Drug Products for Biological Medicines

Novel Delivery Devices, Challenging Formulations, and Combination Products, Part 2

Anthony Mire-Sluis, Donna French, Jennifer Mercer, Gerd Kleemann, and John Dougherty

The California Separation Science Society (CASSS) held a Chemistry, Manufacturing, and Controls (CMC) Strategy Forum on drug products for biological medicines in July 2012 in Bethesda, MD. Topics included novel delivery devices, challenging formulations, and combination products. This CMC Strategy Forum aimed to promote an 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. 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 for all participants to gain common understanding and consensus on a range of topics.

Product Focus: All biologics, combination products, parenterals

Process Focus: Formulation development, fill–finish, analytics

Who Should Read: Process/product development, manufacturing

Keywords: Drug delivery, devices, extractables, leachables, regulations

Level: Intermediate

This CMC Strategy Forum comprised four sessions — each followed by an interactive discussion with a panel and moderator facilitating questions and comments from the audience. The first two sessions were discussed in part 1 of this article, published in the April 2013 issue of BPI. This month, Part 2 concludes with presentations on human factors studies, regulatory pathways, and marketing applications.

Human Factors Testing and Clinical Studies

The third session covered combination products for biologicals, including human factors studies testing and clinical studies conducted for combination products. Mark Marley (Eli Lilly and Company) and Jacqueline Ryan (US Food and Drug Administration's Center for Devices and Radiological Health, CDRH) were session cochairs.

Molly Story (CDRH) spoke on human factors studies for combination products, including the impact on design and development, as well as regulations and scientific foundations for these studies. She focused on the human factors engineering process for medical devices and design validation testing. Story also reviewed FDA expectations for human factors data: conducting a comprehensive risk assessment, performing human factors studies including identifying and mitigating use-related risks, and documenting development in a design history file.

Desiree Crisolo (Genentech, a Member of the Roche Group) spoke on regulatory considerations for developing a human factors studies strategy. She provided an industry perspective on the draft FDA guidance on human factors. According to Crisolo, human factors studies and the final design validation have been challenges for pharmaceutical companies integrating drug delivery devices as part of their drug product configurations. Many lack understanding about how to effectively apply human factors principles throughout the device development process. Companies' inability to provide adequate human factors information as part of their dossiers has led to significant delays in approval and completed response letters. Crisolo described the limitations of conducting usability assessments in a controlled clinical setting, noting that human factors studies (simulated use) are the most rigorous means to assess usability.

With the release of the 2011 draft guidance from the CDRH, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, the FDA provided information about how manufacturers are to approach, execute and analyze human factors data to support use of a device. The regulatory landscape continues to evolve, and understanding how to successfully integrate human factors principles within a device development process will be essential in commercialization of combination products. Crisolo highlighted the technical and regulatory considerations

in developing and documenting a human factors strategy and presented a case study of current experience gained with a drug delivery device.

Carol Holquist (FDA's Center for Drug Evaluation and Research, CDER) spoke on lessons learned from adverse events, patient feedback, and labeling of combination products and their influence on existing and developing guidance. She reviewed human factors considerations for design and development for labeling drug and drug–device combination products. Holquist provided examples of medication errors reported to CDER relating to poor product design, described current practices for human factors submissions to CDER, and presented the top five problems associated with those submissions.

Mark Marley (Eli Lilly and Company) and Jennifer Visich (Genentech) provided an industry perspective on clinical trials for combination products. Development of drug delivery systems for therapeutic proteins can be challenging because of the need to concurrently develop a drug and appropriate delivery device (combination product) while ensuring adequate clinical evaluation. Published regulatory guidance regarding clinical data requirements for incorporating drug delivery systems during development is limited.

