NEW ENGLAND PDA NEWSLETTER

01 October 09 | Volume 4, Number 3 | Page 1 of 6

Connecting People, Science and Regulation

Chapter Events

November 11th, 2009

Dinner Meeting

TR-45 Filtration of Liquids using Cellulose-Based Depth Filters

Sheraton Portsmouth

Harborside Hotel

Portsmouth, NH

AND

Lonza Biologics

Facility Tour (Members Only),

LOOK FOR THE FOLLOWING ARTICLES IN THIS EDITION

Hot Topics in Parenteral Product Development—2009

By Dr. Michael J. Akers, Dr. Steven L. Nail, and Wendy Saffell-Clemmer

Baxter BioPharma Solutions

Introduction

Product development scientists worldwide are working diligently to meet the challenges in developing stable, soluble, deliverable, and "manufacturable" formulations for all kinds of therapeutic molecules—small molecules, peptides, proteins, vaccines, genes, and other biologics. This article summarizes some of those challenges involving formulation, packaging, analytical, and process development of parenteral dosage forms.

Formulation

The most common challenges in developing injectable formulations are:

1. Overcoming solubility issues for drugs to be injected intravenously. Common approaches include the use of cyclodextrins (especially Captisol®, Cydex Corporation) and the design of liposomes and nanosuspensions.
2. Overcoming stability limitations of injectable drugs, particularly biopharmaceutical (i.e. large molecular weight) drugs. Lyophilization technologies come into play here.
3. Overcoming potential pain and/or tissue irritation properties of the drug and/or its formulation.
4. Achieving the desired rate of release of a drug formulated in a prolonged (sustained, long-acting, controlled) delivery system after intramuscular or subcutaneous injection.

Two drivers—biotechnology and novel treatments for cancer--are primarily responsible for the growth in parenteral drug delivery systems. Biotechnology products typically are proteins with very short life-lives, thus requiring frequent injections. Sustained delivery systems designed to reduce injection frequency, save some costs, and increase patient compliance, have seen important contributions for biotechnology drugs. Cancer drugs—many requiring solubilization, stabililization, and targeting technologies—also have stimulated significant advancements in parenteral formulation and delivery systems.

An explosion of advances and commercial successes in controlling and/or sustaining the delivery of injectable drugs has occurred in the past few years. Major technologies developed for injectable controlled release include primarily microspheres, implants, or hydrogels. For pharmaceutical protein controlled or sustained release, pegylation, microsphere or hydrogel technologies are the most likely choices.

The advent of formulation development of monoclonal antibodies (at least 20 antibodies approved and approximately 200 in clinical development) has brought new challenges to formulation scientists to overcome potential problems with high dose proteins. Among these problems include overcoming issues with highly viscous solutions and the tendency of highly concentration proteins to aggregate and become physically unstable.

Packaging

Components (glass-plastics-rubber) used to package parenteral dosage forms potentially can produce many serious problems, e.g.

- Insoluble, unsafe leachables
- Leachates causing aggregation and other incompatibilities with formulation components
- Protein aggregation due to silicone interactions
- Hydrophobic interactions and denaturation (e.g. protein adsorption)
- Foreign particles from rubber and glass
- Glass delaminated particles from glass

In the past few years, packaging advances related to sterile dosage forms have been concentrated in these areas:

- Pre-filled syringes
- Use of plastic bags, vials, and syringes
- Reducing or eliminating the use of silicone
- Reducing the level of leachable substances
- More user-friendly packaging systems for home health care (e.g. auto-injectors, combination systems, dual chambered syringes and cartridges, and needleless injectors.

Prefilled syringe usage especially has grown significantly because of the emergence of biotechnology and the need to eliminate the overfill (reduced waste) of expensive biomolecules compared to vials and other containers.

Biopharmaceutical Analytical Methods

The increase in high-dose therapeutic proteins and monoclonal antibody products has increased the likelihood of the formation of aggregates in solution and lyophilized products. Aggregation in protein formulations has negative consequences, including loss of activity, altered half-life, and increased immunogenicity.

Analytical techniques used to determine the potential presence of protein aggregation include:

- Size exclusion chromatography (SEC) with detection by Ultraviolet-Visible (UV-Vis).
- Analytical ultracentrifugation (AUC)
- SEC coupled with multi-angle light scattering (SEC-MALS)
- Field-flow fractionation coupled with multi-angle light scattering (FFF-MALS)
- Dynamic light scattering (DLS)

There are major advantages and disadvantages of each of these analytical techniques. No one ideal methodology exists for the characterization of aggregation in protein solutions. A combination of orthogonal techniques is required for the development of stable protein solution formulations and for the validation of accurate, precise, and specific quality control tests.

