges is necessary, and administration is via the subcutaneous or intramuscular route, it is advisable to conduct *in vivo* studies to assess the level of pain on injection (see the section “Pain”). An important consideration in terms of the tolerability of a formulation is its buffering capacity of; this may be more important than the pH *per se*. The pH of commercially available 0.9 percent w/v Sodium Chloride Infusion, for example, can be as low as 4, but the lack of any buffering capacity means that it will have negligible effect on the pH of the blood into which it is infused, even when administration is rapid.

The use of buffers often can (and should) be avoided if the active ingredient is itself a salt which can be titrated with acid or base to a suitable pH for parenteral administration. Buffers may legitimately be required when the pH must be controlled at that of maximum stability or solubility. In the former case, the buffer concentration should be kept to a minimum so that after injection, the buffering capacity of physiological fluids will outweigh the buffering capacity of the formulation. Where buffers are used to improve solubility, the buffer concentration may need to be a little higher to prevent precipitation after injection. *In vitro* models have been developed which can be used to screen formulations for the potential to precipitate after injection. These are discussed further in the section “*In Vitro* and *In Vivo* Testing Methods”.

The buffers most commonly encountered in parenteral products are phosphate, citrate or acetate. Phosphate is useful for buffering around physiological pH, whereas acetate and citrate are used when the required pH is lower. Table 9.1 summarises the buffers which are encountered in approved parenteral products. Typically, buffer concentrations are in the 10–100 millimolar range. In most cases, the sodium salts of acidic buffers are used, although potassium salts are occasionally encountered. Hydrochloride salts of basic buffers are usually used. It is preferable to avoid the combination of anionic drugs with cationic buffers (or vice versa) due to the risk of forming an insoluble precipitate.

Table 9.1
Buffers used in approved parenteral products.

Buffer	pH Range
Acetate	3.8–5.8
Ammonium	8.25–10.25
Ascorbate	3.0–5.0
Benzoate	6.0–7.0
Bicarbonate	4.0–11.0
Citrate	2.1–6.2
Diethanolamine	8.0–10.0
Glycine	8.8–10.8
Lactate	2.1–4.1
Phosphate	3.0–8.0
Succinate	3.2–6.6
Tartrate	2.0–5.3
Tromethamine (TRIS, THAM)	7.1–9.1

Data abstracted from Powell et al. (1998), Flynn (1980) and Strickley (1999).

Tonicity Considerations

Wherever possible, parenteral products should be isotonic; typically, osmolarities between 280 and 290 mOsm/L are targeted during formulation. Isotonicity is essential for LVPs, but again, a wider range of osmolarities can be tolerated in SVPs, since either rapid dilution with blood will occur after injection, or the product itself will be diluted with an LVP prior to administration. Hypertonic solutions are preferable to hypotonic solutions because of the risk of haemolysis associated with the latter. Fortunately, hypotonic formulations can be easily avoided by the use of excipients, often sodium chloride, to raise osmolarity. Mannitol, dextrose or other inert excipients can also be used for this purpose and may be preferable if the addition of sodium chloride is likely to have an adverse effect on the formulation. Gupta et al. (1994a), for example, found that the presence of 0.9 percent w/w sodium chloride reduced the solubility of their candidate drug (Abbott-72517.HCl) by a factor of 3. Tonicity adjusters frequently have dual functionality; for example, mannitol often functions both to increase the osmolarity and to act as a bulking agent in lyophilized formulations.

CHOICE OF EXCIPIENTS

As with all pharmaceutical products, the most important “rule” to bear in mind when formulating parenterals is the “keep it simple” principle. Wherever possible, formulations should be developed using excipients which have an established use in parenteral products administered by the same route as the product under development. Both the excipient concentration, rate

of administration and total daily dose should fall within the boundaries established by precedent in existing marketed products. The (U.S. Food and Drug Administration) FDA Inactive Ingredient Guide is a good place to start a search for information about a potential excipient, as it consists of an alphabetical list of all excipients in approved or conditionally approved drug products, and includes the route of administration of the products containing them. The *Physicians' Desk Reference* (PDR) provides an essential source of detailed information on products available on the U.S. market and includes the quantitative formulation of each product. This enables both the rate of administration and total daily dose of excipients in existing products to be calculated. The PDR can be obtained in a CD-ROM format which has a word search facility, thus providing a convenient means of searching for products containing a specific excipient. The PDR is also available in a web-based format, but unfortunately, this version does not have the word search capability. In addition to these reference sources, two excellent recent publications have specifically examined excipient usage in parenteral products on the U.S. market. Powell et al. (1998) have developed a compendium which provides a comprehensive list of excipients present in commercial formulations, together with their concentrations and the routes of administration of products containing them. Nema et al. (1997) carried out a similar review; their article presents the data as summary tables, enabling the frequency of use and concentration range of a particular excipient to be obtained at a glance. As this book goes to press, the first part of a review article entitled "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)" has been published in the *PDA Journal of Pharmaceutical Science and Technology* (Strickley 1999). This article provides information similar to the publications of Powell et al. and Nema et al., but collates the information in terms of formulation type and includes the structure of the active ingredients. It also lists the concentration of excipients administered following dilution as well as the concentration in the supplied preparation, thus saving formulators the trouble of performing these calculations themselves! Subsequent parts of this article are awaited with interest.

The information sources described above thus provide an invaluable resource to the parenteral formulator. The publications of Nema et al., (1997), Powell et al. (1998) and Strickley (1999) provide an instant, comprehensive and up-to-date reference source on U.S. licensed formulations, which can save the formulator many hours of trawling through the *Physicians' Desk Reference*! It is unfortunate that the same level of detail is not available for products outside the United States where manufacturers are not obliged to disclose the quantitative details of their formulations.

When considering the use of unusual excipients, or exceptionally high concentrations of "standard" excipients, it is important to bear in mind the indication for which the product is intended. An excipient which may be acceptable as a last resort in a treatment for a life-threatening condition should not be considered for a product to be administered chronically or for a less serious condition. A good example of this is the use of the solvent Cremophor EL in parenteral formulations of cyclosporin. This surfactant is associated with a range of toxic effects, and its use would not be envisaged unless all other more acceptable formulation strategies had been exhausted and the potential benefit of the treatment is such that the risk associated with the excipient is outweighed.

Another important consideration for excipients to be used in parenteral products is their quality, particularly in microbiological terms. Commonly used parenteral excipients can often be obtained in an injectable grade which will meet strict bioburden and endotoxin limits. Pharmacopoeial grades of other excipients may be acceptable, but it is prudent to apply in-house microbiological specification limits, where none are present in the pharmacopoeias. For non-pharmacopoeial excipients, the best approach is always to purchase the highest grade available and apply internal microbiological specification limits.

STERILITY CONSIDERATIONS

The requirement for sterility in parenteral products is absolute and must be borne in mind at all stages of formulation and process development. The regulatory environment now requires that parenteral products be terminally sterilized unless this is precluded, usually by reason of instability (see the section “Manufacturing of Parenteral Products”).

