Drug Delivery Technologies – Autoinjectors

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The 21st Century Care Act (CCA) offers the promise of a quicker regulatory review and lower cost for medical devices, drugs, and combination products. Within the medical device and combination product sectors the autoinjector is positioned as a major contender with the potential to expand the target patient audience for many biotech therapies. Globally, autoinjectors are expected to reach USD 85.31 billion by 2023 from an estimated 28.91 billion in 2018, at a CAGR of 24.5% during the forecast period (2018-2023).[1]* One of the FDA's charters for the Center for Devices and Radiological Health (CDRH) is to protect and promote public health by utilizing evidence-based decision-making, and the innovative manufacturers of autoinjectors are listening. With guidance for industry issued, companies are developing studies to understand how people interact with technology and how user interface design affects the interactions people have with technology—the focus for human factors engineering (HFE) and usability engineering (UE).

Shortages in the Headlines

Recent news has included stories about the shortage of epinephrine autoinjectors for use by children going back to school. Most parents have mastered the organization of critical medications for their children since the first shortage was announced and the escalation of pricing due to the shortage in 2016. Such headlines have become a marketing snag that benefits no one single company within the autoinjector sector except possibly newer suppliers within the sector.

Autoinjectors are also part of the inventory for the military, protecting personnel from possible chemical warfare agents. The US Department of Defense (DoD) has worked with industry to refine their autoinjector platforms and to create specifications and tests for chemical antidote delivery. The physical characteristics and strength of the syringe and accompanying parts/accessories need to survive the harsh environments the military face.

Both populations, whether youngsters getting ready for a new school year or soldiers going off on military assignment need to be assured drug delivery systems will provide efficient, discrete, and administration-friendly autoinjectors. The task is eased and delivered by utilizing evidence-based decision-making during the development process through the guidance for industry from the FDA's Center for Devices and Radiological Health (CDRH).

Development of a combination product starts at the outset of the development process when developing your product Quality Target Product Profile (QTPP) for the drug, device, and the system, which refers to the performance requirements of both together.

Human Factors Testing and Validation

In the current regulatory environment, the Center for Devices and Radiological Health (CDRH) believes that human factors testing is a valuable and necessary component of medical device product development. Both human factors engineering and or usability engineering processes during development should be a high priority when a product is under development. Human factors testing is defined as, "…. testing conducted at the end of the device development process to assess user interactions with a device user interface to identify use errors that would or could result in serious harm to the patient or user. Human factors validation is also used to assess effectiveness of risk management measures."[2]

Can the patient access the autoinjector in a timely manner? Does it fit comfortably in the hand of a child and in the hand of an adult to provide the correct dose? When utilizing the human factors and usability engineering guidance toward the end of development a company should be able to identify that products are safe and effective for the intended users, uses, and environments.

Human factors validation testing should be designed as follows:

- The test participants represent the intended (actual) users of the autoinjector.
- All critical tasks are performed during the test.
- The autoinjector user interface represents the final design.
- The test conditions are sufficiently realistic to represent actual conditions of use.[2]

The validation testing should be performed under conditions where the autoinjector is going to be used, such as a clinical trial. But, if there is agreement with the FDA, and a simulated-use test method is identified and verified it can also be used to provide the appropriate data.

Each population targeted for use of autoinjectors should have at least 15 participants from each user population included in the validation testing. The FDA views user populations as distinct when their characteristics would likely affect their interactions with the device or when the tasks they perform on the device would be different.

As discussed above, the autoinjector population can be children of various ages, teachers, parents, medical office staff, or military personnel on assignment. Data collected and evaluated can either eliminate or reduce the possibility of harm to the user or degradation of the treatment.

