

Drug Products for Biological Medicines

Novel Delivery Devices, Challenging Formulations, and Combination Products, Part 1

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Traditionally, the CaSSS CMC Strategy Forum meetings have provided a scientific focus on the development of biotech drug substances and their manufacture and characterization, leaving the development of drug product formulation and filling, understanding primary containers, and considering novel delivery systems somewhat out of scope. Over recent years, however, the importance of investing more science and technology into drug product development has become evident as different product types, higher protein concentrations, and doses and requirements for improved delivery of biological drug products have increased. The need to give patients larger and more concentrated doses has challenged formulation scientists, who now collaborate with early protein scientists to develop sequences at the earliest stages of



Pharmaceutical production: filling prefilled syringes with NeoRecormon and Mircera
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development with final drug products in mind. Increasing such volumes and concentrations of drug products is driving the need for development of new technologies that can deliver high doses. Delivery devices fall under device regulations and have distinctly different design, development, and validation requirements from those of protein drug products alone (e.g., design verification and validation requirements). The regulatory environment also has evolved, whereby a biological drug product (in even simple delivery systems) is now considered a combination product, making additional development consideration and additional requirements applicable.

The objectives of this Chemistry, Manufacturing, and Controls (CMC) Forum were to explore those new challenges, discuss potential solutions, and gain a better understanding in collaboration with FDA representatives of the current and future regulatory landscape around novel formulations and devices as combination products.

CONFERENCE OVERVIEW

A CMC Strategy Forum on drug products for biological medicines, including novel delivery devices, challenging formulations and combination products was held in July 2012 in Bethesda, MD. The purpose of this forum was to promote an

PRODUCT FOCUS: ALL BIOLOGICS, COMBINATION PRODUCTS, PARENTERALS

PROCESS FOCUS: FORMULATION DEVELOPMENT, FILL-FINISH, ANALYTICS

WHO SHOULD READ: PROCESS AND PRODUCT DEVELOPMENT, MANUFACTURING, DEVICE DESIGN

KEYWORDS: DRUG DELIVERY, DEVICES, EXTRACTABLES, LEACHABLES, REGULATIONS, CONTAINER CLOSER SYSTEMS

LEVEL: INTERMEDIATE

understanding of how best to increase the speed and effectiveness of drug product and device development for both large and small companies. Participants focused on areas that improve the likelihood for regulatory success, reduce risk, and decrease the time it takes to get a combination product through development. Topics discussed included drug product formulation challenges, device development, design verification and validation, and clinical testing. The forum included input from regulators on how to prevent delays during review of regulatory applications. Biopharmaceutical companies and regulatory agencies both presented case studies, and open discussions provided opportunities to gain common understanding and consensus on a range of topics.

The forum comprised four sessions — each followed by an interactive discussion with a panel and a moderator facilitating questions and comments from the audience. Part 1 of this article describes the first two sessions.

The introductory talk, “Combination Products: Challenges and Opportunities in Developing Guidance and Regulations,” was presented by Anthony Watson of the FDA’s Center for Devices and Radiological Health (CDRH). He described how combination products hold the promise of innovative solutions to deliver complex therapies. The process of regulating and creating guidance for combination products requires balancing the need to provide clarity and ensure that products are safe and efficacious, enabling such innovative products to the market as efficiently as possible. Incorporating the scientific and regulatory needs of several centers poses multiple challenges that have to be addressed. Challenges to ensure that guidances and regulations are timely and relevant are exacerbated by the unique issues associated with combination products. Efforts to address those issues extend to recent and future regulations and guidances, review practices, and design and testing standards.

FORMULATION DEVELOPMENT

The first session of the meeting was entitled “Developing Formulations for Biotechnology and Combination Products” and cochaired by Jay Gerondale (Amgen Inc.), Joel Goldstein (ImClone Systems Corporation), Gerd Kleemann, (Amgen Inc.), and Kathy Lee (CDER, FDA).