For a solution product, one of the earliest investigations carried out during formulation development will be a study of the stability to moist heat sterilization. The results of this study may impact the formulation selection; for example, the stability to autoclaving may be affected by solution pH. Where stability is marginal, attempts should be made through the formulation process to stabilize the product such that it can withstand the stresses of moist heat sterilization. The regulatory authorities will expect to see good justification for new products that are *not* terminally sterilized. In many cases, however, the product will simply not withstand the stresses associated with autoclaving, and in this case, the usual alternative is filtration through sterilizing grade filters followed by aseptic processing. For the formulation scientist, it is important to select a suitable filter early on in development and ensure that the product is compatible with it.

Whilst the vast majority of parenteral products are rendered sterile either by moist heat sterilization or by filtration through sterilizing grade filters, other methods of sterilization should be considered, particularly in the development of non-aqueous formulations or novel drug delivery systems. For implants, for example, gamma irradiation is an option that should be explored early on in development.

Preservatives should not usually be included in parenteral formulations except where a multidose product is being developed. The Committee for Proprietary Medicinal Products (CPMP) “Notes for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products” states that the physical and chemical compatibility of the preservative (or antioxidant) with the other constituents of the formulation, the container and closure must be demonstrated during the development process. The minimum concentration of preservative should be used, which gives the required level of efficacy, as tested using pharmacopoeial methods. Certain preservatives should be avoided under certain circumstances, and preservatives should be avoided entirely for some specialised routes. The guidelines also require that both the concentration and efficacy of the preservative are monitored over the shelf life of the product. In multidose injectable products, the efficacy of the preservative must be established under simulated in-use conditions. Table 9.2 shows some of the most commonly encountered preservatives in licensed products and their typical concentrations.

STRATEGIES FOR FORMULATING POORLY SOLUBLE DRUGS

Increasingly, formulation scientists are being asked to develop parenteral formulations of compounds with solubilities in the order of nanograms or micrograms per millilitre. This presents enormous challenges, particularly given the limited range of excipients which have been used historically in injectable products. This section briefly describes some of the strategies which can be considered and highlights some of the issues associated with each. For a more detailed review of this area, the reader is referred to the recent review by Sweetana and Akers (1996).

Table 9.2
Preservatives used in approved parenteral products.

Preservative	Typical Concentration (%)
Benzyl alcohol	1–2
Chlorbutanol	0.5
Methylparaben	0.1–0.18
Propylparaben	0.01–0.02
Phenol	0.2–0.5
Thiomersal	≤0.01

Data abstracted from Nema et al. (1999) and Powell et al. (1999).

pH Manipulation

As discussed in the section “Guiding Principles for Simple Parenteral Solutions”, the acceptable pH range for parenteral products is reasonably wide. Where the poorly soluble compound is a salt, pH manipulation may be all that is necessary to achieve adequate solubility. The potential for precipitation after administration should be considered when using this approach, however. When administration is via the intramuscular and subcutaneous routes, consideration must be given to the possibility of pain on injection, particularly when the product is intended for chronic use. This may preclude the use of pH extremes and favour alternative formulation strategies.

Co-solvents

Co-solvents are reportedly used in 10 percent of FDA approved parenteral products although the range is limited to glycerin, ethanol, propylene glycol, polyethylene glycol and N,N-dimethylacetamide (Sweetana and Akers 1996). Some marketed formulations containing co-solvents are shown in Table 9.1. The use of co-solvents is often one of the earliest options considered by the formulator when solubility is an issue. Quite often, mixtures of co-solvents are used so that the dose or concentration of individual solvents can be minimized, and any synergistic effects can be maximised. The concentration of co-solvent(s) which is acceptable will vary depending on the route, rate of administration and whether the product is to be given chronically. Again, the formulator will do well to be guided by the established precedent in marketed products and is once again referred to the publications of Powell et al. (1998) and Strickley (1999).

Non-aqueous Vehicles

Poorly soluble drugs for intramuscular administration can be formulated in a non-aqueous vehicle; this can have the additional benefit of providing a slow release of the active moiety. Oily vehicles have been used historically; the most commonly encountered is sesame oil, and

six products containing it are listed in the PDR (Nema et al. 1997). Federal regulations, however, now require the specific oil to be included in the product labelling, because of the risk of allergic reactions to certain vegetable oils. This and the irritancy of oily vehicles has led to their decreased use. Formulations consisting entirely, or almost entirely, of organic solvents have also been developed, and examples are included in Table 9.3.

Surfactants

Surfactants, generally the polysorbates, are frequently encountered in parenteral products but generally at very low levels (<0.05 percent) and most commonly to prevent aggregation in formulations of macromolecules (see the section "Strategies for the Formulation of Macromolecules"). Few IV products contain significant levels of surfactant; two notable exceptions are Cordarone IV and Etoposide IV which contain 10 and 8 percent respectively, of polysorbate (Tween) 80. Both products require dilution before administration, such that the maximum concentration of polysorbate 80 in the infusion solution is 1.2 and 0.16 percent, respectively. It

Table 9.3
The formulations of some co-solvent containing marketed products.

Active Ingredient	Route	Vehicle Composition	Special Instructions
Diazepam	IM/IV	40% Propylene glycol 10% Ethyl alcohol 5% Benzoate buffer 1.5% Benzyl alcohol	Inject slowly (at least 1 min/mL) if giving IV. Do not use small veins.
Co-trimoxazole	IV	40% Propylene glycol 10% Ethyl alcohol 0.3% Diethanolamine 1% Benzyl alcohol 0.1% Sodium metabisulphite	Must be diluted with 5% dextrose infusion. Discard if cloudy or if there is evidence of crystallization.
Etoposide	IV	65% w/v PEG 300 30.5% w/v Alcohol 8% w/v Polysorbate 80 3% w/v Benzyl alcohol 0.2% w/v Citric acid	Must be diluted. At concentrations >0.4 mg/mL, precipitation may occur.
Loxapine	IM	70% Propylene glycol 5% Polysorbate 80	
Lorazepam	IV/IM	80% Propylene glycol 18% Ethanol 2% Benzyl alcohol	Dilute twofold for IV injection.

is worth noting, however, that the polysorbate component of Cordarone IV has been implicated in a few cases of acute hepatitis which have developed within hours of the start of administration. Somewhat higher levels of surfactants can be tolerated in products intended for the subcutaneous or intramuscular route. Aquasol A (vitamin A palmitate as retinol) for intramuscular administration, for example, contains polysorbate 80 at a level of 12 percent.

Complexing Agents

Complexing agents, in this context, are molecules that have the ability to form soluble complexes with insoluble drugs. The most well-known examples are the cyclodextrins which have been widely studied as agents for solubilization and stabilization. They are able to increase the aqueous solubility of some poorly soluble drug molecules by orders of magnitude, as a result of their ability to form inclusion complexes. Cyclodextrins are oligosaccharides obtained from the enzymatic conversion of starch. Depending on the number of glucopyranose units, they are named as α (six units), β (seven units) or γ (eight units). These parent molecules can then be further substituted at the hydroxyl groups to alter the properties of the molecule. The nature of the substituents and the degree of substitution will influence the aqueous solubility, complexing capacity and safety of the molecules. An excellent review of the characteristics of cyclodextrins has recently been published (Thompson 1997). In addition, Stella and Rajewski (1997) have reviewed the use of cyclodextrins in drug formulation and delivery, and this provides an excellent summary of the "status quo" in terms of their toxicology and use in pharmaceutical formulations.