There is also a guidance on human factors specific for combination products, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development-Draft Guidance for Industry and FDA Staff (February 2016).[3]

Requirements in the Field

During a short course this summer I had the privilege of meeting a couple of DoD professionals responsible for the registration of product specifically for military use, which provided an eye-opening perspective. When human factors and user engineering were presented in the course each brought up additional needs required for autoinjectors on the battlefield. For example, a soldier may carry multiple autoinjector systems to combat biologic agents, analgesia for a wound, etc. Framing the human factors requirements changes significantly if the user must be able to identify the correct autoinjector quickly and without reading the label. How does the individual know what injector to pull out and use? Colored caps or shields do not help, a lighted device

Table 1. Drug vs. Device Development - General

	Drug	Device
Mode of Action	Pharmacological, immunological means	Mechanical, physical, electrical means
Industry	Mostly large multi-national companies	Mostly small companies with diverse technologies
Regulatory Body	FDA CDER or CBER	FDA CDRH or OIR
Regulatory Process	Burdensome & more formalized regulatory process	Less burdensome but more complex regulatory process due to the: • Complexity of device (simple – sophisticated) • Complexity of device (simple – sophisticated) • Types of products/components (e.g. bioabsorbable implants, electronic laser devices, software driven surgical robots, active implantable devices, etc.) • Multiple end users (patient, physician/surgeon)

upon opening cannot be used; a special shape texture and size to diff erentiate one autoinjector from another is not useful due to the need for protective gloves, and an aural indicator could be dangerous in the military theater.

Table 2. Drug vs. Device – Development and Quality System

	Drug	Device
Development Lifecycle	• Long development process • Extensive clinical studies • Product and process development often occur concurrently with clinical studies	• Shorter lifecycle • Product and process development are usually complete prior to clinical studies
Quality System	21 CFR 210/211 (cGMP)	• US: 21 CFR 820 (QSR) • Not prescriptive due to the different nature and type devices • CAPA requirements more specific for devices • Design Controls examine the intended use and design of a product BEFORE manufacturing

Carefully and methodically, technological advancements have expanded the autoinjector platform as a viable solution for many disease therapies here-to-fore relegated to physician-administered therapy.

As functionality increases and features get added the complexity of establishing control within your organization's QMS and the complexity of testing performance goes up as well. Compatibility of the components for an autoinjector needs to be confirmed and tested for the final product for patients. The FDA may request testing of materials for basic extractables and leachables on the many parts of the autoinjector even if the material does not come in contact with the actual product, unless a compelling risk and design analysis can satisfy the FDA that the likelihood of interaction is acceptably low.

Combo Products

Autoinjectors will be considered a major component of your combination product fi ling and a drug sponsor or medical device company fi ling the product will need to fi nd a way to integrate the two quality systems. Close attention must be paid to the diff erent regulations for drug, biologic and device when pursuing a combination product. A common pitfall some drug sponsors make is delaying the decision to pursue a combination product until later in the drug development cycle resulting in unanticipated delays and having to repeat work such as container-closure integrity, extractables-leachable and stability testing to name a few. The additional requirements and mindset for a drug/biologic and a device can be daunting for existing systems currently in place. A drug/biologic company undertaking a combination product will need to increase the quality system and procedures to support the device requirements.

The issuance of 21 CFR Part 4 in 2013 has also provided a framework for medical device developers and drug developers to navigate the integration of the Quality Management Systems requirements (21 CFR 211, 600 and 820).

Table 1 provides a general side-by-side comparison of a drug vs. device development.

Table 2 provides a drug vs. device comparison of the development and quality system.

There are substantial hurdles for drug manufacturers in developing, marketing, and manufacturing combination drug products.

First and foremost, a product will need to be classified as a combination product. Second, manufacturers will need to cope with new and different regulatory pathways. The 21st

Century Cures Act passed in 2016 created new initiatives specifically addressing combination products. Having a clear plan for how you will apply 21 CFR Part 4 is essential to not complicating your development and quality programs. It's important to ask how will you measure quality in the device, drug/biologic, and at the system level. How will you release and track each element?

Will they be matched and released as a system or will each piece be pre-released and matched separately? Have you done the Error Allocation analysis of the design and release specifications for each element to ensure that when your system comes together you can consistently meet the system CQAs? How will you manage your supply chain when upstream and intermediate contract manufacturers impact your ability to manufacture the final product?

There is tremendous business upside in the decision to develop a combination product, but the complexity associated with pursuing such a strategy must begin at the early development stage if an organization is to avoid costly delays or repeat major development steps.

References

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