Marley and Visich provided briefly summarized the regulatory framework and provided an example of regulatory guidance for a combination product clinical development plan. In the absence of regulatory guidance, they proposed a risk-based approach to determine the appropriate clinical bridging strategy for introduction of new combination products. The presentation identified clinical and device variables as part of a framework for discussion on the types of clinical studies that are appropriate for clinical evaluation of combination products in a development program. A recent case study including regulatory feedback illustrated proposals for incorporation of combination products during clinical development. A key point was that the purpose of a clinical bridging study is to evaluate clinical outcomes (of a drug administered by a device) rather than usability, which is the purpose of the human factors testing.

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).

Session Three Panel Discussion

Session presentations were followed by roundtable questions posed to the presenters and audience.

What considerations do I need to take in designing human factors studies for combination products? The study should include a representative patient population and a use environment that simulates actual use. Critical tasks should be identified with a formative human factors testing and risk-management process — such as user failure modes and effects analysis and hazard analysis — according to each given device. Formative studies should support the final design validation, and all residual risks should be mitigated to acceptable levels.

Before initiating a human factors study, a sponsor should identify the intended use, users, the use environment, and the potential use-related hazards of a device by implementing tools such as risk assessments and task analysis to prioritize potential use-related risks.

Use errors should be mitigated as possible through the design of the device to an accepable level before final design validation testing. Risks should be mitigated before validation, which should demonstrate and provide evidence that a medical device, as designed, can be used safely and effectively. All aspects of human factors assessments should be included in design history files.

What are key considerations for determining whether to conduct an "actual use" clinical evaluation human factors study instead of "simulated" use for drug delivery devices? Formative human factors studies are conducted to obtain data that will inform a device design. Such studies are essential to developing the design of a device. Summative human factors studies (design validation) are conducted to confirm that a device meets intended user needs, so they should be performed using a representative device.

The lead center (CDER) determines whether safety and efficacy of a combination product could be established independently from its device constituent. CDER/CDRH can review user testing protocols and provide feedback before the final study. Human factors studies are not clinical studies. Companies have received a Complete Response Letter (CRL) for using clinical study data in place of summative usability studies to validate their products.

Human factors engineers are trained to perform usability assessments and identify use errors. The goal in their studies is to include whatever aspects of real use (e.g., environmental conditions, ergonomics, delivery of training) that could affect the nature or quality of user–device interactions. Human factors studies assess aspects of user interactions with combination products and identify use errors, such as whether operation of a device exceeds users' capabilities (e.g., force required to remove a cap exceeds user capability); errors in device operation (e.g., twisting instead of pulling cap); environmental conditions having negative effects (e.g., household noise distractions); aspects of device use that are inconsistent with user expectations; unexpected use of a device; use of a device in inappropriate but foreseeable ways, for which adequate controls were not applied.

Design validation should be focused on ensuring successful mitigation of critical use failures that can be attributed to the device — those that can lead to unacceptable patient harm — which would be identified through a risk-management process and formative human factors testing. Use risks must be mitigated to an acceptable level.

For injection device combination products, simulated use (e.g., injecting into a pad placed against the injection site instead of into the body) studies are typically adequate to identify use errors and assess user interactions with the device. Such studies are usually appropriate because injection surrogates are adequate in representing injection sites and patient handling, operation of a device is the same as the actual use conditions, and environmental effects can be simulated (e.g., noise).

Simulated studies may be inappropriate for some unusual circumstances, such as when the injection is unusually painful or completion of task requires sensory feedback from the injection site. Actual-use studies might be appropriate when variables (use scenarios) cannot be adequately simulated but could potentially lead to critical use errors or failures.

Obtaining reliable usability data during clinical testing is difficult because clinical trial patients are highly trained and monitored or coached. In addition, the user training and environment do not reflect real-use postmarketing environments. Usability assessments must allow for patient error, which could compromise clinical testing outcomes. No specialist human factors personnel are typically present, and clinicians are not trained to identify use errors. Clinical assessments of usability can provide only exploratory or formative human factors information.

