Traditionally, biologics have been distributed through rigid containers (glass bottles or vials). The product was thawed or reconstituted using diluents and/or syringes and delivered to the patient using intravenous delivery sets. The delivery was usually done either manually at home or gravimetrically in outpatient settings. The last decade has seen a dramatic increase in user and clinician interest in alternative container closures, preparation systems, and delivery modalities for biopharmaceuticals. This has spurred an evolving market space for the developers and manufacturers of biologics and their delivery systems. This article identifies some of the critical development tasks that are shared across a wide range of biologics device projects.

This article identifies some of the critical development tasks that are shared across a wide range of biologics device projects. We focus on usability, system design and integration, material selection and planning, chemical, and biological compatibility, manufacturing, and the regulatory environment to provide a brief overview of design and production challenges associated with primary containers and closures, reconstitution and preparation devices, and delivery systems (access and propulsion devices).
Usability

Primary containers and delivery devices for biologics span a wide spectrum in the range of interfaces (form factor, materials, auditory and tactile feedback, software interface, etc.). Existing versions tend to vary widely due to a lack of standardization among the numerous manufacturers. It is particularly important for developers to consider the varied end user systems into which their product will be delivered.

A device’s usability also depends on whether it is designed for a home or clinical setting, whether it is administered by the caregiver or the patient, and whether its use requires a series of workflow steps.

Although manufacturers design products based on usability\(^1\) and human factors engineering standards\(^2\), and FDA has published draft guidance on human factors engineering\(^3\) and position documents on combination products\(^4\), designing for usability in this rapidly evolving field is not straightforward. For the sake of the patient and their therapy, a balance must ultimately be struck between technological complexity and therapeutic needs, with a strong bias for the technology to be useful in the therapy, such as increasing the safety and effectiveness of the product or facilitating patient compliance. In the case of type I diabetes\(^5\), for example, patient compliance with insulin administration regimes has been shown to minimize hypoglycemic events, helping to reduce such comorbidities as macro- and microvascular disease.

Some examples of human factors that manufacturers should consider for improving the usability of drug-delivery devices include the following:

- **Use, misuse, and abuse of the device**—failure modes and effects analysis. During this analysis, a complete set of use environments, users, and workflows are explored, not merely for use cases but also for foreseeable misuse cases. The latter requirement demands adequate knowledge not only of the physical environment in which the device will be used, but also of the cognitive context in which it will be placed, including off-design conditions.
- **Physical ergonomic characteristics** of the user population and their ability to activate connections using axial (push-pull) force and torque must be well characterized. Understanding the users’ capabilities ultimately helps to define the engineering requirements for specified workflow actions. For example, the target user population may lack the dexterity or acuity required to use a device, as a result of such conditions as neuropathy or rheumatoid arthritis, thus introducing unique design requirements.
- **In the case of software-embedded devices**, it is critical to consider appropriate user interface designs that display errors, occlusion alarms, delay-of-therapy messages, or delivery interruptions. Ultimately, the end-user level of clinical knowledge will determine most user interface requirements, which could encompass communication with other devices for data storage and analysis, access to bolus and basal rate modifications, and biologic-dosing adjustments.

\(^{1}\) Manufacturing and Design of Combination Products: Regulatory Guidance. FDA, 2011.
\(^{3}\) FDA Draft Guidance on Human Factors Engineering.
\(^{4}\) FDA Position Documents on Combination Products.
\(^{5}\) Type 1 diabetes - Wikipedia.
System Design and Integration

A typical drug-delivery system can be partitioned into the following subsystems:

- Packaging that facilitates the final assembly, storage, and distribution of the biologic, including labeling and instructions for use.
- Primary containers, such as vials, cartridges, and syringes, which are prefilled with a biologic in liquid or lyophilized form.
- Reconstitution or preparation subsystems such as vial access devices, dual-vial reconstitution systems, and double-chamber syringes.
- Fluid-propulsion subsystems such as disposable single-use pumps, autoinjectors, implantable pumps, and ambulatory infusion pumps. Wearable drug-delivery pumps vary widely, from disposable, single-use, and purely mechanical devices to full-featured electromechanical devices with embedded software that controls the delivery mechanism, processes data from auxiliary sensors, and contains multiple user interfaces for performing monitoring and managing functions.
- Access devices and accessories, including fine-gauge needles, subcutaneous bent-needle sets, IV catheters, and injection ports.

Because providers of drug-delivery devices commonly do not own all of the components or subsystems incorporated into their products, collaboration is necessary among developers of systems, internally developed subsystems, and third-party off-the-shelf subsystems.

**Systems.** At the system level, developers of drug-delivery devices should employ development processes that include defining requirements and specifications, conducting risk management, compiling documentation, and performing verification and validation. The system-level development process must recognize and adapt to the development and design control needs of both the delivery device and the biological product it is intended to deliver.

Thus, the work product should demonstrate that system operation does not affect the biologic adversely or vary its potency or availability throughout the delivery process. For example, developers should ensure that the system does not cause shear-induced damage to proteins or crystallization of the biologic in the delivery line. Such system-level modeling tools as computational fluid dynamics may be used to shear-map the flow path, to assess and mitigate identified risks.

**Internally Developed Subsystems.** For internally developed subsystems, appropriate design controls or container development practices can be followed. For example, the selection of a fluid propulsion subsystem is influenced by delivery accuracy, minimal basal and/or bolus dose, length of delivery or therapy, required device portability, and other factors. It is expected that, during the feasibility phase or while assessing improvements to existing delivery mechanisms, intensive performance testing will be performed. Typical tests for a mechanical and software system include basal and bolus accuracy.
Depending on the complexity of the device, tests involving mechanical and software interactions, such as occlusion detection, can also be performed. To define verification testing requirements, manufacturers typically refer to such published standards as IEC 60601-2-24.