Molecule Selection: Margaret Ricci (Amgen Inc.) spoke on using sequence analysis and design to mitigate formulation concerns during preclinical development. She described how selecting an optimal therapeutic molecule candidate to progress into clinical development is critical to proactively mitigate manufacturing, formulation, and delivery challenges. Ricci presented several case studies showing the importance of leveraging preclinical molecule candidate assessment to mitigate issues related to solubility, viscosity, and stability.

Solubility limitations were encountered in formulation and delivery of a human cytokine. Such limitations were overcome by using the murine sequence as a blueprint for generating analogs of increased solubility. Within the antibody modality, screening assays were implemented to select low-viscosity molecules. Researchers applied molecular modeling to select favorable sequence attributes and to eliminate localized charge patches. Amgen has demonstrated that engineering the molecule for desired solution properties is a viable approach to mitigate formulation and delivery concerns in preclinical development. Furthermore, molecule candidate selection principles can be effectively applied with formulation, process, and delivery device strategies.

Heiko Nalenz (F. Hoffmann–La Roche Ltd.) spoke on **high-dose delivery** of biologics, specifically on the development of hyaluronidase coformulations. The subcutaneous administration route provides patients with a convenient alternative to an intravenous infusion. Nevertheless, limitations in the volume that can be administered have to be overcome for efficient administration of biologics.

CMC FORUM SERIES

The CMC Strategy Forum series provides a venue for biotechnology and biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the lifecycle of such products and thereby foster collaborative technical and regulatory interaction. The forum committee strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the forum meetings are published in this peer-reviewed journal with the hope that they will help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS, an International Separation Science Society (formerly the California Separation Science Society), and is cosponsored by the US Food and Drug Administration (FDA).

Potential strategies to overcome this challenge include increasing the concentration of the monoclonal antibody (MAb) and/or increasing the interstitial space at the injection site. Recombinant hyaluronidase (rHuPH20) is transiently increases the subcutaneous tissue space to aid in drug delivery.

This presentation highlighted the scientific approaches for drug product development of high-dose antibody/rHuPH20 coformulations. Nalenz focused on the particular challenges of keeping two very different proteins in a stable and active state within one formulation and controlling any unwanted interactions.

Device Compatibility: Mariana Dimitrova (MedImmune) spoke on proteins at interfaces and formulation approaches to minimize device–interface incompatibilities. Patient convenience, accurate dosing, and the need to deliver high-concentration protein formulations are driving the development of advanced drug delivery systems, including large-volume autoinjectors. Development of combination products combining sensitive biologics with drug delivery devices is often

associated with compatibility challenges with primary container components. When exposed to incompatible interfaces, protein therapeutics may be susceptible to structural perturbations, aggregation, particle formation, oxidation, and other degradation pathways.

Dimitrova discussed formulation challenges encountered when developing combination products for high-concentration protein therapeutics. She presented a case study highlighting the incompatibilities of a protein therapeutic to components made of high-density polyethylene and certain types of polypropylene. Dimitrova also described interface incompatibility, which manifests formation of visible and subvisible particles as well as conformational and colloidal destabilization of a protein. Two formulation approaches were successfully developed that resolved protein structural and colloidal destabilization, preventing particle formation at the incompatible interfaces. Dimitrova's talk highlighted the importance of compatibility risk assessment input into the design of the device or primary container early in development as well as balancing formulation compatibility requirements with device performance and user requirements considerations.

Microneedle Delivery: Peter Johnson (3M Drug Delivery Systems) spoke about formulation considerations for microneedle delivery systems, including his company's microneedle delivery technology, the Microstructured Transdermal System (MTS) for intradermal delivery of biologicals. His presentation addressed opportunities and formulation considerations for intradermal delivery.