Although the potential of cyclodextrins as solubilizing and stabilizing excipients has been the subject of numerous research papers over the last decade, the FDA has only recently approved the first commercial parenteral products containing them. Edex (alprostadil) for injection contains α -cyclodextrin at a concentration of approximately 1 mg/mL. This product is unusual, however, in that it contains an unsubstituted cyclodextrin. In general, the unsubstituted α - and β -cyclodextrins are not considered suitable for parenteral use because they can cause severe nephrotoxicity. This has led to the development of modified cyclodextrins. Hydroxypropyl- β -cyclodextrin is the most popular of the cyclodextrin family for use as a solubilizer in parenteral solutions because of its low toxicity and high inherent solubility. The first parenteral product containing this derivative (itraconazole) was approved in April 1999. This product contains 40 percent hydroxypropyl- β -cyclodextrin and is administered intravenously after a two-fold dilution with saline (Strickley 1999). Although IV grades of hydroxypropyl- β -cyclodextrin are now commercially available, its widespread use has been hampered not only because of the inherent difficulties associated with introducing a new excipient but also because it is the subject of a Janssen/National Institutes of Health (NIH) patent which does not expire in Europe for several years. Until this time, other companies wishing to incorporate this derivative into a commercial IV formulation will need to obtain a license from either NIH or Janssen. The sulphabutyl ether derivative is also suitable for parenteral use and is present in at least one formulation in clinical development, but here again, there are patent issues hampering its widespread application. Nevertheless, the use of cyclodextrin derivatives is often the only method of achieving sufficiently high aqueous concentrations of poorly soluble molecules, and they are now widely used within the pharmaceutical industry in preclinical formulations. One could speculate that the upcoming expiry of the Janssen/NIH patent, coupled with the recent approval of the itraconazole formulation, is likely to lead to their routine consideration as a first-line approach in the formulation of poorly soluble drugs.

Emulsions

Parenteral emulsions were first introduced to provide an IV source of essential fatty acids and calories. This has developed into the extensive and routine use of products such as Intraplipid, Lipofundin and Liposyn in total parenteral nutrition. There are relatively few commercially available emulsions containing active compounds; the only example on the U.S. market is Diprivan® Injectable Emulsion, the formulation of which is shown in Table 9.4. Diazepam is also available as an injectable emulsion on the UK market (Diazemuls®). For a more detailed discussion of the issues involved in developing parenteral emulsions, the reader is referred to Collins-Gold et al. (1990).

All parenteral emulsions are oil-in-water formulations, with the oil as the internal phase dispersed as fine droplets in an aqueous continuous phase. An emulsifier, usually egg or soy lecithin, is needed to lower the interfacial tension and prevent flocculation and coalescence of the dispersed oil phase. Mechanical energy, usually in the form of homogenization, is required to disperse the oil phase into droplets of a suitable size. For IV administration, the droplet size should be below 1 μm to avoid the potential for emboli formation.

Clearly, physical stability is of critical importance for emulsion formulations, and care must be taken to ensure not only that the product itself is physically stable but that any infusion solutions which may be prepared by dilution of the emulsion are also physically stable over the required period of time. In addition, parenteral emulsions should be able to withstand the stresses associated with moist heat sterilization. Alternatively, if this cannot be achieved, it may be possible to prepare an emulsion aseptically from sterile components, provided the process can be suitably validated. For a good introduction to the formulation and preparation of IV emulsions, the reader is referred to Hansrani et al. (1983).

STRATEGIES FOR FORMULATING UNSTABLE MOLECULES

Water Removal

The most common mechanism of instability in parenteral formulations is hydrolysis. Regardless of whether the formulation is a true solution, co-solvent solution, emulsion or contains a complexing agent, the largest component of the formulation is likely to be water. Frequently, the only formulation strategy which will result in adequate stability is water removal. This is usually (although not exclusively) achieved by means of lyophilization. Lyophilization has a number of advantages over other potential drying methods, such as the ability to obtain an elegant end-product with a very low moisture content, and significantly, the fact that it is amenable to being carried out in an aseptic environment.

Lyophilization is essentially a three-stage process. Following standard aseptic filling, partially stoppered vials are transferred to a steam sterilizable lyophilizer in which drying is carried out. Initially the product is frozen to a low temperature (typically, -30 to -40°C). During primary drying, a high vacuum is applied, and ice is removed via sublimation. In the secondary drying stage, the product is heated under vacuum to 20 – 40°C , and any remaining water is removed by desorption. Products with very low moisture contents (<2 percent) can easily be achieved. The process also allows vials to be backfilled with nitrogen, usually to slightly less than atmospheric pressure, prior to stoppering, thus creating an inert environment within the vials. At the end of the lyophilization cycle, the stoppers are fully inserted into the vials before removal of the product from the chamber.

Table 9.4
Diprivan® injectable emulsion formulation.

Component	Concentration
Propofol	10 mg/mL
Soybean oil	100 mg/mL
Glycerol	22.5 mg/mL
Egg lecithin	12 mg/mL
Disodium edetate	0.005%
Sodium hydroxide	qs
Water for Injection	to 100%

The development of lyophilized products is a specialized area and requires a detailed understanding of the thermal properties of the formulation. Subambient differential scanning calorimetry studies are required to identify the eutectic melting temperature (T_e) (in the case of a crystalline solute) or the glass transition temperature of the maximally concentrated solute (T_g') (for an amorphous solute). The latter is closely related to the collapse temperature (T_c) which effectively represents the maximum allowable product temperature during the primary drying or sublimation phase of the process. Both T_c and T_e can be estimated using freeze-drying microscopy, a technique in which the freeze-drying process is observed on a microscale, and the collapse or melting temperature visually determined. Lyophilized products usually contain excipients to act as bulking agents and/or improve the stability of the product. When the requirement is principally for a bulking agent, mannitol tends to be the favourite choice of formulators. Mannitol is a crystalline material with a T_e of about -2°C and, as such, is easily freeze-dried to give a self-supporting cake with good aesthetic properties. On the other hand, where an increase in stability is desired, an amorphous excipient (such as sucrose) is preferred since, once dry, the unstable compound will be “dispersed” in an amorphous glass with often greatly improved stability. The downside of formulating with amorphous excipients is that their low T_g' values (approximately -32°C for sucrose) result in long lyophilization cycles. The formulator must also ensure that the product reconstitutes rapidly and that reconstitution time as well as chemical integrity are not adversely affected by storage.

For a detailed discussion of lyophilization, the reader is referred to Jennings (1999). In addition, a thorough review of the manufacturing and regulatory aspects of lyophilization is provided in *Good Pharmaceutical Freeze-Drying Practice* (Cameron 1997).

Use of Excipients

Excipients may be useful in preventing chemical and physical instability. Antioxidants are included in parenteral formulations, although their use is now in decline, and EU guidelines discourage their use unless no other alternative exists (see the section “Parenteral Products and the Regulatory Environment”). A preferred method of preventing oxidation is simply to exclude oxygen; this is usually achieved by purging the product with nitrogen and creating a

nitrogen headspace within the container. Where this is insufficient, a metal chelator, such as disodium edetate, or an antioxidant compound, such as ascorbic acid or sodium metabisulphite, may be considered. These are included in marketed products typically at levels of up to 0.05, 1 and 0.3 percent, respectively.