**Third-Party or Off-the-Shelf Subsystems.** These subsystems, including the biologic and the larger delivery system, should be qualified and documented. For example, the connection on an externally developed delivery set can be tested to ensure that it is compliant with ISO 594-2:1998, “Conical Fittings with 6% (Luer) Taper for Syringes, Needles, and Certain Other Medical Equipment—Part 2: Lock Fittings,” or an externally delivered vial access device can be tested to ensure that it can be docked with acceptable force, does not generate particulate matter through coring, and does not result in excessive residual volume.

**Materials Selection and Chemical/Biological Compatibility**

The process of selecting adequate materials for storing and delivering biopharmaceuticals throughout the total product lifecycle of the system includes consideration of the risks associated with undesired biological and chemical interactions. Because interactions between the storage container and the delivery device are influenced by temperature variations, light, humidity, user conditions, and other factors, materials selection is critical during the early design phase. The choice of materials is rather small. Two commonly used materials are borosilicate glass and acrylonitrile butadiene styrene (ABS), both of which are well characterized, exhibit excellent functional stability and inertness, and have been used frequently in primary biopharmaceutical containers and reconstitution and delivery devices.

Although efforts are made continuously to develop new materials, the associated costs and time to market are often prohibitive. Analytical testing and experimentation are necessary to demonstrate whether they are safe and to determine whether they ensure the stability of the drug. At the same time, new materials must meet tolerance, manufacturing, and sterilization requirements.

During the material selection phase, the manufacturer should also consider environmental regulations, which vary depending on the target market. Even in the United States, regulations can vary from state to state. For example, California’s Proposition 65 is an example of state legislation covering the use of chemicals in products that manufacturers should consider before marketing products in the United States.

In the European Union, the use of chemicals in products is regulated by the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) legislation. Some European countries are also introducing legislation that regulates such healthcare issues as sharps disposal. Because many delivery-device components are disposable, manufacturers should consider how they will be handled, disposed of, and recycled after use, if possible. During the development process, these issues can become decisive when choosing among design options.
It is useful to summarize in a single document the choice of materials and the rationale for selecting them. During the late development phase and the regulatory submission process, such a document—including design, manufacturability, and compatibility results—is especially useful. This approach can also be helpful when dealing with such life-cycle management issues as discontinuing the product, selecting a different material supplier, revising the manufacturing methods, moving to a new facility, or choosing improved materials.

**Manufacturing Considerations**

The process used to manufacture such primary containers as vials, cartridges, stoppers, and blow-molded ampules for biopharmaceuticals must be able to maintain stability while preventing denaturation, aggregation, loss of potency, and contamination. Because light and temperature can affect sensitive biologics, these parameters must be controlled from the moment the product is packaged in a primary container until it is delivered to the patient. In the case of equipment design, for example, the use of filling lines to manage product denaturation and minimize such process costs as “priming” and testing has special relevance for biopharmaceuticals. The objective is to manage particle and bioburden risks at every step in the process.

When vial adapters, pooling bags, and compounding systems are used during reconstitution and preparation, managing air and unintentional foaming becomes crucial. Moreover, understanding the physics of delivery or the dissolution rate to shorten the preparation time without compromising component potency and availability is critical. Knowing the unique properties of a biologic, such as viscosity, surface tension, or porosity in lyophilized form, enables manufacturers to create custom reconstitution systems that add clinical value to the therapy and the device/delivery mechanism.

In addition to developing adequate manufacturing systems, manufacturers of drug-delivery devices should understand the importance of documentation to keep track of changes in equipment, manufacturing processes, and raw materials. The involvement of external suppliers increases the manufacturing challenges; therefore, adequate protocols, audits, and an effective document control system are essential to ensure that changes are identified and risks are evaluated before implementing modifications.

**Regulating Delivery Devices**

In its guidance document**, “Infusion Pumps Total Product Life Cycle,” issued in 2010 and reissued in 2014, FDA introduced the concept of a safety assurance case for evaluating the safety claims that manufacturers make about their devices. As described in the guidance, “The safety assurance case (or safety case) consists of a structured argument, supported by a body of valid scientific evidence that provides an organized case that the infusion pump adequately addresses hazards associated with its
intended use within its environment of use.” Typically used in other industries in which safety is critical, this approach is now followed by the agency when it evaluates new submissions.

FDA separates infusion pumps into subsystems depending on their complexity and recommends that manufacturers analyze eight hazardous situations, including operational, environmental, electrical, hardware, software, mechanical, biological and chemical, and use-related sources. While the guidance document addresses Class II infusion pumps—that is, devices requiring 510(k) premarket notification for sale in the U.S.—such devices can also be considered Class III or combination devices, depending on their specific biologic or system characteristics. In such cases, the devices must undergo premarket notification approval.

Another FDA guidance document, published by the Office of Combination Products in 2013, offers recommendations for pen, jet, and related injectors that are used to dispense drugs and biologics.

Conclusion

The development of biologic-delivery devices requires input from a variety of disciplines, including materials science, biology, chemistry, toxicology, human factors, drug/biologic development, biomedical engineering, mechanical engineering, and software engineering. In addition, effective leadership and experience are critical for coordinating this multidisciplinary team effort to design, manufacture, and support the lifecycle of safe and effective products that will improve patient health.

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Acknowledgements: The author thanks Erasmo Lopez, Ph.D., for his contributions. Additional details about this topic are available in an article by Drs. Lopez and Yardimci.

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