3M's hollow Microstructured Transdermal System (hMTS) technology is for intradermal delivery of a liquid formulation through an array of small, hollow microneedles. The technology has attributes of both an autoinjector and a transdermal patch. The device adheres to skin while delivering up to 2 mL of liquid

formulation into the dermis (rather than the volume limit of 1 mL subcutaneous delivery for most autoinjectors). The hMTS device has an array of 16 hollow microneedles covering an area of ~1 cm² and delivers a formulation into the dermis ~0.5 mm below the surface of the skin. Delivery of a formulation to the dermis enables rapid uptake of drug by the lymphatic system and results in more rapid systemic availability (faster T_{max}) than what is typically observed when formulations are delivered subcutaneously, especially for macromolecules.

3M's solid Microstructured Transdermal System (sMTS) technology targets the epidermis and upper dermis for delivering drug formulation that has been coated and dried onto the tips of microneedles. A patch containing an sMTS microneedle array is applied to the skin using an applicator. Microneedles in the array are hollow or solid square pyramidal structures, 250–700 μm tall, with ~1300–300 microneedles per array (1 cm²), respectively.

SESSION ONE PANEL DISCUSSION

The morning presentations were followed by a roundtable discussion of specific questions posed to the presenters and the audience.

What challenges come with developing biopharmaceutical formulations for combination products? Several quality attributes of proteins can cause problems in the development of formulations suitable to store and deliver biotechnology products.

Protein solubility depends on a molecule's inherent characteristics (e.g., hydrophobicity, charge patches/dipole/pI, tendency to self-associate, and viscosity). Such properties can be modulated by solution properties developed for a given formulation (e.g., pH, salt concentration, and protein concentration). Protein solubility is an important formulation property because it can influence device function and manufacturability. A manufacturing process can cause issues with protein formulation stability during transportation, light

exposure, freeze–thaw cycling, heat, exposure to different buffers, filter–container surface interactions, extractables/leachables, shear forces, and nanoparticles.

Untoward interactions at interfaces can induce protein unfolding (most likely less potent), which can lead to adsorptive losses, aggregates, particles, and potentially an immunogenic response). Use of molecule-specific excipients, however, can impart colloidal stability. Leachables from process equipment or containers and fluid paths can cause all of the above, in addition to chemically modifying proteins. Subvisible and visible particles can assemble because of an interaction with silicone oil, the levels of which must be controlled and appropriately maintained to prevent issues related to consistency or comparability of product quality attributes. So proposed containers or delivery devices should undergo extensive evaluations, including assessments of surface interactions, transport, actual delivery (e.g., needle size) and adequacy of lubrication of primary container components.

A lack of the availability of concentrated protein for molecular assessment during early phase development often means that a surrogate assay needs to be developed (e.g., a high-throughput dynamic light-scattering (DLS) assay using polystyrene beads requiring less than 100 μL to measure viscosity properties (1). Excipients themselves can degrade (or contain contaminants) to react with products and so need careful study and control. Sterilization of plastics and glass can affect the durability and reactivity of containers (e.g., create reactive species) and in turn chemically modify proteins.

What technologies or strategies can mitigate some limitations for high-viscosity formulations for combination products? Several approaches can be used to mitigate high-viscosity issues, the most fundamental being analysis of protein sequences and protein surface properties. Molecular modeling can be applied to predict surface charge and identify areas of clustering of charge (“charge patches”).

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Site-directed mutagenesis can be applied to disrupt charge clusters on protein surfaces by substituting amino acids responsible for viscosity. However, when making amino acid mutations, you must consider their effects on potency, stability, and expression.

Another approach is to use excipients that modify protein self-association (colloidal stability), such as calcium acetate, amino acids (e.g., proline), surfactants, or pH modifiers. But one size does not fit all, and you should take into account tonicity, osmolality, and solubility under physiological conditions as well.

