

Change Protocols

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Office of Pharmaceutical Science (OPS)

CDER/OPS

New Drug
CMC

Generic
CMC

Biotech
CMC

Microbiology
CMC

Chemistry Manufacturing and Controls (CMC)

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“Protocols”

n 21 CFR 314.70(e)

- n An applicant may submit one or more protocols describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes

Distinction

n Traditional Supplement

- n For changes being approved after commercial data (or surrogate) is available
- n Based on data alone

Protocol Supplement

- n For changes being approved based on risk assessment and criteria for commercial data
- n Based on risk assessment and criteria for future data

Protocol Contents

- n Description of studies to be performed
- n Analytical procedures and criteria to be achieved
- n Data analysis to be performed and how it demonstrates lack of adverse effect
- n Description of the risk assessment to be performed

Draft Guidance February, 2003

- n 21st Century Initiative
 - n Started August, 2002 and was in an early stage
- n Draft Guidance tends to be old style
 - n Prescriptive
 - n Content
 - n Filing Mechanisms
- n Needs to be more Risk Based
- n <http://www.fda.gov/cder/guidance/5427dft.pdf>

Daisy Chain

- n Review practice tends to create protocol approvals requiring additional supplement requirements
 - n What is being approved?
 - n What is gained?
- n Creates needless submissions
 - n Some approvals require a supplement only to compare the COA
 - n What does this accomplish?
 - n Is this the best way to assure quality?

Scope

- n Manufacturing Process
- n Analytical Procedures
- n Equipment
- n Facilities
- n Container Closure Systems
- n Process Analytical Technology

Scope

- n More than one change in a protocol?
 - n Yes
- n More than one product in a protocol?
 - n Yes
- n Protocol that can be used again and again?
 - n Yes
- n Limitation
 - n If the change requires clinical data
 - n If the criteria can't be clearly defined

Scope

- n Guidance Limited to Post Approval Changes
 - n Greatest benefit
 - n Easiest to describe
- n Concepts could be used for new applications, but are not described this way in the latest guidance drafts

Supporting Information for Risk Assessment

- n Relevant knowledge from previous experience
 - n Similar products and procedures
- n Technical literature that adds to the body of knowledge
- n Pharmaceutical Development information
- n Experimental Design
 - n Previous
 - n Planned

Commercial Implementation of Change

- n Implementation Plan
 - n Timing
 - n Process Control Strategy for Commercial Production
 - n Criteria for expected results
 - n Analysis that will be done with the results to determine that the implementation was successful
 - n Keep data for inspection

What if I don't meet the criteria?

n Scenario

- n Approved protocol
- n Implementation does not meet criteria

n Result

- n Inform the review division that the implementation failed
- n Choose if you want to seek approval based on the results you received
 - n Not part of the original protocol approval

Implementation

- n All goes well with the implementation plan
- n All criteria and analysis of data go well
- n What is next?
 - n Special Report; 21 CFR 314.81(b)(3)(ii)
 - n Subset of the annual report
 - n Allows for report of information that is off the normal annual report cycle.

Step by step

- n Assess basis for change
- n Assess potential effects of the change
- n Consider relevant prior knowledge
- n Conduct supporting studies
- n Develop plan for implementation
- n Notify FDA and request approval
 - n Prior approval supplement in most cases
- n Conduct studies promised in protocol

Step by step

- n Analyze implementation data
- n Report implementation status
 - n Success: special report
 - n Failure: call review division
- n Keep data for potential on-site inspection
- n Ongoing activity to ensure continued drug product quality

Emphasis

- n Benefit to patients through better control strategy
- n Rationale for the risk determination
- n Planning for implementation
- n Encourage technological advances
- n Reduce unnecessary burden

Shift gears

Standards Development

- n Congress: National Technology Transfer and Advancement Act (NTTAA); 1995
- n Office of Management and Budget (OMB): Circular A-119; 1998 (original in 1993)
- n http://standards.gov/standards_gov/index.cfm

The Mandate...

- n OMB Circular A-119
 - n "...this Circular directs agencies to use voluntary consensus standards in lieu of government-unique standards except where inconsistent with law or otherwise impractical."
 - n "This circular applies to all agencies..."
 - n "Agency means any executive department..."
 - n "It also includes any regulatory commission..."
 - n "All federal agencies must use voluntary consensus standards in lieu of government-unique standards in their procurement and regulatory activities..."

In lieu of...

- n This term is used 15 times in the Circular

- n Common definition:
 - n Instead of
 - n In place of

What if it is impractical?

- n “The head of your agency must transmit to [NIST], an explanation of the reason(s) for using government-unique standards in lieu of voluntary consensus standards.”
- n Organizational decision

What if I'm working on a guidance on the same topic?

- n "If a voluntary consensus standards body is in the process of developing or adopting a voluntary consensus standard that would likely be lawful and practical for an agency to use, and would likely be developed or adopted on a timely basis,
- n an agency should not be developing its own government-unique standard and
- n instead should be participating in the activities of the voluntary consensus standards body."

What about my authority?

- n "This policy does not preempt or restrict agencies' authorities and responsibilities to make regulatory decisions authorized by statute."
- n These include
 - n "Determining the level of acceptable risk"
 - n "Setting the level of protection"
 - n "Balancing risk, cost and availability of technology in establishing regulatory standards."

“Use voluntary consensus standards”

- n “To determine whether established regulatory limits or targets have been met”
 - n “Test methods”
 - n “Sampling procedures”
 - n “protocols”

What is a standard?

- n “Common and repeated use of rules
- n Conditions, guidelines or characteristics for products or related processes
- n Production methods, and related management systems practices”

Standards Include...

- n "Definition of terms;
- n Classification of components;
- n Delineation of procedures;
- n Specification of dimensions, materials, performance, designs, or operations;
- n Measurement of quality and quantity in describing materials, processes, products, systems, services or practices;
- n Test methods and sampling procedures;
- n Descriptions of fit and measurements of size or strength."

Performance Standards...

- n "...required results with criteria for verifying compliance but without stating the methods for achieving required results."

- n "...may define the functional requirements for the item, operational requirements, and/or interface and interchangeability characteristics."

Not Considered Standards...

- n "Professional standards of personal conduct."
- n "Institutional codes of ethics."

Why move to standards?

- n "Eliminate the cost to the Government of developing its own standards and decrease the cost of goods procured and the burden of complying with agency regulation."
- n "Provide incentives and opportunities to establish standards that serve national needs."
- n "Encourage long-term growth for U.S. enterprises and promote efficiency and economic competition through harmonization of standards."

Last, but not least...

- n “Further the policy of reliance upon the private sector to supply Government needs for goods and services.”

Standards Classification in A-119

- n Voluntary Consensus Standards
 - n More on next slide
- n Non-Consensus Standards
 - n Company standards
- n Government Unique Standards
 - n Guidance
- n Standards Mandated by Law
 - n USP/NF referenced in 21 U.S.C. 351

Consensus Standards

- n How does OMB describe a Consensus Standard Organization (CSO)?
 - n Openness
 - n Balance of Interest
 - n Due process
 - n Appeals process
 - n Consensus meaning not necessarily unanimity, but that each objector is advised of the disposition of the objection and the reason why and the body members can then change their votes

Thank you

- n Say what you do
- n Do what you say