Protein Pharmaceutics

Perhaps the “hottest” topic in development and manufacture protein pharmaceutical products is protein aggregation. In particular, the immunological consequences of protein aggregation generate high interest to academicians, industrial scientists, and regulatory agencies. Below is a list of questions that protein pharmaceutics studies in the future might be able to elucidate:

- Is there a relationship between size of aggregates and immunogenicity?
- Are protein particles nucleated by foreign particles (e.g., glass, rubber) of any immunological consequence?
- How important is glycosylation or PEGylation in stimulating an immune response?
- How relevant are animal models in predicting immunogenicity?
- What are the most appropriate assays for preclinical characterization of immunogenicity?
- How does the shift from formulation conditions to in vivo conditions affect aggregation? Is in situ aggregation at the injection site an issue? Does this contribute to the generally observed higher immunogenicity after subcutaneous administration versus intravenous administration?
- How do we differentiate between particles arising from protein aggregation from particles arising from foreign materials?
- How much is known about engineering intrinsic properties of proteins to minimize aggregation? ***(Continued on page 4)***

GLOBAL SUPPLY CHAIN QUALITY PROBLEMS – WHAT NEXT?

By Helena Champion, MS, MBA

DRUG QUALITY ASSURANCE, LLC.

DrugQualityAssurance@gmail.com

Adulterated and defective products have made headlines in recent years, regarding contaminated heparin in drugs causing deaths, recalls of medical devices containing contaminated heparin, melamine in pet food and milk products, to name a few. Medical device companies have had problems with contractors not meeting specifications, sometimes with disastrous consequences to patients. The globalization ideal of lowering costs by sourcing materials and services from countries with low labor rates has turned out to have quality and safety risks which take a great deal of effort and expense to mitigate.

The observer may well ask – what next? Updated heparin standards, such as those in the United States Pharmacopeia effective October 1, 2009, should ensure detection of heparin contamination but that is only the tip of the iceberg. "What next" is a question that we have to explore proactively, to ensure all our products are safe and effective. We need to perform risk analysis to determine which components in our supply chain are at risk, and control risk as much as possible, to prevent problems.

The FDA has just published a cGMP Guidance "Pharmaceutical Components at Risk for Melamine Contamination", August 2009. Although melamine has not yet been found in the U.S. in drugs or components, the risk of melamine contamination does extend to materials used for drugs and the melamine Guidance requires that all drug product manufacturers determine whether the components they use are at-risk for melamine contamination and if they are at-risk, it recommends testing them for melamine before use. The components considered by the FDA to be at-risk for melamine contamination include commonly used materials such as albumin, ammonium salts, calcium pantothenate, caseinate, copovidone, crospovidone, gelatin, guar gum, lactose and povidone and others. They state that manufacturers need to know and monitor their supply chain for any at-risk components, and they need to know the identity and role of the actual manufacturer of such components and any repackers and distributors who handle the components before receipt by the manufacturer. Manufacturers should obtain certification from the manufacturer of at-risk components that these components are tested for the absence of melamine contamination as well as audit their component suppliers to ensure CGMP compliance.

In response to problems and increased trade in excipients and drug substances with China and India, the U.S. Food and Drug Administration has set up offices in those countries to facilitate FDA inspections and to help their authorities improve their regulatory capacity. While this is helpful, inspections only occur periodically and may not cover a particular company's product, so the onus will still be on the sponsor company to carefully qualify and audit all suppliers and regularly review their quality performance as well as their upstream supply chain.

The FDA is actively addressing the situation in other ways. In January 2009 a Draft Good Importer Practices Guidance, relating to consumer products in general, was published by the FDA and other Federal agencies, including the Departments of Homeland Security, Agriculture, Commerce, Transportation, the U.S. Consumer Product Safety Commission, U.S. Environmental Protection Agency and the Office of the United States Trade Representative. This Draft

Guidance recommends that companies establish a well resourced Product Safety Management Program and emphasizes that corporate responsibility for product safety should start at the very top of the organization. The Product Safety Management Program recommended comprises many responsibilities already required for drugs and medical devices and the FDA recommends that a company use a system for communication and information that allows the sharing of relevant information on safety and compliance not only internally, but also with third parties and federal, state, and local authorities.

An international pharmaceutical supply chain consortium called Rx 360 is being developed by volunteers from the pharmaceutical and biotech industry and their suppliers, with the intention of improving the performance of supply chains and sharing supplier audits and sharing information on safety problems in the supply chain. Rx 360 should be a good resource for sharing information with third parties in the drug and device industries and this is one of its objectives.

The security of finished drug product supply chains and prevention of counterfeiting is also a challenge and the January 2009 Draft Guidance "Standards for Securing the Drug Supply Chain - Standardized Numerical Identification for Prescription Drug Packages" is an example of efforts by the FDA to address this.

There are numerous conferences and workshops this year on supply chain quality and the issue will grow in importance. Ensuring the safety of your supply chain is a challenge and will need close coordination between purchasing, operations and quality to successfully qualify and monitor suppliers and distributors. Considering the high stakes in terms of patient safety, company reputation and the enormous direct and indirect costs of product recalls, companies need to know much more about their supply chains and control them even more actively than before, to avoid problems.

