DESIGN CONTROLS: CHALLENGES FOR PHARMA COMPANIES

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CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - Explains how to apply* existing CGMP predicate rules to combination products containing drug, biologic or device constituent parts
    - Does not create new predicate rule requirements
    - Does not modify existing predicate rule requirements

**Note: The predicate rules allows entities engaging in only certain regulated activities to be subject only to portions of predicate rules that pertain to those activities*

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - Container closure systems which serve as drug delivery devices (e.g., a prefilled syringe), which may be considered as drug manufacturing components, are also constituent parts of combination products
  - If a facility manufactures a finished prefilled syringe from drug and device components, that facility must comply with 21 CFR 4 and therefore QSR and CGMP regulations

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - Explains how combination product manufacturers are required to *demonstrate* compliance with the Predicate Rules
    - *Demonstrating* compliance includes establishing and maintaining written procedures and records that verify and document compliance with **applicable quality system requirements** described in the respective predicate rules

COMBINATION PRODUCT QUALITY SYSTEMS RULES AND DESIGN CONTROLS

- To comply with combination product CGMP requirements (21CFR4), compliance with drug (and biologic) CGMP (21CFR211) **and device QSR (21CFR820)** must be *demonstrated.*
    - *Parallel/redundant* or streamlined*/hybrid* approaches are acceptable
    - Must have procedures and records
- Most pharmaceutical companies will to establish their streamlined quality system on a CGMP platform

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - Regardless if a device-containing combination product manufacturer chooses to establish its quality system on a CGMP or QSR platform, the Design History File (DHF) requirement of Design Controls must be fulfilled to *demonstrate* that the combination product was developed in accordance with a prospectively established design plan

COMBINATION PRODUCT QUALITY SYSTEMS RULES AND DESIGN CONTROLS

- For a streamlined quality system that is based on a drug/biologic CGMP-based platform (21CFR211)
  - If the CGMP platform conforms to ICH Q10, then the major QSR gap that needs to be filled is Design Controls
    - Management Responsibility, Purchasing Controls and CAPA are mostly satisfied by conformance to ICHQ10
      - Management Responsibility and CAPA fine tuning may be necessary

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - Each constituent part of a combination product, when manufactured and marketed separately are subject only to predicate quality system rules pertaining to that type of constituent part
  - The constituent parts of a single-entity and co-packaged combination product **retain their regulatory identity before and after they are combined** into a combination product
    - Quality system requirements that apply to the individual constituent parts of a combination product continue to apply even after they are combined to form of a single-entity or co-packaged combination product

COMBINATION PRODUCT QUALITY SYSTEMS RULES AND DESIGN CONTROLS

- Since 1996 Design Controls, a QSR are required for the development of almost all medical device containing medical products
- Design Controls are a set of engineering principles and practices intended to
  - Assure that product development proceeds in a step-wise and rational way
  - That the product that is ultimately developed is the product that was intended to be developed
  - That design flaws and the potential for use errors are minimized in the final design
  - That the final product design satisfies intended use and user needs
- Design Controls is an under-appreciated tool and alien concept to pharmaceutical manufacturers developing combination products, and those having developed legacy combination products

DESIGN CONTROLS

- Interrelated set of QSR required practices, principles and procedures (SOPs) incorporated into the device design development process that systematically and continuously assess device design as an integral part of development
    - Provides improved design process transparency and ability to adjust resource allocations
        - Enables deficiencies in design inputs and discrepancies between designs and requirements to be detected and corrected early in the development process
    - Produces enhanced understanding of the degree of design conformance to user/patient needs
    - Improves communications/coordination among participants during the product design and development process
    - Increases likelihood that design transfer to production translates to a device appropriate for its intended use

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - **The Design Control requirements of the QSR apply whenever a device constituent part is incorporated into a combination product**
    - In utilizing Design Controls manufacturers may rely (*in part*) on existing information for the constituent parts

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - Should a Sponsor wish to use an existing, or *off-the-shelf,* product as a constituent part of a combination product, Design Controls must ensure that the existing product meets appropriate and prospectively established design requirements to assure that the combination product will be safe and effective when used for its intended use *by its intended users, in intended use environments*
    - *Often modification/customization is necessary to use the "off-the-shelf" constituent part in the manufacture of a combination product, Design Controls must then be followed*