Non-aqueous Vehicles and Emulsions

For the intramuscular and subcutaneous routes, the use of non-aqueous vehicles may be considered as a method of avoiding hydrolysis. For IV administration, the use of an oil-in-water emulsion is a possible, although little used, option. These approaches are discussed in the section "Strategies for Formulating Poorly Soluble Drugs".

STRATEGIES FOR THE FORMULATION OF MACROMOLECULES

Macromolecules present unique challenges to both the formulator and the analyst. Their large size and complex structural nature make degradation difficult to detect and sometimes difficult to prevent.

Proteins are composed of an amino acid backbone which defines their primary structure. The amino acid side chains hydrogen-bond to each other, creating areas of local order such as α helices and β -pleated sheets. These types of arrangement are known as secondary structure. The overall folding of the molecule, which defines its three-dimensional shape, is known as the tertiary structure. Finally, some proteins, such as haemoglobin, are composed of more than one subunit; the spatial arrangement of these subunits is known as the quaternary structure.

The challenge to the formulator is ensuring the preservation of both the chemical integrity of the constituent amino acids and the overall three-dimensional folding or conformation of the molecule. Several amino acids are susceptible to degradation by oxidation (e.g., methionine, cysteine, histidine) and deamidation (e.g., glutamine and asparagine). Peptide bonds in the backbone can undergo hydrolysis, and disulphide bonds between amino chains can also be disrupted and refold incorrectly (disulphide interchange). Chemical modification may be detected by high performance liquid chromatography (HPLC) techniques, but it is often extremely difficult to pinpoint where in the molecule degradation is taking place. Protein molecules frequently undergo aggregation, both covalent (through disulphide bond formation) and non-covalent. Non-covalent aggregation cannot be detected by normal HPLC methods, and techniques such as sodium dodecyl sulphate–polyacrylamide gel electrophoresis (SDS–PAGE) and size exclusion chromatography are required to detect this type of instability. In addition, protein molecules have a tendency to adsorb to surfaces such as filters.

It is clear that the formulation of a macromolecule is far from simple and requires a good understanding of protein chemistry in order that degradation pathways can be understood and degradation prevented. However, one faces the same limitation as formulators of small molecules, namely, a relatively small armoury of established excipients which can be safely used in parenteral products. Some of the excipients commonly encountered in formulations of macromolecules are listed in Table 9.5. For further guidance on the formulation of macromolecules, the reader is referred to Wang and Pearlman (1993). This text provides some excellent examples of strategies which have been used to develop commercial formulations of proteins and peptides, such as human growth hormone and alteplase.

Table 9.5
Excipients encountered in formulations of macromolecules.

Excipient	Function
Polyhydric alcohols, e.g., mannitol	Stabilisation, bulking agent
Carbohydrates, e.g., sucrose	Stabilisation
Amino acids, e.g., glycine, arginine	Stabilisation, buffer, solubilisation
Serum albumin	Prevention of adsorption
Surfactants (e.g., Tween 80, Pluronic F68)	Prevention of adsorption and aggregation
Metal ions	Stabilisation
Antioxidants	Prevention of oxidation
Chelating agents (e.g., EDTA)	Prevention of oxidation

LIPOSOMAL DELIVERY SYSTEMS

Liposomes are single or multilayer phospholipid vesicles, typically less than 300 nm in size. They are capable of entrapping both water-soluble and lipid-soluble compounds. Their use in parenteral formulations has exploited their preferential distribution to the organs of the reticuloendothelial system (RES) and their ability to accumulate preferentially at the sites of inflammation and infection. Liposome encapsulated amphotericin B is considerably less toxic than the free drug because of the altered pattern of biodistribution (Betageri and Habib 1994). A sophisticated approach has been developed (commercialised as Stealth[®] liposomes), in which polyethylene glycol is grafted to the surface of the liposome, resulting in prolonged circulation of the liposomes in the bloodstream. A doxorubicin product which uses this approach (DOXIL[®]) is now commercially available (Martin 1999).

SUSTAINED-RELEASE PARENTERAL FORMULATIONS

The chronic administration of molecules, which have a short biological half-life and cannot be given orally, presents a difficult challenge to formulators. One strategy which might be considered is the development of a sustained-release intramuscular or subcutaneous injection. Other non-parenteral options could include the inhalation or intranasal route, both of which have their own unique challenges. Sustained-release parenteral formulations might also be required in circumstances where patient compliance is likely to be poor. This consideration has led to the development of some antipsychotics and contraceptives as sustained-release injections. Table 9.6 lists some of the sustained-release parenteral products which are available on the U.S. market and their respective formulations. The typical approaches used in the formulation of sustained-release parenterals are summarised in this section.

Table 9.6
Examples of sustained-release parenteral formulations.

Compound	Route	Formulation
Penicillin-G benzathine	IM (aqueous suspension)	0.5% Lecithin 0.6% Carboxymethylcellulose 0.6% Povidone 0.1% Methylparaben 0.01% Propylparaben in sodium citrate buffer
Haloperidol	IM (oily vehicle)	1.2% Benzyl alcohol in sesame oil
Leuprolide acetate	IM (microsphere suspension)	After reconstitution: 0.13% Gelatin 6.6% dl-Lactic and glycolic acid copolymer 13% Mannitol 0.2% Polysorbate 80 1% Carboxymethylcellulose in WFI
Dexamethasone acetate	IM/ soft tissue (aqueous suspension)	0.67% Sodium chloride 0.5% Creatinine 0.05% Disodium edetate 0.5% Sodium carboxymethylcellulose 0.075% Polysorbate 80 0.9% Benzyl alcohol 0.1% Sodium sulphite in WFI

Oily Vehicles

The use of oily vehicles as an approach for the formulation of poorly soluble molecules is discussed in the section "Non-aqueous Vehicles". For molecules which possess good oil solubility, a sustained-release profile may also be achievable. The nature of the sustained-release profile will depend to a large extent on the oil/water partition coefficient of the molecule in question. Molecules which are not oil miscible could also be formulated as oily suspensions. The latter will usually result in a longer duration of action, because the drug particles must dissolve in the oily phase prior to partitioning into the aqueous medium (Madan 1985). The use of oily vehicles would not normally be considered as a first-line approach for new formulations, however, because of concerns over allergic reactions to the oils.

Aqueous Suspensions

This approach can be used to prolong the release of compounds with limited aqueous solubility. A suspension of a compound in its saturated solution can provide both immediate-release and sustained-release components of a dose (Madan 1985). A number of water-insoluble prodrugs are also formulated as suspensions, including hydrocortisone acetate and medroxyprogesterone acetate. As with any other type of suspension, excipients will usually be required to ensure the physical stability of the formulation. Strickley's (1999) article provides a table of parenteral suspension formulations; the most popular excipient combinations are clearly polyethylene glycol/Tween 80 and carboxymethylcellulose/Tween 80.

