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About BioPharm Conference '95

Now in its sixth year, BioPharm Conference serves the information needs of scientists, engineers, regulatory personnel, and corporate management executives responsible for applied research and development, quality assurance/quality control, process development, and production/manufacturing in the biopharmaceutical industry.

BioPharm Conference, produced annually by *BioPharm* magazine, brings together the leading manufacturers, researchers, academicians, and regulators who are shaping the future of the industry. BioPharm Conference '95 features more than 60 speakers drawn from leading biopharmaceutical and classical pharmaceutical companies, colleges of pharmacy, and the Food and Drug Administration.

This proceedings includes conference materials that lend themselves to this format. Every attempt has been made to secure materials from all presenting speakers. BioPharm Conference cannot assume responsibility for reference materials that are not submitted. The Proceedings is a unique reference source for biopharmaceutical research, manufacturing, and regulation. The presentations herein critically examine the latest developments and practical approaches to the manufacture and production of biotechnologically derived drugs, including problem solving and troubleshooting, and cover the issues that have a direct bearing on the industry's future.

BioPharm Conference '95 wishes to thank the members of the *BioPharm* editorial advisory board and the moderators and speakers whose guidance and participation provided the strength and scope that characterize this proceedings.

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BioPharm Editorial Advisory Board

Table of Contents

Perspectives on the Development of Pharmaceutical Biotech Products

Moderator: ***Joseph G. Habarta, PhD,*** *Executive Director, Quality Assurance and Quality Control, Serono Laboratories, Inc.*

Current Viral Safety and Testing Issues

Moderator: ***Gail Sofer,*** *Director, International Validation Development, Pharmacia Biotech Inc.*

Technology Transfer: Mapping the Path to Success

Moderator: ***Scott W. Compton,*** *President, Marketing Services Management*

Surviving the Slippery Path of Biopharmaceutical Process Development and Scale-Up

Moderators: ***Howard L. Levine, PhD,*** *President, BioProcess Technology Consultants; and* ***Sally S. Seaver, PhD,*** *President, Seaver & Associates*

Manufacturing Biologics in a GMP Facility

Moderator: ***Donald E. Hill,*** *President, Don Hill & Associates, Inc.*

Project Management for Start-Up Biotech Firms

Moderator: ***James Fenno,*** *Vice President, Product Development, Lexin Pharmaceutical Corporation*

Perspectives on the Development of Pharmaceutical Biotech Products

Moderator: Joseph G. Habarta, PhD, Executive Director, Quality Assurance and Quality Control, Serono Laboratories, Inc.

POINTS TO CONSIDER IN THE SUCCESSFUL DEVELOPMENT OF PARENTERAL DOSAGE FORMS FOR PROTEINS AND PEPTIDES

John A. Bontempo, Ph.D., Consultant
Biopharmaceutical Product Development

INTRODUCTION

The successful development of biopharmaceutically acceptable, sterile parenteral formulations of recombinant proteins and peptides requires first, the unique design to include key points to consider for such a development. Secondly, the successful development of formulation requires the close interactions and understanding of interdisciplinary sciences encompassing molecular biology, fermentation, process development, protein chemistry, analytical biochemistry, pharmacology, toxicology, preformulation, formulation, clinical development, quality assurance, bulk manufacturing, packaging, sterile manufacturing, regulatory affairs, marketing, and others.

The contents and understanding of each scientific discipline, when incorporated sequentially, will result in the scientific understanding of the product development formulation process.

PURIFICATION PROCESS

Based upon the physicochemical characteristics of the bulk active substance, the process most desirable to achieve and implement should be the one yielding most consistently, purity, homogeneity, stability, and quality, lot after lot after lot. In

addition, this process should also be easily scaled up to manufacturing complying with CGMPs requirements and be cost effective.

PREFORMULATIONS

The initial objective of preformulation designs should focus on:

- Drug solubility and compatibility with various solvents
- Initial analytical developments
- Determination of initial bulk stability
- Effects of pH changes on solubility and stability of the bulk active substance
- Selection of excipients
- Initial decomposition pathways
- Initial stability

FORMULATIONS

Formulation designs should be based on preformulation results indicating potential desirable interactions leading to marketable dosage forms with acceptable shelf life. Some of the key final parameters to focus on should be:

- The final choice of buffer
- The final pH
- Isotonicity
- Stability-indicating analytical methods to demonstrate reproducible purity and identity lot after lot
- Optimal temperature and humidity
- Freeze-thaw effect(s) on the formulation

- Selection of specific stabilizers to achieve long shelf life
- Mechanical stresses
- Photolysis
- Container/closure interactions
- Methods of sterilization
- Routes of decomposition via physical and chemical stress

SUMMARY

Successful marketable products are the direct results of multi-disciplinary close interactions with constructive open communications with the sole objective of "doing it right the first time". This is perhaps the fastest way to bring the product to the health field.