What specific considerations do I need to take into account when designing clinical studies for combination products, including clinical bridging strategies to support safety and efficacy? Clinical bridging studies are often required when adding or changing configurations (e.g., change from a prefilled syringe to an autoinjector during phase 3). The timing of the introduction of combination products, clinical attributes, and device attributes should be assessed in a risk-based manner to design those studies. Study design should depend on the nature of the device configuration change and associated risks to patient safety and efficacy. Clinical attributes (e.g., therapeutic window, patient variability, pharmacokinetic differences in route of administration) and device attributes (e.g., volume, rate of injection, injection depth) need to be taken into consideration in the design of clinical studies for combination products.

Several types of clinical bridging studies can be carried out to compare delivery systems from a pharmcokinetic/pharmacodynamic (PK/PD) standpoint. The study can be a PK characterization with a comparison to historical data. It can also be a BE study, with direct comparison of the drug administered with the device to its reference configuration. Typically single-dose studies in healthly volunteers are adequate, and the testing should be done in patients or as multidose only if needed from a disease/molecule perspective.

Because it may not be practical to conduct a pivotal phase 3 clinical study using a final commercial device or combination product, is it possible to use a risk-based assessment to determine the level of clinical evidence or clinical data required, if any, for registration of a combination product (e.g., literature, BE study, postmarket data and technical evidence)? A risk-assessment approach is a valid mechanism for making decisions on the extent of bridging studies and whether they are required.

Considerations to take into account include the phase of development, clinical attributes of a combination product, and the nature/complexity of a device. Clinical attributes include factors such as PK data variability, previous experience with a device in clinical studies or as marketed products, clinical experience with the drug, and width of the therapeutic window.

Device attributes include changes in product contact materials, hand posture, injection technique, injection rate, injection angle and depth, pressure applied to skin at the injection site, and the volume or number of injections. Device attributes may affect product quality (should be detectable through analytical comparability), potential for intramuscular (rather than subcutaneous) injection, or different drug dispersion in the subcutaneous space that could affect PK parameters. Design of a clinical bridging study should include detailed assessment and justification based on a thorough understanding of clinical and device attributes.

If a device in development has been used commercially for other products and/or the same patient population, are additional "ease of use" studies necessary? No clear definition is available for *ease of use*, so use of that term should be discouraged. The specific desired outcomes of such usability assessments should be clearly defined. Human factors studies and design validation are the most robust ways to assess usability.

For simulated-use human factors studies with and without drug product, is an institutional review board (IRB) approval needed, and is submission of an investigational device exemption (IDE) or protocol to an investigational new drug (IND) application needed? The decision to obtain IRB approval should be based on risk to patient safety. From a Health Information Privacy Act (HIPA) or patient-consent

perspective, seeking IRB approval should be considered. The agency preference from a filing perspective is to review a human factors study protocol, but it is generally not required as an amendment to an IND application. Although that depends on the device and study, whether a device is well known or new, and whether a product poses a risk to patient safety.

Regulatory Pathways, Marketing Applications, and Postlicensure

The fourth session, cochaired by Jeanmarie Sales (Medtronic Neuromodulation) and Nikhil Thakur (CDRH), covered regulatory pathways for combination products, including marketing applications and postlicensure. Lana Shiu (CDRH) spoke about navigating FDA channels for combination products approval. Shiu discussed the need for increased understanding of how the agency regulates combination products as well as various ways to navigate the application process to avoid regulatory pitfalls.

Jacqueline Ryan (CDRH) spoke on challenges with applications for combination products. Her presentation identified some regulatory difficulties in early product development, premarketing applications, phase 3 device bridging, and postmarketing device changes in the context of PFS delivery systems and provided some advice on overcoming those problems.

Suzanne Kiani (MedImmune) and Douglass Mead (Janssen R&D, LLC) spoke on developing a marketing application for a combination product in the United States. In preparing an NDA or biologics license application (BLA) (marketing application) for a drug–device combination product, a sponsor must consider the principles and content requirements of a device submission. Kiani and Mead reviewed 510(k) content requirements that might apply to a device constituent part alone and discussed challenges in merging that information into an electronic common technical document (eCTD) format.