Perhaps the most well-known example of a parenteral suspension formulation is insulin. Many insulin formulations also take advantage of the different physical forms which can be produced when insulin is complexed with zinc. Suspensions of the amorphous form of insulin zinc have a faster onset of action and shorter duration of action compared to those of the crystalline form. In order to provide both a rapid onset and a long duration of action, many formulations are composed of a mixture of amorphous and crystalline zinc insulin.

Emulsions

For a molecule with a high aqueous solubility, the use of a water-in-oil two-phase emulsion or a multiple phase water-in-oil-in-water emulsion may enable a measure of sustained-release to be achieved. In either case, the nature of the sustained-release delivery profile will be a function of the partition coefficient of the molecule between the two phases, which will define the rate at which the molecule is available for absorption.

Microspheres

Polymeric microspheres, particularly those prepared from the biodegradable polylactide/polyglycolide polymers, have been widely investigated as a means to achieve sustained parenteral drug delivery. The advantage of formulating the polymeric matrix as microspheres is the ability to administer them via a conventional needle and syringe as a suspension formulation, rather than as an implant (see below). Lupron[®] depot formulations are available which can provide therapeutic blood levels of leuprolide acetate for up to four months. These products are presented as lyophilized polylactic acid microspheres which are reconstituted to form a suspension prior to administration.

Implantable Drug Delivery Systems

Implantable delivery systems extend the concept of sustained release beyond the capabilities of the strategies discussed so far in this section. Continual drug delivery lasting for months or even years has been achieved. Because these products must be administered as a solid rather than a liquid, they are usually supplied with a customised injection device.

The number of marketed implantable products is relatively limited, probably due in part to the limited market for this type of product. The most well-known example of an implantable delivery system is the Norplant[®] contraceptive device which can deliver levonorgestrel for up to five years. The device is composed of a number of capsules fabricated from Silastic[®] (dimethylsiloxane/methylvinylsiloxane copolymer)

The Norplant® device has been somewhat controversial, however, due to difficulties associated with its removal. A second example of an implantable drug delivery system is Zoladex®, which is an implantable biodegradable lactide/glycolide polymeric delivery system for the administration of goserelin acetate. It is available in one-month and three-month presentations and can be injected through a wide-bore needle.

IN VITRO AND IN VIVO TESTING METHODS

When developing formulations for compounds with limited solubility or stability, where extremes of pH or co-solvents might be used, it is desirable to carry out screening studies to assess their potential to cause pain or other adverse events following injection. Haemolysis and phlebitis may occur as a consequence of IV therapy, whilst pain may occur on administration of any type of injection. Several *in vitro* and *in vivo* models have been developed to evaluate the potential for adverse effects following parenteral administration; these are discussed briefly below. For a more detailed discussion of this subject, the reader is referred to the excellent review by Yalkowsky et al. (1998).

In Vitro Precipitation

Clearly, when a drug is formulated at a non-physiological pH, or using organic solvents because of low solubility, there is a real risk of precipitation immediately following injection into the bloodstream. Crude models have therefore been used in the past to assess formulations for their potential to result in *in vivo* precipitation. These have generally involved performing dilutions in a medium resembling blood and monitoring the formation of a precipitate by visual or other means. More recently, dynamic methods have been developed which more realistically simulate the *in vivo* situation. Typically, these involve a continuously circulating system of plasma or a medium representing plasma. After “injection” of the test formulation, the resulting solution passes through a flow-through cell within a spectrophotometer where light scattering associated with particle formation is monitored. Although it is obviously difficult to precisely mimic *in vivo* conditions, these models can prove useful in terms of discriminating between a number of potential formulations. In addition, they can be used to assess the effect of injection rate. Yalkowsky et al. (1983) have shown that, perhaps counterintuitively, the degree of precipitation of diazepam injection is in fact *inversely* proportional to injection rate.

Haemolysis

Haemolysis occurs when the red blood cell membrane is disrupted, resulting in release of cell contents into the plasma. Severe adverse events can occur if high levels of haemoglobin are released into plasma. Clearly, hypotonic formulations have the potential to cause haemolysis, and as discussed earlier, the administration of such formulations should be avoided. Other excipients, such as surfactants and co-solvents, can cause haemolysis, as may the drug itself. *In vitro* models to evaluate haemolytic potential typically involve exposing the formulation to blood, either in a static or a dynamic configuration, and then assessing the quantity of free haemoglobin released. The contact time between blood and the formulation is critical, as an

unrealistic contact time can result in a substantial overestimation of the haemolytic potential of a given formulation (Wakerley 1999). Haemolysis can also be measured *in vivo* by the measurement of free haemoglobin in blood or urine, and Krzyzaniak (1997) has reported agreement between a dynamic *in vitro* method and *in vivo* results.

Phlebitis

Phlebitis refers to inflammation of the vein wall. It can result in clinical symptoms such as pain and oedema, and can cause thrombus formation which may have serious consequences. Particulate matter is the most widely implicated cause of phlebitis. It is not surprising, therefore, that a link has been proposed between precipitation and phlebitis. The *in vitro* precipitation models described above may therefore be a good indicator of the phlebitic potential of a formulation. Phlebitis can be tested *in vivo*, usually by means of a rabbit ear vein model in which the “test” ear is visually compared with the “control” ear.

Pain

Pain on injection is usually of greatest concern with intramuscular injections because of the long residence time of the formulation at the injection site. Not surprisingly, there are no *in vitro* models to test the potential of a formulation to cause pain! It is therefore necessary to test for the potential to cause pain by means of an *in-vivo* model. Gupta et al. (1994b) describe the use of the rat “paw lick” model for the assessment of pain in response to formulation pH and co-solvent concentration. The potential for muscle damage should also be evaluated when developing an intramuscular formulation, and the industry standard is the rabbit lesion volume model (Sutton et al. 1996).

PACKAGING OF PARENTERAL PRODUCTS

Pack Selection

The packaging of parenteral products presents unique challenges in terms of the requirements for the packaging components to withstand sterilization prior to use and the requirement for the complete primary pack to maintain sterility throughout the shelf-life of the product. Traditionally, SVPs have been packaged in ampoules which are heat sealed after filling. Because of the inherent variability in the sealing process, products packaged in ampoules must be 100 percent integrity tested after sealing, usually by means of a dye immersion test. The use of ampoules for new products is now diminishing, partly because of the desire to avoid exposing medical personnel to injury on opening. This has led to an increase in the use of glass vials sealed with rubber stoppers for the packaging of SVPs. Regardless of whether an ampoule or a vial is used, the glass quality must be type I neutral. An increasing number of simple solutions are now being filled using blow-fill-seal technology, in which the (plastic) ampoule is moulded, aseptically filled and sealed in a continuous process. These manufacturing systems operate to high levels of asepsis and are validated by media fills in the same manner as conventional filling processes.