Delivery devices can be used to either assist in delivery of viscous solutions or accommodate increased volume so that more dilute formulations can be delivered. Using an MTS with multiple hollow microneedles, for example, allows more volume and higher viscosity to be delivered to the upper dermis than with traditional prefilled syringes and allows for improved pharmacokinetics and bioavailability. Solid microneedles have also been used effectively with high-viscosity materials. Although not often used, a “suspension” or crystalline formulation can increase the amount of material delivered when volume is limited by a container or device.

Increasing availability of the interstitial space by using a recombinant enzyme (e.g., hyaluronidase) allows for more volume to be delivered (e.g., 5–20 mL for

MAbs), which also improves bioavailability. To create such a formulation, you need to ensure that both proteins remain stable in the same formulation and that they do not interact.

For biotech combination products, what would be effective but product-quality-friendly container sterilization techniques? Sterilization of glass containers by irradiation can discolor the glass. E-beam sterilization, which can be applied over a shorter time than gamma radiation, does not discolor glass. However, when it is used with plastics, e-beam sterilization can elicit reactive materials that chemically modify proteins (e.g., surface peroxides). Residual agents such as ethylene oxide can yield adduct formation for low-dose protein therapeutics. Autoclaving and depyrogenation can change glass by increasing delamination potential and can modify physical properties of plastics as well. The use of light in the ultraviolet spectrum has been explored, but that method requires a transparent container to allow light to pass through without reflection.

What small-scale, high-throughput methodologies would offer predictability of product quality attributes at scale? The availability of protein during early phase characterization can be challenging. So small-scale assays are needed that can be used as predictors of liquid properties at larger scales. For transport studies in which material is limited, microplate wells can be used to agitate protein solutions with silicone-coated beads to study the effect on product attributes. DLS and differential scanning fluorimetry (DSF) can be used in a microplate format for colloidal and conformational stability screenings in early stage formulation development.

A gap exists for freeze–thaw studies in which scale does matter (e.g., what will happen in a large drug substance (DS) carboy versus in a small container). Such issues may be addressed by freeze–thaw cycling with controlled freezing and thawing rates (specialized freezers). In silico methods for predicting sequence hot

spots (e.g., chemical modifications like deamidation) is a valuable asset to formulation scientists. To this end, the ever-increasing power of mass spectrometry (MS) methods to provide data on multiple quality attributes at once and in complex solutions will no doubt be added to the list of useful tools.

What is a supplier's motivation to develop new solutions for biocompatible container closure materials? With the growth of the biotechnology industry and the number of its commercial products, the demand for primary containers has increased substantially over the years. Understanding user and technical requirements can benefit suppliers as they develop products that better meet user and pharmaceutical company partner needs. Suppliers should understand the robustness of their manufacturing processes and the potential effects on drug products (e.g., extractables and leachables).

What do suppliers need to make that effort profitable? Suppliers need the industry to agree on user requirements and specifications for devices or primary containers to maximize efficiency in manufacturing and profitability. Aligned industry standards would allow those suppliers to justify improvements in container quality and compatibility with biotherapeutics. The Association for the Advancement of Medical Instrumentation (AAMI) organizes ISO groups focused on consolidating the requirements for medical devices and is recognizing combination products (e.g., TC 84/WG11-Syringes).

One challenge is that very few biotech and pharmaceutical companies are included in those groups. So their needs and requirements have not been in scope for a long time, and the partnership is still in its infancy. The Parenteral Drug Association (PDA) also has task forces working on industry alignment (e.g., syringes).