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - Design Controls apply not only to the device constituent part of a combination product but also to the *overall combination product, possibly including certain aspects of the drug constituent part*
    - For a co-packaged combination product, the **compatibility of the constituent parts should be assessed using a design control approach, in particular if drug constituent part characteristics are optimized for the combination product**

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Final Rule **Preamble**
  - All manufacturers are responsible for ensuring compliance with all quality system regulations applicable to development and manufacturing operations conducted at their facilities and vendor facilities
  - Where multiple facilities are responsible for various aspects of the manufacturing process, **the holder of the combination product marketing authorization is responsible for assuring compliance applicable to the entire manufacturing process across all facilities**

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- **Final Rule**
  - Predicate rules
    - Current Good Manufacturing Practice regulations for drugs and biological products (21CFR210 and 211) apply to combination products that include a drug or biologic constituent part
    - Current Good Manufacturing Practice regulations for medical devices (i.e., the Quality System Regulation, QSR, 21CFR820), applies to combination products that include a device constituent part
    - Additional regulatory requirements and standards may apply if certain biological products described in 21CFR 600 through 680 (e.g., blood products, allergenic products) and 21CFR1271 (i.e., HCT/Ps) are incorporated as constituent parts of a combination product

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- **Final Rule**
  - Predicate rules
    - ▪Articles which in the absence of the Final Rule would be considered to be device components (not subject to the QSR) do not become subject to the QSR as the result of the Final Rule
    - ▪Drug manufacturing components are subject to CGMP requirements and continue to be under the Final Rule
    - ▪In some cases, the quality system requirements applicable to a constituent part may arise from one or more predicate rule

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- **Final Rule**
  - Demonstrating compliance
    - For single entity or co-packaged combination products, compliance with combination product quality system must be achieved by utilizing a quality system *demonstrated* to comply with Predicate Rules applicable to the constituent parts included in a combination product
    - To demonstrate compliance for single-entity or co-packaged combination products two options exist:
      - Demonstrating compliance with the specifics of all quality system regulations applicable to each constituent part
      - Or, **under certain conditions**, a ***hybrid*** quality system approach can be used if it assures full compliance with applicable parts of both regulations (i.e., a **streamlined quality system**)

CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

- Demonstrating compliance (continued)
  - A manufacturer that chooses to base its streamlined quality system on a CGMP-platform is required, as applicable, to additionally demonstrate compliance with specified QSR provisions, these are:
    - Management Responsibility (21CFR820.20)
    - Purchasing Controls (21CFR820.50)
    - Corrective and Preventive Action (21CFR820.100)
    - **Design Controls (21CFR820.30)**
    - *Installation (21CFR820.170)*
    - *Servicing (21CFR820.200)*