Depending on the complexity of the device involved, that content may be included in limited sections in the dossier (e.g., container–closure sections), or it may involve additional eCTD modules. Format choices may need to be based on the specific device characteristics and should consider consolidation of device information either in a single section or through a 510(k) reference or master file strategy. Other device-specific information, such as assembly information and control strategies, specifications based on device design controls, or delivery device instructions for use may pose unique questions or review timing challenges. The potential requirements and strategies for handling post-approval changes will also be discussed.

Session Four Panel Discussion

Session presentations were followed by roundtable questions posed to the presenters and the audience.

How do you appropriately file approval for a combination product when multiple offices or divisions are involved in its ultimate approval? A combination product can be defined in one of three ways: as a drug within (stored or chemically bound) a device; as a drug and a device copackaged and combined before use; or as a drug and a device packaged separately but labeled for use together. Regulatory oversight is defined by the primary mode of action (PMOA). However, each constituent part retains its regulatory status even when it becomes a constituent part of the whole combination product.

The Office of Combination Products (OCP) classifies and assigns each such product when it is filed. The Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices, Office of Device Evaluation deals with the most common drug delivery systems — including syringes, pens and needle-free injectors, metered-dose inhalers, nebulizers, and infusion pumps — and works directly with CBER and CDER.

When filing a combination product, you must consider the PMOA. It is the single mode of action of a combination product that provides the most important therapeutic action. The most important therapeutic action is that mode of action expected to make the greatest contribution to the overall intended therapeutic effects of a combination product.

For example, a drug-eluting stent's main use is to open an artery, and its secondary use is to deliver a drug that has other clinical effects dealt with by the CDRH as a primary review. A drug-containing disk that is implanted to deliver drug is reviewed by CDER as a primary review. PFS or drug-within-pen injectors are assigned to CBER or CDER for primary review, which will are then included in a BLA or an NDA.

Generally, only one investigational application to the lead center should include all information for all constituent parts. Those include drug master files (DMF) or cross references to existing applications for proprietary data that cannot be included in an IND or IDE. The FDA can require two submissions according to 21 CFR 3.4(c). Some companies may request two applications (a 510(k) and a BLA or NDA), but when one is sufficient, OCP will decide case-by-case.

Sometimes one constituent part of a combination product is already approved for another use, so the labeling of the already-approved product would need to be changed to reflect its new intended use in a combination product. In such a case, the FDA may determine that two applications are necessary if the labeling of the already-approved product is subject to legal requirements different from those that will apply to the combination product.

Under what specific regulations does a manufacturer of a combination product need to comply to ensure that a product (pre- or postmarket) is approved? In the proposed rule *Current Good Manufacturing Practice Requirements for Combination Products*, section 4.4(b) offers two options for demonstrating compliance with current good manufacturing practice (CGMP) requirements for each constituent part in copackaged or single-entity combination product (**1**). The first is to demonstrate compliance with the specifics of all CGMP regulations applicable to each constituent part. The second option is to demonstrate compliance with the specifics of either the drug CGMPs or the quality system regulation, rather than both.

If you follow drug CGMP regulations 21 CFR 210 and 211, you

must also follow specific provisions of the quality systems regulation, including §820.20 management responsibility, §820.30 design controls, §820.50 purchasing controls, §820.100 corrective and preventive action, §820.170 installation, and §820.200 servicing.

Participants recognized that submission (eCTD) content plans for the device information should be matched to the complexity and regulatory status of the delivery device(s). The panel also discussed the difference in the approach for determining release specifications for drugs and devices. Release specifications for drugs are typically established late in development through clinical batch analysis, whereas device performance specifications can be derived from design inputs (user requirements) and then verified and validated. For example, regarding PFS piston travel force specifications (measured at a fixed velocity), there was some consensus that such release specifications could be determined through a use assessment and glide characterization rather than based on clinical batch data.