What are critical challenges with container closure systems, and what new or next-generation systems should be considered to overcome those challenges? All container

closure systems present difficulties, depending on how a container will interact with a product. All containers exhibit extractables and leachables. In

ANALYTICAL TOOLS

Current technologies in formulation development and their roles in analysis

- size-exclusion high-performance liquid chromatography (HPLC): aggregates and truncations
- sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) silver or Western blots: aggregates and truncations
- ion-exchange HPLC: chemical modifications and charge heterogeneity
- mass spectrometry (MS): in depth characterization of primary and secondary structure
- HIAC counters: subvisible particles
- microflow imaging (MFI): subvisible particles
- field flow fractionation (FFF): subvisible particles and aggregates
- human eye or automated camera technologies: visible particles
- dynamic light scattering (DLS): aggregates, particles, and hydrodynamic radius
- viscometry: viscosity
- differential scanning calorimetry (DSC): thermal stability
- osmometry: osmolality.
- analytical ultracentrifugation (AUC): aggregates
- Inductively coupled plasma MS (ICP-MS): extractables/leachables
- Gas chromatography MS (GC-MS): extractables and leachables
- Scanning electron microscopy/energy-dispersive X-ray spectroscopy (SEM/EDX): particles
- Fourier transform infrared spectroscopy (FTIR): particles and protein structure
- Raman spectroscopy: protein structure
- Nephelometry: turbidity
- Spectrophotometry: color
- pH analysis
- bioassay: potency
- binding assays: potency, affinity
- Biacore technologies: affinity
- Capillary electrophoresis (CE): charge, glycosylation, aggregates

general, glass will exhibit mostly inorganic elements such as silicate and sodium, whereas plastics can produce a range of organic compounds that are probably more reactive toward proteins. Glass vials can delaminate, break, adsorb proteins, and change pH through leachables, yet we have a great amount of experience with them, and they are easy to use on a manufacturing line. The container closure of a vial is simpler than that of a syringe and its components. For example, glass syringes with a staked-in needles contain silicone oil, tungsten, and glue, which can all interact with a drug product.

Plastic containers (e.g., vials and syringes) may not require silicone oil for lubrication (plastic-device dependent). They do not break as easily as glass and have tighter tolerances and greater thermal expansion capabilities. Their disadvantages include oxygen permeability, organic leachables, stress cracking, protein adsorption, UV light sensitivity, and potential problems in container closure integrity.

What are current limitations and challenges of analytical technologies used for the characterization of high-concentration formulations? The “Analytical Tools” box lists current analytical tools used in formulation development.

Product quality assessments with low-volume, low-protein concentration formulations are a challenge (e.g., Epogen (epoetin alfa) in human serum albumin formulation, hyaluronidase in a high-protein product formulation). High-concentration formulations can influence the ability to analyze many protein attributes directly without having to dilute product or change its solution properties to suit the method. High-protein concentration formulations can cause nonlinearity of data (e.g., particle analysis requiring dilution) and even affect osmolality results.

What do new and innovative analytical technologies need to focus and deliver on to overcome current analytical limitations and challenges? It is well known that each method

used for particle characterization (e.g., HIAC, DLS, MFI) can give different quantitative results for the same sample. But it is unclear whether the algorithms used to differentiate silicone oil droplets from protein particles with MFI are realistic. If we know that such particles are not relevant, then why continue those studies with ambiguous results? It would be valuable to have a method that can characterize particles within a container itself because the extrusion of product through a syringe (or into a syringe from a vial) can change particles. No single technique can provide quantification, differentiation of particles, and analysis of content of particles without multiple assays. Quantitating smaller particles and trying to deconvolute signals of those particles from noise in assays is currently a challenge. It would also be valuable to know the relationship of measurable values from particle characterization to clinical outcomes.

Structural techniques give a meaningful, quantifiable analysis of tertiary and quaternary structure that can be routinely used. It would be valuable to have technology to identify degradation related to proteins directly at interfaces to characterize primary container incompatibilities, especially when minimal protein is available and methods are laborious. The ability to monitor and measure the stability and activity of different proteins in a single formulation in vitro and in vivo (what is really going on in the body regardless of the formulation) would be valuable.