APPROACHES TO THE DEVELOPMENT OF AN IMMUNOISOLATED XENOGENEIC CELLULAR THERAPY PRODUCT FOR THE TREATMENT OF CHRONIC PAIN

William E. Tente, Director, Clinical Production
CytoTherapeutics, Inc., Providence, RI

The undertreatment of pain constitutes a major health issue in the United States, resulting in unnecessary suffering, prolonged hospitalization and recovery, and increased morbidity. For example, nearly 75% of patients with advanced cancer have pain, with 20 to 25% describing it as very severe (AHCPR, 1994). It has been estimated that about one-quarter of cancer patients die with severe, unrelieved pain (Joranson et al, 1992).

Opioid analgesics are considered first-line therapy for the management of severe, chronic pain. While effective when used at adequate doses for many patients, their long term use is often unsatisfactory due to the development of tolerance in some patients or systemic complications that limit their usefulness, including cognitive dysfunction, constipation, nausea, and potentially life-threatening respiratory depression. The use of epidural or subarachnoid opioids can present additional problems related to the mechanical malfunction of catheters, injection ports and pumps, along with the possibility of infection.

One novel approach to the management of chronic pain is the sustained delivery of natural neuroactive substances to pain modulatory regions in the CNS. Adrenal medullary chromaffin cells, with their ability to release high levels of catecholamines, including norepinephrine and epinephrine, as well as enkephalin peptides (Livett et al, 1981; Wilson et al, 1982), provide a source of such analgesic substances. Activation of α_2- and opioid receptors in the spinal cord each result in antinociception and are profoundly synergistic (Yaksh and Reddy, 1981; Kuraishi et al, 1985; Yaksh and Malmberg, 1994). Norepinephrine and epinephrine have similar affinities at α_2-receptors (Bylund, 1992) and therefore both potentially contribute to analgesia. The enkephalin peptides, especially met-enkephalin, selectively activate δ-opioid receptors (Reisine and Bell, 1993). Activation of δ- versus μ- opioid receptors results in less adverse side effects in experimental animals, including respiratory depression, constipation, and addiction liability (Porreca et al, 1984). In addition, the combined delivery of different opioidergic and adrenergic agents may decrease the magnitude of tolerance that develops to a single agent (Yaksh and Reddy, 1981) and lead to sustained relief.

Investigations performed by Sagen and colleagues over the last several years have clearly established that adrenal medullary cell transplantation results in significant antinociception in experimental models of acute and chronic pain (Sagen et al, 1986). Increased tail-flick latencies, paw-pinch thresholds, and hot-plate latencies were observed following low dose nicotine stimulation in rats having an adrenal medullary transplant in the spinal subarachnoid space;

similar results were not apparent in animals given control transplants (Sagen et al, 1986a, 1986b). Notably, the reduced pain sensitivity in these tests correlated with cerebrospinal fluid (CSF) catecholamine levels (Sagen et al, 1991), and the observed reduction in pain sensitivity was attenuated by both opioid and α-adrenergic antagonists (Sagen and Pappas, 1987). Adrenal medullary transplants have also been shown to significantly attenuate nociceptive responses in two rodent models of chronic pain, the arthritis model and the peripheral neuropathy model (Sagen, 1992; Ginzburg and Seltzer, 1990). Further, neurochemical analyses have demonstrated sustained increases in met-enkephalin-like immunoreactivity (Sagen and Kemmler, 1989) and catecholamines (Sagen et al, 1991) in the CSF for at least 6 months following transplantation in rats.

Winnie et al (1993) recently presented preliminary evidence that spinal subarachnoid transplants of adrenal medullary allografts can provide analgesic benefit to cancer patients with intractable pain. Four out of five patients were reported to demonstrate progressive reductions in their pain scores after the transplant procedure, with concomitant reductions in opioid intake. Cerebrospinal fluid (CSF) samples revealed increased concentrations of met-enkephalin in three of the five patients and elevated catecholamine levels in the four patients in whom they were determined.

Despite this initial success, the widespread applicability of this procedure was questionable given the limited availability of human donor tissue for allografts. Moreover, although the central nervous system has been described as immunoprivileged, transplants are eventually rejected necessitating the use of immunosuppressants. The five patients who received the adrenal medullary allografts were given cyclosporine A (Winnie et al, 1993).

Immunoisolation by encapsulating the transplant in a permselective membrane, such as that provided by CytoTherapeutics' proprietary CRIB™ (Cellular Replacement by Immunoisolatory Biocapsule) technology, may resolve the problem of rejection and permit the use of xenogeneic cells. These membranes block immune cells, antibodies, and lytic factors of the complement system from the transplanted host yet still permit two-way diffusion of active substances and nutrients. Immunoisolation using a semi-permeable membrane has been evaluated with several endocrine tissues, such as pituitary (Hymer et al, 1982) and thymus (Christenson et al, 1988). This approach has also been successfully used in the transplantation of dopaminergic tumor cell lines and chromaffin cells in rodent and primate models of Parkinson's disease (Aebisher et al, 1991a; 1991b; 1994) and for the transplantation of pancreatic islet cells in patients with diabetes (Scharp et al, 1994).

Sagen and colleagues (1993) recently demonstrated that bovine adrenal chromaffin (BAC) cells immunologically isolated by a semi-permeable polymer membrane could survive for at least 3 months when transplanted into the rat spinal subarachnoid space and continue to produce and release catecholamines and opioid peptides. Moreover, significantly greater antinociception was evident in animals with BAC cell-containing implants