During this session, someone proposed that design controls could be used to establish acceptance criteria for other specification related to functionality (e.g., autoinjector delivery time). That is an important point because many of those parameters cannot always be based on what is used in the clinic.

If you follow the device quality systems regulations in 21 CFR 820, you must also follow specific CGMPs, including §211.84 testing and approval or rejection of components, drug product containers, and closures; §211.103 calculation of yield; §211.132 tamper-evident packaging for over-the-counter (OTC) human drug products; §211.137 expiration dating; §211.165 testing and release for distribution; §211.166 stability testing; §211.167 special testing requirements; and §211.170 reserve samples.

This dual system allows for manufacturers who make combination products either in the same facility or separately to select the appropriate regulatory pathway. For human factors studies, the FDA guidance *Medical Device Use–Safety: Incorporating Human Factors Engineering into Risk Management* (July 2000) and draft guidance *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (Draft guidance 2011) are appropriate (**2**, **3**)

ISO and ANSI materials — specifically, ANSI/AAMI HE75:2009 and ISO/IEC 62366:2007 — may be useful.Specifically for injector devices, the guidance document *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* covers a continuum of pen, jet, and related injectors. It also discusses general use, common device platform, and combination products and considerations for injectors provided in NDA, BLA, PMA, or 510(k). It addresses scientific and technical issues and provides a roadmap for injector submissions. The 2006 guidance *Early Development Considerations for Innovative Combination Products* may also be useful (**5**).

For making postmarket changes to a drug within a device, you use current processes for postmarketing changes as directed by CBER/CDER. When a combination product is approved through the device pathway, it is unclear how a change to the drug constituent would be handled and vice versa.

For device constituents approved by CDRH, if changes must be made to combination products and kits, you can refer to the guidance *Deciding When to Submit a* 510(k) *for a Change to an Existing Device* (**6**) or related premarket approval (PMA) guidance. For device constituents approved through CDER or CBER, a top-level decision tree, flow chart, or matrix can be used to identify appropriate regulatory handling of the modification — depending on the specific combination product scenario. The choice must incorporate a risk-based model that considers the safety and efficacy of the finished product.

What are the top causes of delays for approval of combination product filings? Not understanding the regulatory or development pathway, agency expectations for filing, and content for a combination product can negatively affect timelines. The FDA offers early collaboration meetings to ensure that during the development of a combination product both the FDA and the company understand what route to take. That also applies to development of a combination product itself. Meeting with the FDA to discuss comparability and clinical strategies is always advisable to prevent delays in approval. Labeling or "instructions for use" reviews during marketing application review can lead to changes of devices or use. Getting to the Division of Medication Error Prevention and Analysis (DMEPA) sooner rather than later is best!

Human factors studies remain a big challenge to industry, especially when and how to carry them out. Issues regarding human factors studies experienced by the agency include those listed in the "Regulatory Concerns" box.

The amount of formative and summative human factors data needed for a new device technology is well described in current guidance. But the amount of data from mature devices (e.g., preexisting design validation data for a commercially approved product) that can be leveraged remains ambiguous. Risk assessments can be used to assess how much prior knowledge can be used.

Regulatory Concerns

Human factors studies issues include

- Protocol is not submitted for comment before conducting study.
- Risk assessment and identification are inappropriate and/or unclear, thereby leading to a need for additional studies.
- Essential and critical tasks are not identified.
- Study objectives are inappropriate.
- Actual assessments of identified risks or correct risks cannot be made.
- Study is not reflective of real-world use (inappropriate nonrepresentative user population, not totally representative of patients ability, level of understanding by user, study is too short, and assessment is made too soon after training.
- Data collection and assessment using success or failure only is poor (subjective and/or qualitative data, close calls, difficulties, and poor definition of success).
- Data submissions to CDER may be incomplete or hard to follow (jumbled tables, poorly referenced text, undefined terminology, previous studies referenced but not submitted, summary data only, verbatim data needed).