COMBINATION PRODUCTS

The second session, “Combination Products for Biological Products: Early Design and Characterization,” was cochaired by Andrew Donnelly, (MedImmune), Jennifer Mercer, (Genentech, a Member of the Roche Group), and Lana Shiu (CDRH, FDA). This session focused on difficulties associated with combination products, particularly the technical and scientific issues that can arise from drug-device combinations for novel delivery devices. Understanding how to evaluate and assess the effects of the

interaction between a drug or biologic and a device is critical in developing combination products that is safe and effective. Other unique challenges include the development path and potentially divergent demands on developing a drug–device and understanding the manufacturing and quality requirements for both elements. Often a device is introduced late in development, shortening design and characterization times. The goal of this session was to provide a general understanding of the regulatory expectations for characterization of a combination product, as well as the difficulties that sponsors face when dealing with design and characterization of an innovative combination product with a unique delivery system.

Kathy Lee (FDA) presented on **regulatory expectations** for the characterization of biotechnology products in combination products. Characterization of combination products present unique challenges compared with characterization of traditional biotechnology products. Her presentation highlighted the regulatory expectations for combination products submitted in investigational new drug applications or investigational device exemption applications focusing on early phase product development.

Jay Gerondale (Amgen Inc.) gave an industry perspective on **design controls**. When developing and manufacturing combination products, manufacturers must determine the applicability of the quality system regulations, current good manufacturing practices (CGMP) for drugs and biologics, and the quality systems regulation (QSR) for medical devices. Multiple aspects of a design control process can reduce risk for both manufacturers and end users to ensure that designs are easy to use, robust, and safe. Gerondale's presentation reviewed the processes used to design and develop the device portion of a combination product and the design control requirements that may be followed.

Steve Christenson and Deanna Lane (Medtronic Neuromodulation)

presented about **design perspectives on implantable devices** for targeted drug delivery. Their company manufactures implantable devices for targeted drug delivery into the central nervous system. They reviewed design perspectives on chronic implantable drug delivery systems, focusing on the considerations for characterizing interactions between a device and its physiological operating environment, as well as interactions between a device and the therapeutic agent being delivered.

Development Challenges: The final speaker of this session was Paul Jansen (Sanofi), who provided industry perspectives of the challenges with developing combination products for biotechnology products. For successful combination product development, he said, managing development cycle time and regulatory compliance is critical. Jansen said the use of device platforms and representative or “equivalent devices” in clinical studies is critical to meet development timelines.

SESSION TWO PANEL DISCUSSION

The second session presentations were followed by a roundtable discussion of specific questions posed to the presenters and the audience.

What studies are required during development to characterize combination products? Such studies include characterization and understanding of a drug/biologic; design, design verification, and functionality of a device; and assessing the impact of the drug–device combination.

The main difference between characterizing a traditional drug product and a device is the use of design controls (FDA 21 CFR 820.30) and the need for characterization of a combination product. A significant aspect of design controls is the testing required to ensure that a design will function reliably (design verification) design outputs meets design inputs (requirements) and that a device design meets its intended use (design validation). User requirements are identified and translated into

engineering requirements (design inputs).

Design verification testing can include a number of tests and methods to confirm that specified requirements (design inputs) have been met. For a combination product, compatibility testing demonstrates that a device and its components do not adversely affect the drug. Device functionality must be appropriate to meet specified injection requirements. Design validation is then performed on production-equivalent devices to ensure that they conform to user requirements. The device manufacturing process is transferred to a commercial site where process validation will occur, with further device verification testing to verify the commercial process manufactures a device that functions as expected.

What studies are required during development to characterize a combination product?

Characterization of a combination product is conducted to assess potential impacts of a device and its constituents on a drug product as well as the functionality of the product to deliver a drug safely and effectively. Product-contact components should be evaluated for the potential of a protein to adsorb to component surfaces.