Hot Topics in Parenteral Product Development—2009 *(Continued from page 2)*

- What studies have been done to justify rejection criteria for visible particles in syringes or vials of protein drug product? How do we set criteria for percentage of vials or syringes with particles that is acceptable for a given commercial lot?
- Better understanding of the stresses imposed on proteins by freeze-drying processes including influences of ice crystal growth, ionic strength, cold denaturation, pH shifts, ice/freeze-concentrate interfaces, phase separation during freezing, and removal of the water that mediates folding of the protein

Trends in Manufacturing Processes and Equipment

Injectable product manufacturing is booming because of the growth of new biopharmaceuticals and small-molecule anticancer drugs. Companies with existing injectable product manufacturing capabilities either need to upgrade aging equipment and even remodel facilities or choose to outsource manufacturing to the rising presence of cGMP-compliant parenteral contract manufacturing companies. Biotechnology growth has given rise to many new companies, many of which are virtual, so they need to find contract manufacturers for the production of clinical supplies and eventual commercial product.

Here is a list of advances and trends in sterile processing:

- Quality by design (QbD) and process analytical technologies.
- Modular construction
- Growth in production facilities in countries like Ireland and Puerto Rico
- Faster and more reliable filling equipment
- High potency compound process and need for isolation technologies.
- Automated loading and unloading of freeze dryers
- Valid cleaning procedures
- Automated or semi-automated systems for visual inspection, weight checking, and labeling and finishing operations
- Disposable technology
- Continuous improvements in barrier isolator technologies

Summary

We have touched upon a few of a much larger number of interesting and relevant trends and advances in the area of parenteral product formulation, packaging, analytical, and process development. For some elaboration of these and other hot topics in the parenteral sciences, please consult the following publication that is still relevant

Akers, M.J., Nail, S.L., and Saffell-Clemmer, W., "Top Ten Current Hot Topics in Parenteral Science and Technology", J. PDA Pharm. Sci. Tech., 61, 337-361, 2007.

NEPDA PRESIDENT'S MESSAGE

By Jerry Boudreault
President
Drug Development Resources, Inc.

Greetings NEPDA Members,

I hope that everyone enjoyed a marvelous summer. It certainly was eventful. For me personally, it started out on July 2nd with my wife giving birth to our son, Gerard. He is a little bundle of joy who keeps me very busy and I squarely place the blame on him for the delay in getting this newsletter to you!

The summer ended sadly with the passing a huge advocate for the healthcare industry, Senator Edward Kennedy. The NIH funding that he championed certainly contributed to the explosion of life science achievements in our neighborhood over the last 20 years. I had the opportunity to see him in person three times. All celebrating the achievements of a local life science company for either the successful commercialization of a novel therapy to treat unmet medical need or the completion of research and manufacturing facilities that provide local jobs. He will certainly be missed and we can only hope that new Senator from Massachusetts shares his passion for the work that we do.

The New England Chapter has a great program lined up for Fall 2009 and I hope to see you at one of our events. Over 150 attended our very successful meeting on Environmental Monitoring on September 9th in Manchester New Hampshire. Our next meeting will held in Portsmouth New Hampshire on November 11. The topic is on liquid filtration using cellulose based depth filters. A tour of the Lonza Biologics Portsmouth manufacturing facility will be offered for members only. If you are not currently a member, and want to go on that tour, I recommend that you sign up now. The limited tour slots will go quickly once registration opens.

I am extremely pleased to announce that the Chapter Board awarded a $5,000 Transfer Scholarship to Diane Moustafa, Student Chapter Member at Large and Senior Manufacturing Technician at Genzyme. She graduated from Middlesex Community College Biotech program with a 3.75 GPA and has been active in the Student Chapter. The scholarship will help her fund studies at BU where she is working toward a degree in engineering. Speaking on behalf of the Chapter Board I want to wish Dianne continued success and we look forward to seeing her around PDA New England Chapter.

Our Planning Committee meets every other month to develop programming and collaborate on other initiatives like the student chapter and this newsletter. I encourage you to join us and get involved. Don't be shy! It is a great way to meet new people and make a difference. The next meeting is in Cambridge on October 14th from 6-8PM. If you are interested in attending, please send me an email at boudreault@ddres.com.

Best Regards,

Jerry Boudreault

Trying to get Noticed??

***We offer vendors, consultants, operating companies and other organizations the opportunity to promote themselves and also support the NE PDA Chapter by purchasing advertising in our newsletter. A* business-card size advertising opportunities can be purchased at a cost of $100 , half pages for $500, and full page ad for $1,000 per newsletter.**

The newsletter has the following reach:

- **Our direct e-mail distribution reaches over 1,800 contacts throughout New England.**
- **Our membership includes people from manufacturing, research, QA, QC, engineering, contract manufacturers, consultants, and regulatory.**
- **We promote the newsletter at New England PDA's bi-monthly dinner meetings, often with company tours, which regularly attract 50-150 attendees.**
- **We post the newsletter on our chapter's website at Global PDA (www.pda.org), an organization that has over 10,000 members.**

Deadline	Publication Date
October 15, 2009	November 2009
January 15, 2010	February 2010
April 15, 2010	May 2010
July 15, 2010	August 2010

If you are interested in advertising in the newsletter or need more information, contact Melissa Smith at melissa@mjqualitysolutions.com