What are the considerations for reporting postmarket changes made to a device constituent of a combination product? If it has been submitted as part of an overall combination product in a single marketing application, could the sponsor use guidance associated with changes to a medical device to determine reportability of device-specific changes? OCP is finalizing guidance on submission requirements for postapproval changes. Drug changes under PMAs through CDRH will involve consultations with CDER and can have timelines change. The FDA recommends premarket discussions, postmarket comparability assessments (e.g., bench tests, human factors studies, clinical studies), and inventory planning sufficient to allow for agency approval before implementation.

With postmarketing changes for device constituents of combination products approved by CDRH, you can use *Deciding When to Submit a 510(k) for a Change to an Existing Device*. However, that guidance does not address issues unique to combination products, although the principles discussed in it may be applied to submissions for combination products case by case. PMA guidances are applicable to PMA-type devices.

Many types of submission strategies can be used for a kitted or single-entity combination product (single BLA/NDA, BLA/NDA, DMF/MAF, BLA/NDA and 510(k), PMA). Industry would like to be able to maintain as much flexibility in those options as possible to allow for multiple types of combination products. What filing strategies would the FDA not accept? Many strategies can be used for submitting kitted or single-entity combination products. One of the OCP's main goals is to guide the industry in selecting appropriate premarket regulatory pathways. Historically, the FDA has favored a singular submission for kitted or single-entity combination products, for which the regulatory pathway is determined by each product's PMOA. In that case, a premarket drug regulatory pathway will most likely be most appropriate.

Similarly, if the PMOA of a kitted or single-entity product is determined to be the device or biologic entity, that respective center's premarket regulatory pathway is most likely to be preferred. That is the likely path for kitted or single-entity products. For cross-labeled combination products, it is more likely that separate submissions provide a better regulatory path. To avoid confusion, the FDA recommends that sponsors discuss filing strategy with the OCP before submitting an application.

Does the form of a submission and/or a lead review division affect pre- and postlicensure regulatory requirements for the constituents of a combination product? Or are the applicable regulations determined by the nature of the constituents, regardless of submission form or lead review division? The form of a submission (NDA, BLA, PMA, 510(k)) should not affect the pre- and postlicensure requirements for the constituents. Each premarket regulatory pathway has nuances that make it unique. In terms of postmarket requirements, the appropriate statutory and regulatory GMPs (for drugs, biologics, devices) should be followed for each constituent part.

The lead review division should also not affect the pre- and postlicensure requirements for the constituents of a combination product. Industry is encouraged to engage the FDA (and the OCP in particular) early and often to achieve a common understanding about pre- and postlicensure requirements for their particular combination therapy.

Can the FDA provide guidance on how manufacturers should handle postapproval changes to their products? What are the relevant FDA guidance documents associated with that thought process? When making a postapproval change to either constituent of a combination product, the first point that a sponsor should clarify is why that change is being made. If the change is a result of potential adverse events, then the sponsor should address whether some kind of action is required for product that is already distributed to market. Most such actions are voluntary, but the FDA has the authority to mandate various field corrective actions at its discretion. When changing a constituent part, you should be aware of the appropriate guidance documents for the CDER, CBER, and CDRH with regard to changes made to an approved drug, biologic, or device.

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.

Reference

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Anthony Mire-Sluis *is vice president North America, Singapore contract and product quality at Amgen Inc. (amire@amgen.com);* ***Donna French*** *is senior director, device development at Genentech, a member of the Roche Group (french.donna@gene.com);* ***Jennifer Mercer*** *is director of regulatory affairs at Genentech, a member of the Roche Group (mercer.jennifer@gene.com);* ***Gerd Kleemann*** *is principal scientist of drug product development at Amgen Inc. (gerdk@amgen.com); and* ***John Dougherty*** *is senior research advisor, global regulatory affairs CMC at Eli Lilly and Company (dougherty_john_j@lilly.com).*