Chimera Consulting: Combination Product Training Institute®

QUALITY & SYSTEMS USABILITY REQUIREMENTS FOR DRUG DELIVERY DEVICES & SYSTEMS

In this article, Michael Gross, PhD, RAC, Principal Consultant, Chimera Consulting, and Adam Shames, MBA, Chief Executive Officer, Core Human Factors, discuss US FDA quality system requirements for combination products, especially Design Controls, which includes the requirement to validate the design of the medical device constituent part of a combination/borderline product. Design Validation may be accomplished through the conduct of human factors studies that demonstrate that a device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users. This is the first in a series of articles covering quality system requirements for combination products and borderline products in the US and EU. Future articles in this series will further address quality system requirements and the conduct of human factors studies intended to fulfill design validation requirements for registration of combination/borderline products and stand-alone drug delivery devices.

QUALITY SYSTEM REQUIREMENTS

In 2013, the US FDA established quality system requirements for combination products in a regulation entitled, Current Good Manufacturing Practice Requirements for Combination Products (§21CFR4).[1] The regulation applies to all medical products that combine, through either integration or co-packaging, drugs, or biological products, with a medical device constituent part, such as a syringe, auto injector, pen, nasal spray, inhaler, or other devices intended for drug delivery.

The regulation does not create new requirements for the drug (or biological product) and medical device constituent parts of a combination product. It explains how to apply existing quality system requirements for drugs, biological products and medical devices during the development and manufacture of a combination product. The regulation requires that manufacturers demonstrate that the quality system used to develop and manufacture a combination product meets the requirements of both Current Good Manufacturing Practice For Finished Pharmaceuticals [2] for drugs and biologics (§21CFR211, CGMP) and the Quality System Regulation [3] for medical devices, (§21CFR820, QSR).

§21CFR4 does not apply to stand-alone medical devices which are not intended for use with a specific drug or biological product. These requirements are covered only by the QSR.

In 2015, FDA issued, Draft Guidance: Current Good Manufacturing Practice Requirements for Combination Products [4] which is intended to expand and clarify the legalistic language of §21CFR4. The issuance of a final guidance is anticipated in the near future.

According to §21CFR4 and its companion draft guidance, a streamlined (i.e. hybrid) quality system may be structured

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that satisfies both CGMP and QSR requirements. The operating (i.e. platform) quality system for a combination product can be based on either the CGMP or QSR. Typically, a pharmaceutical company will have a CGMP-based quality system in place, so this will likely be the quality system platform used for the development and manufacture of a combination product. FDA notes that many of the requirements of the CGMP and QSR regulations are similar and are intended to achieve the same purpose. However, there are gaps between the two regulations and these must be filled to be fully compliant with §21CFR4.

In §21CFR4 FDA identifies four gaps that may exist between a compliant CGMP platform and the QSR requirements. They are, Management Responsibility (§21CFR820.20), Purchasing Controls (§21CFR820.50), Corrective and Preventive Actions (§21CFR820.100) and Design Controls (§21CFR820.30).

When FDA drafted §21CFR4 it compared the CGMP and QSR to identify gaps between the regulatory language of the two regulations but FDA did not compare current state-of-the art practices under these regulations. The ICH guideline, Pharmaceutical Quality System (ICH Q10),[5] is a pharmaceutical quality system best practices model that defines the "C" (i.e. current) in CGMP. A pharmaceutical quality system that conforms to the recommendations of ICH Q10 will substantially satisfy the Management Responsibility, Purchasing Controls, and Corrective and Preventive Actions requirements of the QSR and therefore comply with most of the requirements of §21CFR4, except for the Design Controls requirement which is unique to medical devices. Therefore, when structuring a hybrid quality system which is based on a state-of-the art CGMP platform, aside from the possibility of minor adjustments to quality system SOPs, the main gap that must be filled to fully comply with quality system requirements for combination product development and manufacture is Design Controls.

DESIGN CONTROLS

Design Controls are unique to medical device development and manufacture. They are are a set of procedures (SOPs) that serve as a framework for device development and are intended to insure that a device, or a device constituent part of a combination product, is safe and effective and meets its intended use and satisfies user needs, throughout its life cycle. The basic elements of Design Controls are:

- Design and Development Planning
- Design Input
- Design Output
- Design Review
- Design Verification
- Design Validation
- Design Transfer
- Design Changes
- Design History File
- *Risk Assessment.*

Risk Assessment is not a formal element of Design Controls. Rather, it is a tool that is used throughout the Design Control process. The use of risk assessment methodologies (e.g. ISO14971 Application of Risk Management to Medical Devices [6]) is important for identifying and mitigating

risks that will be assessed in human factors studies. By following established Design Control procedures during the device development process, design flaws and problems can be identified and mitigated before the device design is finalised.