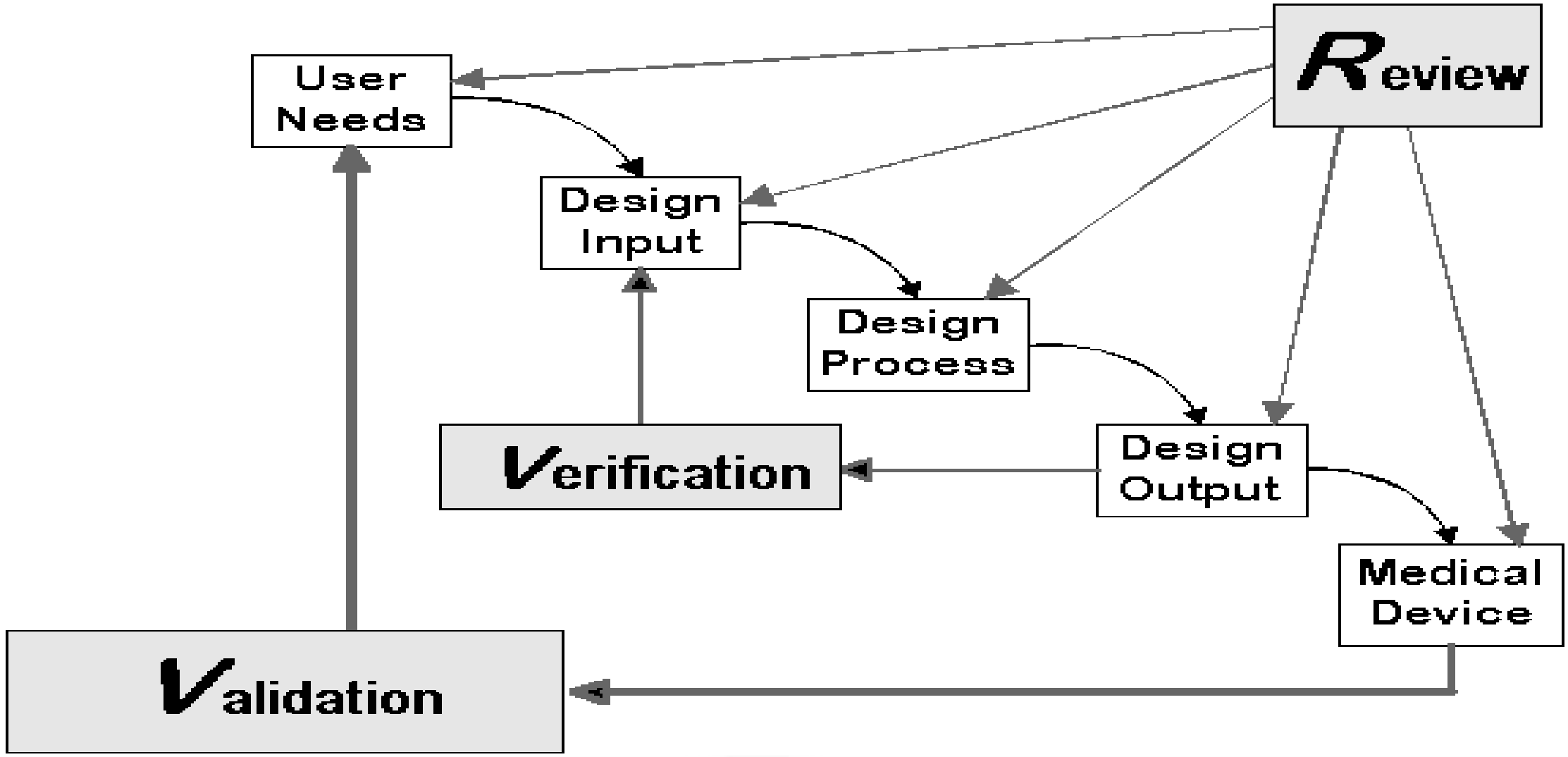
NET DIFFERENCE BETWEEN CGMP AND QSR BASED QUALITY SYSTEMS

- **Design Controls (21CFR820.30)**
  - Design and development planning
  - Design Input
  - Design Output
  - Design Review
  - Design Verification
  - Design Validation
  - Design Transfer
  - Design Changes
  - Design History File (DHF)

DESIGN CONTROL PROCESS

- Design input(s) is/are converted/translated to design output(s)
- Design output(s) is/are verified for conformance to their design input(s) and then becomes the design input for the subsequent step in the iterative design development process
- Design input requirements are ultimately translated into a device design that can be validated as satisfying intended use and user needs

DESIGN CONTROLS "WATERFALL" DIAGRAM



DESIGN AND DEVELOPMENT PLANNING

- Requires the establishment and maintenance of procedures (SOPs) to establish appropriate plans related to, design development activities, implementation of responsibilities, and interfaces between groups participating in design development
  - Reviewed/update/approve development plans as design development evolves
  - Ensure that the design process is appropriately controlled and device quality objectives are met

DESIGN INPUT

- Requires establishment and maintenance of **procedure**s to establish ongoing device design requirements that are appropriate and address intended use and user/patient needs
    - *Establish and maintain procedures to ensure design requirements are appropriate and address the intended use and user/patient needs; include a mechanism for addressing incomplete, ambiguous, or conflicting requirements*

DESIGN INPUT

- Design Input requirements (3 types)
  - **Functional** requirements: specify what the device does, focus on the operational capabilities
  - **Performance** requirements: specify how well the device must perform; includes requirements concerning device reliability and safety
  - **Interface** requirements: specify device characteristics which are critical to compatibility with external systems (e.g., user and/or patient interface)

DESIGN OUTPUT

- Requires establishment and maintenance of **procedures** for measuring, documenting producing design output in terms that allow adequate evaluation of conformance to Design Input requirements
    - Defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements

