Lessons Learned from Combination Products

REGULATORY COMPLIANCE ASSOCIATES® INC.
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cGMP

cGMPs have not Changed but this is Unfamiliar Territory

The Requirements

The manufacturer must simply fulfill the requirements of both the pharmaceutical and the medical device regulations, with the emphasis on the Primary Mode of Action.

Familiar Territory

– Pharmaceutical Current Good Manufacturing Practices - 21 CFR 210/211

Unfamiliar Territory

– Medical Device Requirements – 21 CFR 820
– Streamlined Approach – 21 CFR 4.4(b)

Streamlined Approach Added Requirements:

Pharmaceutical CGMP-based System (21 CFR 210/211)

- Add the Following Provisions from the QS Regulation in Accordance with 21 CFR 4.4(b)(1)
  - – 21 CFR 820.20 Management Responsibility
  - – 21 CFR 820.30 Design Controls
  - – 21 CFR 820.50 Purchasing Controls
  - – 21 CFR 820.100 Corrective and Preventive Actions
  - – 21 CFR 820.170 Installation
  - – 21 CFR 820.200 Servicing

Combination Products Requirements

What

The "Regulatory Strategy" is the Regulatory Planning Document

When

Phase 0/1–as Early as Possible!

- It is a controlled document similar to a project plan
- It defines all regulatory requirements and specifications, timing, resources, cost and strategic decisions
- It is used for a new product or modifications to a currently approved / cleared product
- Used for all FDA-regulated product types (device, drug, biologic, combo)

Critical Pieces of the Regulatory Strategy

- Proposed claims, intended use statement and indications for use
- Device classification (U.S. / CE Mark / Global) and FDA product code
- Regulatory submission pathway (510k, PMA, NDA, BLA) including time and cost
- Planning of communication and pre-submission meetings with FDA / regulatory agencies
- Predicate choices
- Decisions on performance and comparison testing needed including bench, animal and clinical studies
- Standards applicable to the product and regulatory / quality testing requirements
- Reimbursement strategy

Typical Timing for Submission Actions

Regulatory Approval / Clearance Times:

- Medical Devices: 4 months – 1+year (FDA)
- Drugs / Biologics: 9 – 13 months (FDA)
- CE Mark: 2 months - 1+year (w/ clinical trail)
- Globally: Can be multiple years before approval
  - – May include time needed for pre-approval inspections conducted by international regulatory bodies, in-country clinical trial requirements and in-country product certification testing.

Problems Commonly Encountered

Determination of Lead Agency

- Based on Primary Mode of Action, as well as Historical Determinations
- Office of Combination Products utilizes a Request For Determination
  - – Not required
  - – Can be determined by Historical Determinations
- The *Combination Product Council* has been announced in 2016; they offer the *Intercenter Consult Request* (ICCR) process to facilitate questions and processing of Combination Product reviews.

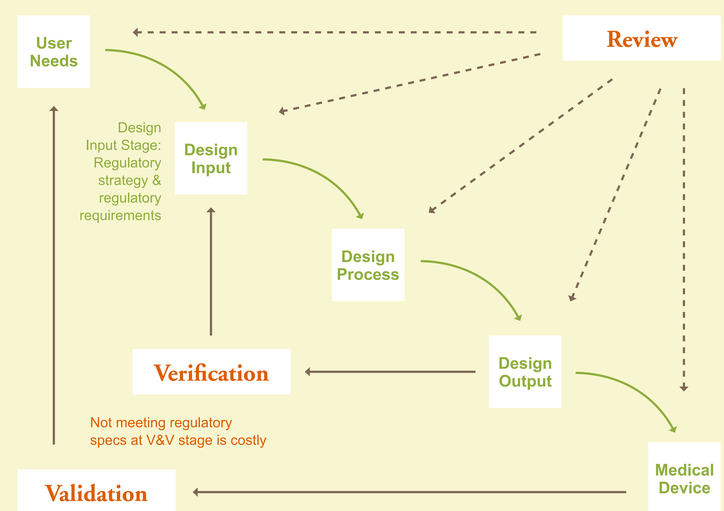
Common Challenges in DHF

- Writing Design History File (DHF)
- Key Examples: Device Requirements, Verification & Validation Plan, Traceability Matrix

Testing Requirements for Products: Lessons Learned

- Clear requirements needed
  - – Think of "Verification and Validation" (Must be able to test the requirements)
  - – Utilize Consensus Standards
- Conflicts?
  - – Good example is biocompatibility testing
  - – ISO 10993 versus Compendia
  - – Be consistent and document rationale

Regulatory Strategy & Design Controls



Avoiding Delays

- Generation 1 Products/Labels as Predicates
  - – Design "Product Platforms"
  - – Generation 2: Reuse Data; Update Risk Management
- Bundling of Minor Differences (e.g., size) into Same Submission
- Use of Postmarket Data to Supplement Newly Derived Data
  - – Use Other Companies' Field Issues During Design Phase

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See www.rcainc.com/combinationproducts/poster for references and handout.