For products packaged in vials, a suitable rubber stopper must be selected. The surface of a rubber stopper is inherently less inert than the glass of an ampoule, and it is therefore important that the formulator ensures that the product and stopper are compatible by

conducting suitable testing. It is also necessary to ensure that the product does not extract an excessive quantity of leachables from the stopper. For lyophilized products, it is advisable to select a stopper with a low capacity to absorb moisture during the autoclaving process, since this can subsequently be transferred to the product during storage, which may lead to product deterioration. Various other specialized stoppers are available, such as Teflon-coated, which may be useful when a highly inert surface is required. Stoppers containing a desiccant are also under development. Stoppers cannot withstand the depyrogenation process and so are autoclaved prior to use, but the presterilization treatment should be designed to ensure a satisfactory level of endotoxin removal. Stoppers will almost always require some degree of siliconisation to allow them to be easily processed in automatic filling lines, and they can be purchased washed, presiliconised to an agreed level and packaged in ready-to-sterilize bags. Stoppers which are purchased in a ready-to-sterilize format should be tested by the supplier to a suitable endotoxin specification.

Increasingly parenteral products are being presented in more sophisticated packages, such as pre-filled syringes. These reduce the potential for needle-stick injuries by reducing the degree of manipulation required and facilitate administration in an emergency situation. A number of companies, such as Beckton-Dickinson and Vetter, specialize in this technology, and can supply purpose-designed filling equipment or can provide contract manufacturing services to fill product into their devices.

Container/Closure Integrity

Considerable emphasis is now placed on providing an assurance of container closure integrity during the shelf-life of sterile products. Historically, this has been achieved by performing sterility tests as a component of stability testing, usually initially and at 12-month intervals, but this approach alone would not now be considered sufficient to validate the integrity of a new container/closure system. Most manufacturers usually perform media immersion tests in which media-filled vials are immersed in contaminated media and subjected to repeated vacuum/overpressure cycles. This provides an assurance of the integrity of specific pack configurations under highly challenging conditions. This test should also be conducted on stored media-filled vials to provide data on the integrity of "aged" packs. FDA guidelines now allow physical tests to replace microbiological tests in demonstrating container closure integrity, but only where those physical tests are suitably validated. This is by no means straightforward because of the difficulty in correlating leakage measured by a physical method with the potential for microbial ingress. Efforts are underway to develop physical methods, however and Kirsch et al. have recently published a series of articles in which they have been able to correlate helium leak rates measured by mass spectrometry and vacuum decay methods with a probability of microbial ingress (Kirsch et al. 1999, 1997a, b, c).

MANUFACTURING OF PARENTERAL PRODUCTS

The manufacture of parenteral products is focussed at all times on the requirement for sterility of the finished product. Despite the fact that the regulators are clear in their preference for products to be terminally sterilized, the vast majority of parenterals are filtered through sterilizing grade filters and filled aseptically, primarily because stability considerations preclude the use of moist heat sterilization. The statistical limitations of sterility testing a sample

from a batch are well known, and attention is now well and truly focussed on process validation. The validation program must encompass facilities, instrumentation, sterilization of container and closures, clean room garments and gowning procedures as well as including regular media simulations of aseptic processes. Guidance on the frequency and numbers of units to be filled in media simulations can be found in the publications of the Parenteral Drug Association and the Parenteral Society (see the section "Parenteral Products and the Regulatory Environment"). In a production environment, a simulation of each aseptic process will typically be carried out at six-month intervals. It is important that media fills include planned interventions, such as filter changes, so that such interventions can be permitted during a manufacture if required. In addition, holding times after filtration should be validated. Where a product is lyophilized, the media simulation must include loading into and removal from the lyophilizer and should also include pulling and releasing partial vacuums. It is obviously essential to ensure that all personnel participating in aseptic processes are adequately trained and aseptic operators are required to participate in regular media fills. Another important element of aseptic process validation is environmental monitoring and particulate monitoring; manufacturers are expected to know the organisms which may be present in their facility and to establish acceptable limits.

With the majority of parenteral products sterilized by filtration, it is not surprising that the validation of filtration processes is receiving increasing regulatory interest. The 1998 PDA Technical Report No. 26 discusses this topic in detail (see the section "Parenteral Products and the Regulatory Environment"). There is now a regulatory expectation that the bacterial retention capability of sterilizing filters is demonstrated in the presence of product rather than simply water. Fortunately, the major pharmaceutical filter companies now have specialised validation laboratories which are able to provide filter validation services. All filters used in a process, including vent filters, must also be integrity tested before and after use. Organisms have recently been identified which are capable of passing through 0.22 μm filters, and the filter companies are now starting to launch 0.1 μm filters. One might imagine that the day will come when the use of 0.1 μm filters becomes the industry "norm", although a 1997 editorial in the *Journal of the Parenteral Drug Association* advised those in the industry to resist this development. Manufacturers are required to have a knowledge of the type of organisms which may be present in the solution to be filtered; provided that these do not have the ability to pass through a 0.22 μm filter, there is no compelling scientific argument for the use of a 0.1 μm filter.

For products which can withstand sterilization in their final container, the focus of the validation exercise will clearly be the sterilization process. A detailed discussion of sterilization is beyond the scope of this chapter (for this, the reader is referred to the recent text by Nordhauser and Olson [1998]) but the premise central to all methods of sterilization is the concept of a log-reduction in viable organisms. Pharmacopoeias now require an assurance that there is less than one chance in a million that viable microorganisms are present in a sterilized article or dosage form (Hall 1994). Achieving the required sterility assurance level of 10^{-6} is of course dependent on the initial microbiological loading of the material to be sterilized, and so it is vital to have knowledge of the initial bioburden and to set limits for this. For terminally sterilized products, the focus of the validation exercise will be in providing an assurance that sterilizing conditions have been reached in all units. Thus only loads and loading patterns which have been validated, usually by means of biological indicators, can be used. The concept of validated loading patterns also applies to the sterilization of equipment and packaging components to be used in an aseptic process.

The final stage in the manufacture of a sterile product is inspection. A 100 percent inspection for particulates, cracks and defects is a regulatory requirement. The inspection may

be carried out visually using suitable illumination, but in a production environment, a semi-automated or automated system is usually used.

Clearly, the manufacture of sterile products is a specialized area, and the above discussion simply serves to highlight some of the critical issues; it is by no means comprehensive. For a detailed discussion of the manufacture of sterile products, the reader is referred to Hall (1994) as well as the publications of the Parenteral Drug Association and the Parenteral Society, which are detailed in the section "Parenteral Products and the Regulatory Environment". In addition, the "Orange Guide" provides a very readable annex covering the manufacture of sterile medicinal products; this includes guidance on clean room classifications, gowning and sanitisation, as well as the manufacture and sterilization of medicinal products (MCA 1997).

ADMINISTRATION OF PARENTERAL PRODUCTS

During product development, it is essential that the formulator keeps in mind the manner in which their product will ultimately be used. This is particularly true for products intended for IV infusion, since these will require dilution with IV infusion fluids prior to administration. The formulator must ensure that the active compound is compatible with all diluents which are to be included in the product labelling and must provide stability data to demonstrate that the resultant infusion solutions are stable for the period of time specified in the labelling. During clinical trials, compatibility and stability must be assured at the maximum and minimum concentrations to be administered during the study; this data will be expected by the regulatory authorities as part of an Investigational New Drug (IND) submission. It is also important to consider other drugs which may be co-administered with the product in question. The practice of mixing more than one drug in a single infusion is diminishing rapidly, and the labelling of new IV products usually specifies that this should be avoided. One must still consider, however, the potential for incompatibilities to occur when different infusion solutions mix in the infusion line or indeed the cannula. In general, mixing prior to the cannula can be avoided by the use of a different line for each infusion, but clearly, mixing in the cannula is inevitable where patients are receiving multiple IV infusions. The labelling of some medications, notably alteplase, specifically instructs that they should be administered in a completely separate infusion line to any other medications. The nature of alteplase may justify this statement, but in practice, such restrictions should be avoided, since they will clearly cause difficulties for medical practitioners.