DESIGN OUTPUT EXAMPLES

- Production specifications, drawings and descriptive documents which define and characterize the design and which may be used to procure components, fabricate, test, inspect, install, maintain, and service the device, e.g.,
  - Assembly drawings
  - Component and material specifications
  - Production and process specifications
  - Packaging specifications
  - Work Instructions
  - Results of risk analysis
  - Results of verification testing
  - Prototypes
  - Finished device
  - DMR

DESIGN VERIFICATION

- Establish and maintain procedures for verifying the device design to confirm that the design output meets the design input requirements
  - The results of design verification testing, including identification of the design, test method(s), the date, and names of individual(s) performing the validation testing are controlled documents that must be signed, dated and are documented in the Design History File (DHF)

DESIGN VERIFICATION

- The nature of design verification activities varies according to the type of design output; any approach which establishes conformance to a design input requirement is an acceptable means of verifying the design with respect to that requirement; complex designs require more and different types of verification activities
- The basis of verification is three-pronged: tests, inspections, and analyses
- In the initial stages of design development, verification is an important quality assurance tool; as the design effort progresses, verification activities become more comprehensive

DESIGN VALIDATION

- Establish and maintain procedures for validating the device design; **performed under actual or simulated use conditions on initial production units, lots, or batches, or their equivalents**
  - The results of design validation testing, including identification of the design, test method(s), the date, and names of individual(s) performing the validation testing are controlled documents that must be signed, dated and are documented in the Design History File (DHF)

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- Design validation encompasses design verification and extends the assessment to determine if devices that have been produced in accordance with the design satisfy user needs and intended uses

DESIGN VALIDATION

- Design Validation testing should also assess packaging and labeling which may have significant human factors implications
- Validation should include simulation of the expected environmental conditions of temperature, humidity, shock and vibration, corrosive atmospheres
- Particular care should be taken to distinguish among customers, users, and patients to ensure that validation addresses the needs of all relevant parties

DESIGN REVIEWS

- Establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development
  - Procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of design development
  - Documented, comprehensive, systematic evaluations of the adequacy of the design requirements, the ability of the design to satisfy design requirements and identify design problems
  - The results of Design Reviews are controlled documents filed in the Design History File (DHF) and include the identification of the design, and the and must be signed and dated by individual(s) performing the review

DESIGN REVIEWS

- Conducted at strategic points in the design process to assure that completion of an activity/phase is acceptable and the next activity/phase can begin, to assure that
  - Design input requirements are adequate before conversion to design specification(s)
  - Device design is adequate before prototypes and final devices are produced
  - No specific requirement for how many and when but typically conducted at the end of each design phase and at important milestones in the design process

DESIGN TRANSFER

- Establish and maintain procedures to ensure that the device design is correctly translated into production specifications
    - Production specifications must ensure that manufactured devices are repeatedly and reliably produced within product and process capabilities
    - Written documents, such as assembly drawings, component procurement specifications, workmanship standards, manufacturing instructions, and inspection and test specifications

DESIGN CHANGES

- *Establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation*
  - Two administrative elements involved in controlling design changes
    - Document control - enumeration of design documents, and tracking their status and revision history
    - Change control - enumeration of deficiencies and corrective actions arising from verification and review of the design, and tracking their resolution prior to design transfer

DESIGN HISTORY FILE (DHF)

- Establish and maintain a DHF for each type of device
  - The DHF contains or reference records necessary to demonstrate that the design was developed in accordance with the approved design plan and QSR requirements; records that describe the design history of a finished device
    - There is no specific requirement in ISO 9001 or ISO 13485 for a Design History File
    - There are no requirements on the location or organization of the design history file (may be distributed, virtual)

RISK MANAGEMENT

- Policies, procedures and practices intended to identify, analyze, control and monitor risk
  - Begins with development of design input requirements; as design evolves, new risks may become evident
  - Integrated into the design process so that unacceptable risks are identified and managed early when changes are easier and less costly to manage

ISO 14971-1(2012)
MEDICAL DEVICES – RISK MANAGEMENT PART 1 APPLICATION OF RISK ANALYSIS

- Harmonized risk management standard for medical devices; contains recommendations for a manufacturer's risk management system intended to identify hazards, eliminate risks, develop, implement, and monitor the effectiveness of risk control measures to assure the safety of a medical devices throughout the product life cycle
    - *Required by regulation (e.g., EU MDD) and other quality standards (e.g., ISO 13485, 15378)*