Additional characterization includes assessing a product in its device over time to understand the effects of storage, exposure to shear, temperature excursions, and light. You should also evaluate the effects of that product on the device's functionality. “In-use” tests should be conducted to expose product to the full fluid path and product contact surfaces. Stability and transportation studies evaluate functionality of a fully assembled drug–device combination over time. Risk assessments can be used to justify the extent, if any, of stability studies on drug product in a delivery device. Some companies note that risk assessments may not be accepted by health authorities. To establish combination product shelf life, the shelf lives of both the drug and device must be established independently and in combination.

Simulated use human-factor (HF) studies are conducted to ensure that a device can be used as intended, that users can effectively follow instructions, that no safety issues are identified, and that use-related errors are mitigated. A use-related risk assessment is conducted and updated during the design process to identify potential use errors and required mitigations. HF studies are needed for home-use devices and for those that would be used in a clinical setting.

Specifically for prefilled syringes, characterization may include the following: leak testing, air ingress, dye ingress, glide force, break-away force, needle shield pull off force, ease of assembly into devices, fractures and breakage, validation of graduation markings, hold-up volume, and needle coring test. Performance of antineedle stick mechanism in accordance with CDRH guidance on needle-stick prevention mechanisms should be considered, as well as appropriate ISO standards and connectivity to other devices necessary for actual use (e.g., needles, adapters, transfer systems, extension tubing, and Luer connectors).

How are changes to a device (to enable licensure) managed during development of a combination product? Protein sequences generally do not “change” during development once a clone has been selected. Devices, however, may change frequently during design and review stages and during design verification and validation. During human factors formative studies, risk mitigation activities may be implemented and could result in redesign and/or modification of a device. Risk assessments during device development may influence the design as it evolves and as risk data are generated.

During development, design changes may be needed to ensure that the final design meets expected performance and safety. Device changes are documented, contained within a design history file, and managed through the quality management system. As part of validation, human factors summative

studies are conducted and “summative study reports” created. Changes that may influence the user interface or functionality of a device, its safety, or its efficacy may require further testing or clinical bridging studies to ensure that such changes do not affect device safety functionality or performance. A risk assessment study can be performed to evaluate the potential impact and need to conduct additional studies.

What expectations for assessment of extractables and leachables during development of a combination product? Assessing both extractables and leachables is essential for any container closure system, including a combination product in which there is direct product contact. For implantable device–drug product combinations, a dynamic leachables characterization study is conducted to evaluate real-time interaction of a drug–biologic with an implantable drug delivery system and to evaluate potential changes to the leachable profile. That provides complete exposure to the drug fluid path and product contact time that represents “in-use” conditions. It also allows evaluation of substances that may leach from a device into drug–biologic product over time (leachables profile).

When developing an extractables program for a combination product, you should take into account the extractable tests required and compendial tests (chapters 1, 87, 88, 381, 1031), ISO 10993 (for the device) using an in-house worst-case, specific buffer program, and appropriate methods to assess possible extractables. Extractables testing must be realistic; going over the top may result in nonrealistic profiles and a lot of wasted analytical and toxicological work.

Solvents that can't be readily analyzed should be avoided. Actual drug–product formulations that do not contain protein should be used because protein at high temperatures will interfere with the analysis. Full length of possible contact in the process is unlikely (except for short duration). Typical analysis includes the use of elevated temperatures or

other exaggerated solvation conditions, taking into account surface areas and sample size, interlot and lot-to-lot variability, and device components.

You should understand the chemistry of the compounds to define the analysis: There is no standard set of techniques. Analytical methods for extractables are not just for organic compounds: total organic carbon (TOC), UV absorbance, gas chromatograph–flame ionization detection (GC–FID); GC–MS; GC–IR; liquid chromatography–photodiode array (LC–PDA), LC–MS; LC– nuclear magnetic resonance (NMR), FTIR, pH, conductivity, visual inspection metals analysis, and ICP–MS. Make sure the solvents don't affect the contact part of the machinery used to analyze extractables. Volatility of organic materials must be taken into account.

