Office of Pharmaceutical Science on 314.70

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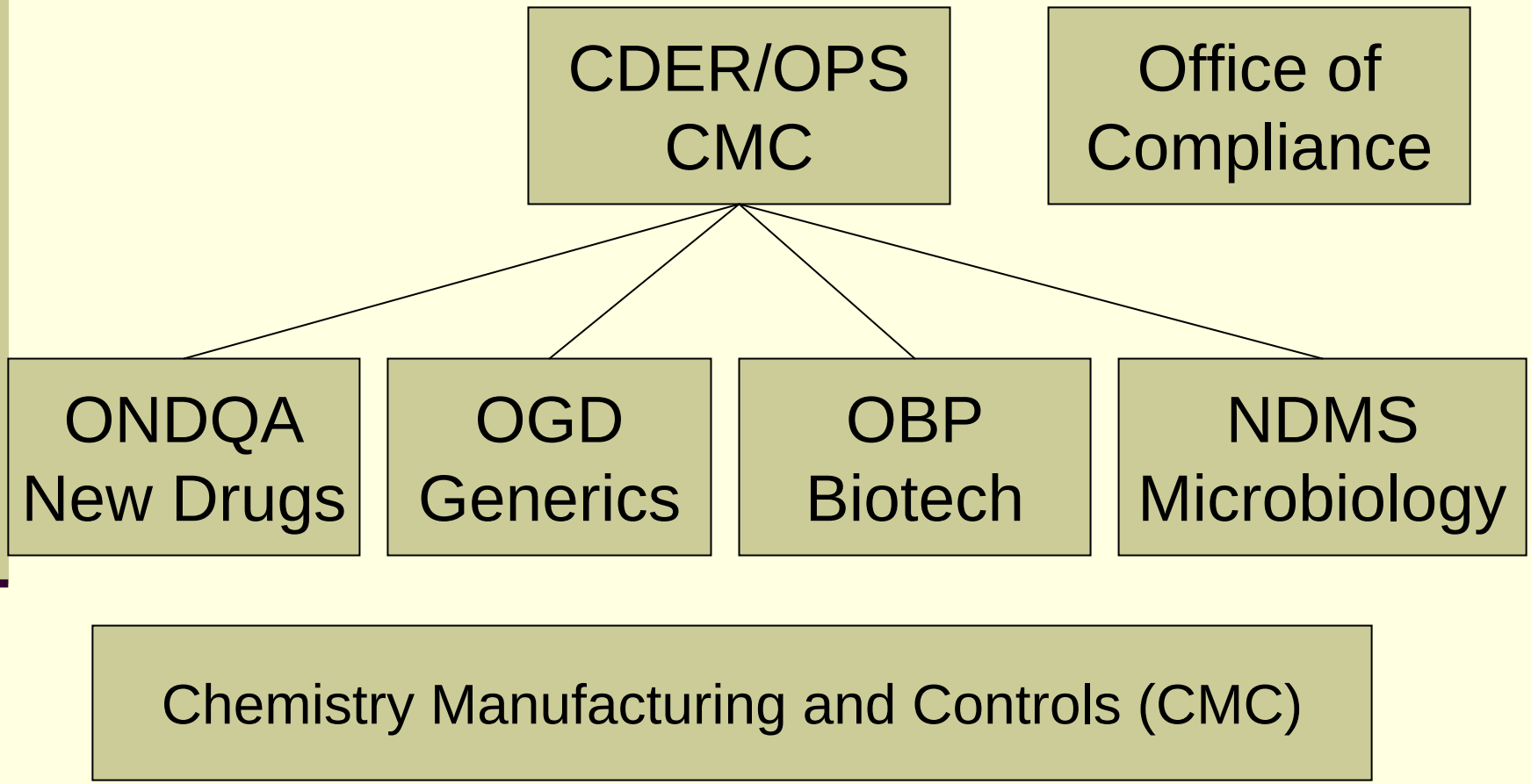

The 21st Century Initiative

- Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach
  - Begun 2002
  - Report 2004
  - Dr. Janet Woodcock's desired state:
    - "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products **without** extensive regulatory oversight."
  - http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm

21st Century Initiative

- Goal
  - “It has been the goal of the CGMP initiative to create a **regulatory framework** that will **encourage** pharmaceutical manufacturers to also make use of these modern tools, to facilitate the implementation of robust manufacturing processes that reliably produce pharmaceuticals of high quality and that accommodate **process change** to support continuous process improvement.”

314.70

- Changes to an approved application.
  - “The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application”
- Categorizes changes
  - According to notification mechanism
  - Without consideration of the applicant’s risk management activities
- Prescriptive and burdensome

Current Change Notices

- Prior Approval Supplement
  - Substantial potential for adverse effect
- Changes Being Effected Supplement
  - Moderate potential for adverse effect
- Annual Report
  - Minimal potential for adverse effect
- Guidance Available
  - http://www.fda.gov/cder/guidance/3516fnl.pdf

Supplement Examples

- "…any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a **moderate potential** to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product"
  - "A change in the container closure system that **does not affect** the quality of the drug product"
  - "An increase or decrease in production scale during finishing steps that involves different equipment; and (B) Replacement of equipment with that of a different design that **does not affect** the process methodology or process operating parameters"

More Supplements

- “Addition to a specification or changes in the methods or controls **to provide increased assurance** that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess”
- “Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium **that is consistent with FDA statutory and regulatory requirements**”

Impacts of Current 314.70

- These prescriptive approaches may not support
  - Beneficial manufacturing changes
  - Desired level of innovation
  - Modernization
  - Flexibility
- FDA resources are spent in review
  - >5,500 supplements last year

Possible Changes for Your Consideration

- Allow for more manufacturing changes to be made without prior FDA approval using a firm's internal change control system
- Allow for consideration of
  - risk-based approaches
  - manufacturing process understanding
  - knowledge of similar products
  - Quality systems

Consideration

- Creating a new reporting category of manufacturing changes that do not require notification to FDA
- Redefining what FDA considers to be a major manufacturing change
- Manufacturers continue to be responsible for ensuring product quality
- Accommodation of those who choose to continue with the current system

Related Efforts

- ONDQA implementing risk-based pharmaceutical quality assessment system (PQAS)
  - Quality by Design
  - Focus on critical pharmaceutical quality attributes and their relevance
- OGD Implementing Question Based Review (QBR)
  - How do the manufacturing processes and controls ensure consistent production of the drug substance?
  - Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?
  - Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture or performance?

Speak to the record

- Today we will hear from people who registered to speak before the January 24 deadline…
- You can comment to the docket until March 7, 2007
  - Docket No. 2006N-0525
  - Division of Dockets Management (HFA–305)
    Food and Drug Administration,
    5630 Fishers Lane, rm. 1061,
    Rockville, MD 20852.
  - to *http://www.fda.gov/dockets/*
- Link to original FR Notice
  - http://a257.g.akamaitech.net/7/257/2422/01jan20071800/edocket.access.gpo.gov/2007/pdf/E6-22588.pdf