When compatibility or stability issues do arise, there are limited options available to the formulator. The diluent cannot usually be controlled unless the manufacturer incurs the additional cost associated with supplying a custom diluent. Leachables from infusion bags can cause degradation, particularly oxidation. In addition, the low concentrations to which drugs may be diluted for continuous infusion can result in adsorptive losses. A number of products, therefore, specify a minimum concentration to which they can be diluted, presumably to address stability or adsorption issues. The infusion set itself can also contribute to instability and/or adsorption. Some product labelling, for example, that of glyceryl trinitrate infusion, specifies that PVC infusion lines should not be used. In extreme cases, it may be necessary to add an additional excipient to the product to prevent degradation on dilution, although this approach should only be considered as a last resort.

PARENTERAL PRODUCTS AND THE REGULATORY ENVIRONMENT

The requirement for sterility in parenteral products means that their manufacture is scrutinised perhaps more closely than that of any other product type. A number of regulatory guidelines specifically pertain to parenteral products, and these are listed below. Included in these lists are also some more general guidelines where these contain sections specifically relevant to parenteral products. European Agency for the Evaluation of Medicinal Products (EMA) publications provide useful guidance in formulation decision making and are essential reading early on in the formulation development process. The “Decision Trees for the Selection of Sterilisation Methods” document provides clear guidance on the selection of a sterilization strategy, this is discussed in detail in Chapter 12. Similarly, the “Notes for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products” is prescriptive in terms of defining the circumstances under which antioxidants and preservatives should be used. The former, for example, should be included only where their use cannot be avoided and where the manufacturing process has been optimised to minimize the potential for oxidation.

FDA guidelines are in general directed more towards the required components of a registration dossier and do not offer much in the way of guidance to the formulator. One exception to this is the “Guide to Inspection of Lyophilization of Parenterals”; this provides a useful indication of areas of specific interest to the FDA which the formulator would be well-advised to address during the development programme.

In addition to the regulatory guidelines, more detailed advice on specific issues relating to the development and manufacture of parenteral products can be obtained from the publications of the Parenteral Drug Association. This is an American organisation representing those involved in all aspects of parenteral product development and manufacture and is very active in lobbying the FDA. The PDA produces a bimonthly journal, the *PDA Journal of Pharmaceutical Science and Technology*, which is essential reading for all those involved in the development and manufacture of parenteral products. In addition, the PDA regularly publishes technical reports which provide a detailed discussion of pertinent issues within the parenteral field. Whilst these reports are not regulatory guidelines, they do provide a good indication of the direction in which the industry and indeed the regulators, are heading and those working in the field should take their recommendations seriously. Some of the recently published technical reports are listed below. In the United Kingdom, the Parenteral Society publishes a quarterly journal in conjunction with similar bodies in France, Germany, Scandinavia and Spain. This journal covers topics similar to those in the PDA journal. The Parenteral Society also publishes a number of monographs, some of which are listed below. These monographs provide a good indication of industry “norms” in the United Kingdom.

►

FDA Guidelines

Inspection Guidelines

- Guide to Inspection of Lyophilization of Parenterals

Guidance for Industry

- Container Closure Systems for Packaging Human Drugs and Biologics
- Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
- Container Closure Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products
- Stability Testing of Drug Substances and Drug Products

EMA Guidelines

- Note for Guidance on Maximum Shelf-Life for Sterile Products for Human Use after First Opening or Following Reconstitution
- Notes for Guidance on Development Pharmaceuticals
- Development Pharmaceuticals for Biotechnological and Biological Products
- Decision Trees for the Selection of Sterilisation Methods
- Notes for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products

PDA Technical Reports

- Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products, 50, S1, 1996
- Technical Report No. 23: Industry Survey on Current Sterile Filtration Practices, 51, S1, 1997
- Technical Report No. 24: Current Practices in the Validation of Aseptic Processing, 51, S2, 1997
- Technical Report No. 25: Blend Uniformity Analysis: Validation and In-Process Testing, 51, S3, 1997
- Technical Report No. 26: Sterilization Filtration of Liquids, 52, S1, 1998
- Technical Report No. 27: Pharmaceutical Package Integrity, 52, S2, 1998
- Technical Report No. 28: Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals, 52, S3, 1998
- Technical Report No. 29: Points to Consider for Cleaning Validation, 52, 6, 1998
- Technical Report No. 30: Parametric Release of Sterile Pharmaceuticals Terminally Sterilized by Moist Heat, 1999
- Technical Report No. 31: Validation and Qualification of Computerized Laboratory Data Acquisition Systems, 53, 4, 1999

REFERENCES

- Agalloco, J. 1997. It Just Doesn't Matter. *J. Pharm. Sci. Technol.* 149–150
- Avis, K. E., H. A. Lieberman, and L. Lachman, eds. 1992. *Pharmaceutical dosage forms: Parenteral medications, volume 1*. New York: Marcel Dekker.
- Betageri, G. V., and M. J. Habib. 1994. Liposomes as drug carriers. *Pharm. Eng.* 14:8, 10, 12–14.
- Cameron, P., ed. 1997. *Good pharmaceutical freeze-drying practice*. Buffalo Grove, Ill; USA: Interpharm Press, Inc.
- Collins-Gold, L. C., R. T. Lyons, and L. C. Bartholow. 1990. Parenteral emulsions for drug delivery. *Adv. Drug Delivery Rev.* 5:189–208.
- DeLuc and Boylan. 1992. In *Pharmaceutical dosage forms: Parenteral medications, Volume 1*, edited by K. E. Avis, H. A. Lieberman, and L. Lachman. New York: Marcel Dekker.
- Ford, J. L. 1988. Parenteral products. In *Pharmaceutics: The science of dosage form design*, edited by M. E. Aulton. New York: Longman.
- Flynn, G. L. 1980. Buffers—pH control within pharmaceutical systems. *J. Parenteral Drug Assoc.* 34 (2):139–162.
- Gupta, L. S., J. P. Patel, D. L. Jones, and R. W. Partipilo. 1994a. Parenteral formulation development of renin inhibitor Abbott-72517. *J. Pharm. Sci. Technol.* 48 (2):86–91.
- Gupta, P. K., J. P. Patel, and K. R. Hahn. 1994b. Evaluation of pain and irritation following local administration of parenteral formulations using the rat paw lick model. *J. Pharm. Sci. Technol.* 48 (3):159–166.
- Hall, N. A. 1994. *Achieving sterility in medical and pharmaceutical products*. New York: Marcel Dekker.
- Hansrani, P. K., S. S. Davis, and M. J. Groves. 1983. The preparation and properties of sterile intravenous emulsions. *J. Parenteral Sci. Technol.* 37 (4):145–150.
- Jennings, T. A. 1999. *Lyophilization: Introduction and basic principles*. Denver, Colo., USA: Interpharm Press.
- Jorgensen, J. T., J. Romsing, M. Rasmussen, J. Moller-Sonnergaard, and L. Musaeus. 1996. Pain assessment of subcutaneous injections. *Ann. Pharmacother.* 30:729–732.
- Kirsch, L. E., L. Nguyen, and C. S. Moeckly. 1997a. Pharmaceutical container/closure integrity I: Mass spectrometry-based helium leak rate detection for rubber-stoppered glass vials. *PDA J. Pharm. Sci. Technol.* 51 (5):187–194.
- Kirsch, L. E., L. Nguyen, C. S. Moeckly, and R. Gerth. 1997b. Pharmaceutical container/closure integrity II: The relationship between microbial ingress and helium leak rates in rubber-stoppered glass vials. *PDA J. Pharm. Sci. Technol.* 51 (5):195–202.
- Kirsch, L. E., L. Nguyen, and R. Gerth. 1997c. Pharmaceutical container/closure integrity III: Validation of helium leak rate method for rigid pharmaceutical containers. *PDA J. Pharm. Sci. Technol.* 51 (5):203–207.
- Kirsch, L. E., L. Nguyen, A. M. Kirsch, G. Schmidt, M. Koch, T. Wertli, M. Lehmann, and G. Schramm. 1999. An evaluation of the WILCO “LFC” method for leak testing pharmaceutical glass-stoppered vials. *PDA J. Pharm. Sci. Technol.* 53 (5):235–239.
- Krzyzaniak, J. F. 1997. Lysis of human red blood cells. 4. Comparison of *in vitro* and *in vivo* hemolysis data. *Amer. Chem. Soc. Amer. Pharmaceut. Assoc.* 86 (11):1215–1217.