One of the final steps in the development cycle for a device design that is intended for initial marketing is Design Validation. Validation that a device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users is typically achieved through the conduct of one or more Summative Human Factors studies.

HUMAN FACTORS STUDIES

Human factors studies should be conducted throughout the device design process. They are not clinical studies; they are engineering studies and are usually conducted under conditions that simulate actual device use. In 2011, FDA issued a draft guidance on the conduct and reporting of human factors studies.[7] The issuance of a final guidance is anticipated in the near future. Formative human factors studies are information gathering studies which are typically conducted on device prototypes or sub-assemblies as the device design process proceeds. They allow for early and iterative assessments of the device, instructions for use, packaging, and training materials (if applicable). They are intended to identify potential design flaws to be mitigated before the design of the device, instructions for use, packaging, and training program are finalised.

Summative human factors studies (a type of Design Validation) are conducted on the final (market image or equivalent) device, instructions for use, packaging, and training materials under conditions that simulate actual use, to demonstrate that the device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users.

SUMMARY & CONCLUSIONS

To be fully compliant with recently established FDA quality system requirements for the development and manufacture of a combination product, manufacturers must simultaneously comply with the requirements of both the CGMP and QSR. To meet this requirement, at a minimum, pharmaceutical manufacturers utilising a previously established CGMP-based quality system that conforms to current industry best practices, must expand their existing set of quality system SOPs to satisfy QSR Design Controls requirements. Validation that a device can be used safely and effectively for its intended use(s), in its intended environment(s) of use, by its intended users is typically achieved through the conduct of Summative Human Factors Studies.

REFERENCES

1. *Final Rule: Current Good Manufacturing Practice Requirements for Combination Products (§21CFR4).*
2. *Final Rule: Current Good Manufacturing Practice For Finished Pharmaceuticals (§21CFR211).*
3. *Final Rule: Quality System Regulation (§21CFR820).*
4. *Draft Guidance for Industry and FDA Staff, "Current Good Manufacturing Practice Requirements for Combination Products", 2015.*
5. *Pharmaceutical Quality System (International Congress on Harmonization Guideline Q10).*
6. *Medical devices - Application of Risk Management to Medical Devices (ISO 14971).*
7. *Draft Guidance for Industry and Food and Drug Administration Staff, "Applying Human Factors and Usability Engineering to Optimize Medical Device Design", 2011.*

THE COMBINATION PRODUCT TRAINING INSTITUTE

In 2016, the Combination Product Training Institute® will conduct two identical three-day training programs that address quality system and design controls requirements for combination and borderline products in the US and EU, and the conduct of human factors studies. These programs will cover requirements for both newly developed and legacy products as well as quality system obligations of device component manufacturers. The first of the two training programs will take place on March 29-31, 2016 at the Chemical Heritage Foundation Conference Center (Philadelphia, PA, US). The second program will take place on June 14-16, 2016 at the NH Barbizon Palace (Amsterdam, The Netherlands).

Throughout the year, the Combination Product Training Institute will offer other venue-based training programs on various combination product topics. In-house training programs are also available. For additional details please visit the Combination Product Training Institute website at: CombinationProductTrainingInstitute.com

ABOUT THE AUTHORS

Michael Gross is the Principal Consultant of Chimera Consulting®, specialising in quality assurance, regulatory affairs and technical development of drugs, biologics, medical devices and combination products. He also heads the Combination Product Training Institute®, which provides professional training programs on combination product topics. Michael holds a PhD in Organic Chemistry and conducted post-doctoral research in biochemistry at the National Institutes of Health. He is a former FDA reviewer and inspector. Michael worked for 30 years in senior quality, compliance and regulatory affairs roles for a number of large and small pharmaceutical and medical device companies. Today, he provides an influential industrial perspective on the regulation of combination products and is a frequent speaker on combination products topics and has published numerous articles in regulatory and scientific publications.

Adam Shames is a recognised human factors expert and consultant and is the Founder and Chief Executive Officer of Core Human Factors, Inc, a leader in human factors and usability engineering consulting services with over 12 full-time employees. Adam holds an MBA in international business and a BS in human factors engineering and psychology. He received the De-Florez Prize in Human Engineering and holds a Certificate in Applied Ergonomics Training from the United States Army Center for Health Promotion and Preventive Medicine. Adam has over 15 years of human factors research experience and has served as the Principal Investigator on hundreds of IRB reviewed usability studies involving thousands of participants in cities around the world.