Toxicologists can help define which extractables may be important to look at during leachable studies. You also need to justify which methods are applicable for a leachables study. To select appropriate analytical methods, a sound understanding of extractables is required to ensure appropriate methods are available to assess leachables in product. What is the importance of sensitivity and interference; what are the specific tests for leachables, within or amended sets of existing product methods? Ensure that appropriate methods are available to detect impact of leachables on product. In some cases, leachables are not readily detectable but may have alter the product; hence, appropriate assays are needed for proper product analysis. Methods need to have an appropriate level of qualification and validation.

Leachable studies are needed to understand whether previously identified extractables could become leachables in real-world cases. Leachable studies are needed during stability at recommended storage conditions up until expiry, testing at regular time points unless you have end of expiry data at filing. Use of actual product (not just its formulation) in some form of

accelerated leachable study is valuable. For leachable profiles in use (e.g., on extrusion), you need to have a method to detect an extractable in drug substance and drug product. Consider that there may be leachables that extract with the protein. You need to take into account the possibility that some chemicals may be modified over time by the product before they become soluble/leachable.

Is it necessary to characterize a combination product using aspects of design controls for a standard prefilled syringe or delivery device?

Design controls are necessary for prefilled syringes and other injection devices. The Center for Biologics Evaluation and Research (CBER) would like to see some aspects of design controls applied to the development of prefilled syringes products. Specific requirements are provided in FDA proposed rule for CGMP processes for combination products (finalized in January 2013) (2). Design verification could include studies such as container closure integrity and glide force. Design validation could include HF studies on the usability aspects of the prefilled syringe, determining, backstop and plunger form factor designs and force profiles required for the intended patient population. Most companies have some basic information on the design of the prefilled syringe that can be captured to comply with design controls for existing products. It does not have to be as extensive as would be expected for a product being in development.

Design controls may not exist for a legacy product already on the market, and the FDA does not expect sponsors to recreate information that did not exist previously. The preamble to the new GMP rule allows for flexibility in design controls because the drug GMPs are comprehensive and may apply to the quality system regulations. CBER has indicated that many sponsors have information that would address some aspects of design control. It cannot tell a company to ignore a regulation, but it can show some flexibility with existing products.

What is defined as the “to be marketed product” or “final finished product” for a drug delivery device? What are the implications for clinical development? The issue appears to be an expectation that a device used in pivotal clinical studies for combination products would be the final commercial version, for which no changes could be made. That is, the device must be ready for commercialization at that time — or bridging studies would be required. However, it should be made clear that this is only for devices that are constituents of combination products. For others, it is understood and accepted that there can be changes in the device design during the pivotal clinical trial. CDRH has issued regulatory guidance on how to address such changes (3). However, some aspects of a device could change, for example with feedback from clinical studies that do not affect its overall safety, efficacy, use or “device platform” (e.g., color, size, site of manufacture, and other changes that do not affect device function and performance). Using a device that may not be the final commercial device but mimics all key performance attributes for clinical testing will facilitate development. Aspects that should be the same include identical physical characteristics, dose increments, dose accuracy, dose principles, administration routes, administration depth in tissue, administration time, and administration speed.

Other approaches could be developed depending on the difference between what is used in clinical studies and the final commercial device. However, justification would be required to ensure that differences would not have adverse effects for patients, use of the device, and its safety and efficacy. It appears that prior knowledge can help, but it depends on the complexity of a device (e.g., a pen or an implantable delivery device).

Part 2 of this article will describe the last two sessions of the forum: human factor validation testing and clinical studies for combination

DISCLAIMER

The content of this manuscript reflects discussions that occurred during the CMC Strategy Forum workshop in addition to personal viewpoints and experiences of the authors. This document does not represent officially sanctioned FDA policy or opinions and should not be used in lieu of published FDA guidance documents, points-to-consider documents, or direct discussions with the agency.

products; and regulatory pathways, marketing applications, and postlicensure.

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