- Madan, P. 1985. Sustained-release drug delivery systems: Part V, parenteral products. *Pharm. Manu.* 2:50–57.
- Martin, F. J. 1999. Stealth liposomes: A pharmaceutical perspective. In *Microspheres, microcapsules and liposomes*, edited by R. Arshady. London: Citus.
- MCA. 1997. Rules and guidance for pharmaceutical manufacturers and distributors. London: Medicines Control Agency.
- Nema, S., R. J. Washkuhn, and R. J. Brendel. 1997. Excipients and their use in injectable products. *PDA J. Pharm. Sci. Technol.* 51 (4):166–171.
- Nordhauser, F. M. and W. P. Olson, eds. 1998. *Sterilization of drugs and devices: Technologies for the 21st century*. Buffalo Grove, Ill., USA: Interpharm Press, Inc.
- Powell, M. F., T. Nguyen, and L. Baloian. 1998. Compendium of excipients for parenteral formulations. *PDA J. Pharm. Sci. Technol.* 52 (5):238–311.
- Stella, V. J. and R. A. Rajewski. 1997. Cyclodextrins: Their future in drug formulation and delivery. *Pharm. Res.* 14 (5):556–567.
- Strickley, R. G. 1999. Parenteral formulations of small molecule therapeutics marketed in the United States (1999)—Part I. *PDA J. Pharm. Sci. Technol.* 53:324–349.
- Sutton, S. C., L. A. F. Evans, T. S. Rinaldi, and K. A. Norton. 1996. Predicting injection site muscle damage I: Evaluation of immediate release parenteral formulations in animal models. *Pharm. Res.* 13 (10):1507–1513.
- Sweetang, S., and M. J. Akers. 1996. Solubility principles and practices for parental dosage form development. *PDA J. Pharm. Sci. Technol.* 50 (5):330–342.
- Takada, S., T. Kurokawa, K. Miyazaki, S. Iwasa, and Y. Ogawa. 1997. Utilization of an amorphous form of a water-soluble GPIIb/IIIa antagonist for controlled release from biodegradable microspheres. *Pharm. Res.* 14 (9):1146–1150.
- Thompson, D. O. 1997. Cyclodextrins—Enabling excipients: Their present and future use in pharmaceuticals. *Crit. Rev. Ther. Drug Carrier Syst.* 14 (1):1–104.
- Wakerley, Z. 1999. In vitro assessment of the haemolytic potential of marketed formulations. *AAPS Pharm. Sci. Suppl.* 1 (4):S-209.
- Wang, Y. J., and R. Pearlman, eds. 1993. *Stability and characterization of protein and peptide drugs, Case histories*. New York: Plenum Press.
- Yalkowsky, S. H., J. F. Krzyzaniak, and G. H. Ward. 1998. Formulation-related problems associated with intravenous drug delivery. *J. Pharm. Sci.* 87 (7):787–796.
- Yalkowsky, S. H., S. C. Valvani, and B. W. Johnson. 1983. *In vitro* method for detecting precipitation of parenteral formulations after injection. *J. Pharm. Sci.* 72:1014–1017.

ABOUT THIS BOOK

Successful pharmaceutical companies must balance development of products of high quality. Striking the correct preformulation/formulation studies, studies that direct development, in addition, consideration must be given to regulatory requirements such as compliance with GLP and GMP, validation of systems and procedures, and comprehensive documentation. In *Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form*, Mark Gibson has answered the need for a practical reference source and pragmatic guide on what studies need to be undertaken, for what reasons, and at what key stages of the drug development process. In addition to preformulation, his book covers biopharmaceutics, drug delivery, formulation, and process development aspects of product development.

Ten contributing authors have shared their experience and expertise in significant chapters divided into three useful sections: *Aiding Candidate Drug Selection*, *Early Drug Development*, and *From Product Design to Commercial Dosage Form*. This book should be especially useful to scientists, technicians, and managers in the pharmaceutical, medical device, and biopharmaceutical industries.

What You'll Learn

- early preformulation/formulation and biopharmaceutical information to aid in selection of the most suitable compound for development
- prediction of potential problems for further formulation development
- best use of drug substance for preformulation studies to aid candidate drug selection
- generation of appropriate preformulation/formulation data to characterize the candidate drug and aid product design and development
- instrumental techniques that use minimal amounts of drug substance to gain useful information
- PC based Expert systems to aid product design
- various dosage forms
- routes of drug administration
- pros and cons of contracting out development

ABOUT THE EDITOR

Mark Gibson, BPharm, PhD, CChem, MRSC, MRPharmS, is responsible for parenteral and oral solid dosage form development at AstraZeneca R&D Charnwood, a division of AstraZeneca, in the UK. His experience includes formulation and preformulation development, both as a bench scientist and a manager, at Cyanamid (Lederle), Fisons Pharmaceuticals, Astra Pharmaceuticals, and AstraZeneca. He has worked on a variety of dosage forms and routes of delivery, including inhalation, oral, nasal, ophthalmic, parenteral, and transdermal, some of which have resulted in patents and marketable products. Dr. Gibson is a member of the UK Academy of Pharmaceutical Sciences, the Parenteral Society, and the Aerosol Society.



IHS® Health Group
An IHS GROUP Company

LIBRARY OF CONGRESS



0 008 002 642 0

market with development
unt when planning
ducts to market. In

ISBN: 1-57491-120-1

15 Inverness Way East • Englewood, CO 80112-5776
800.525.5539 • 303.858.6360 fax
www.ihshealthgroup.com