Lifecycle Management of Approved Drug Products- FDA Perspective

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Presentation Outline

1. Introduction
2. Overview of Drug Development
3. Defining Lifecycle with Examples
4. Changes and Risk Based Evaluation
5. Conclusions

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.

Drugs are no different.


Patients expect safe and effective
medicine with every dose they take.

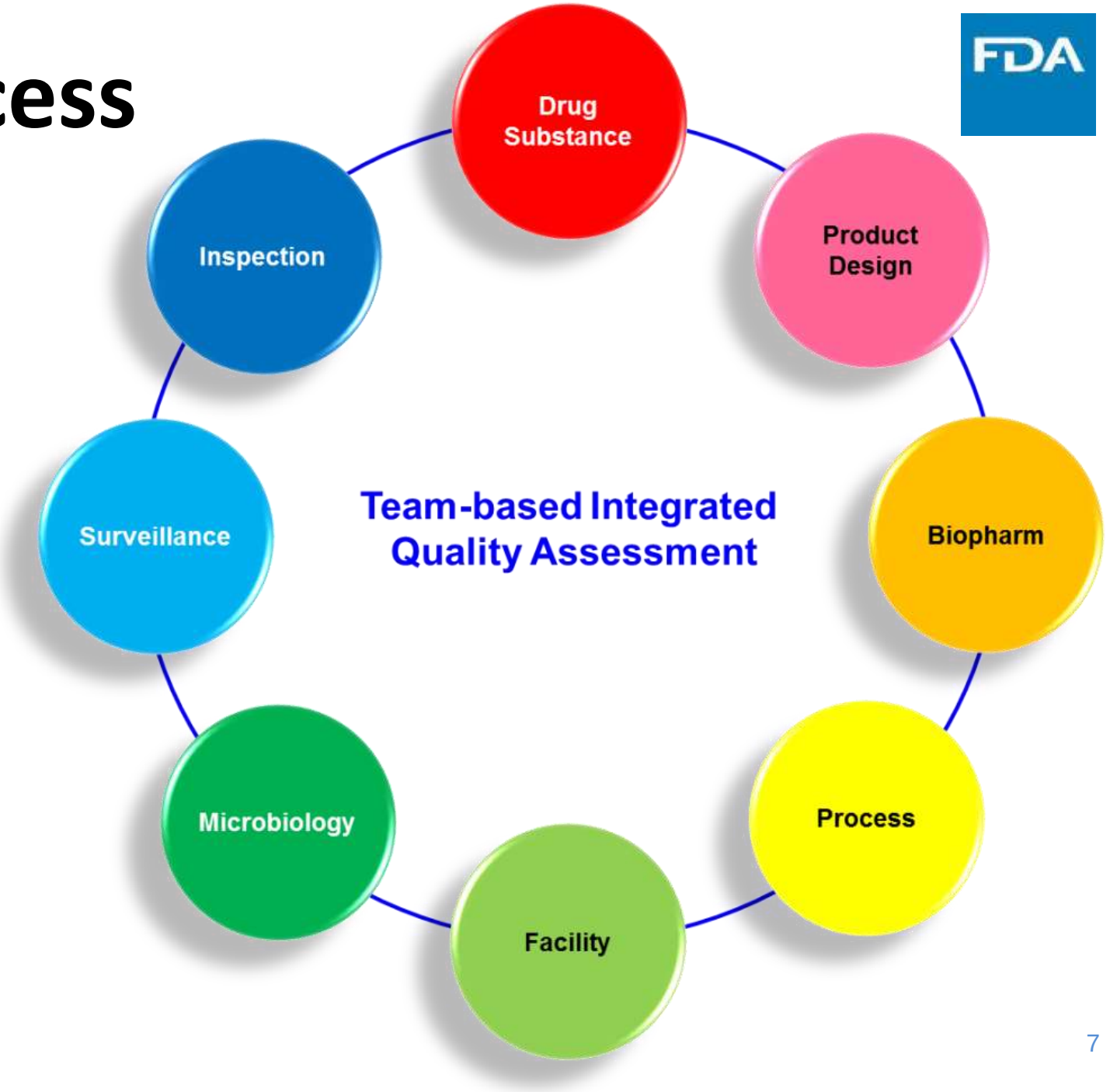
Pharmaceutical quality is

consistently meeting standards that ensure every dose is safe and effective, free of contamination and defects.

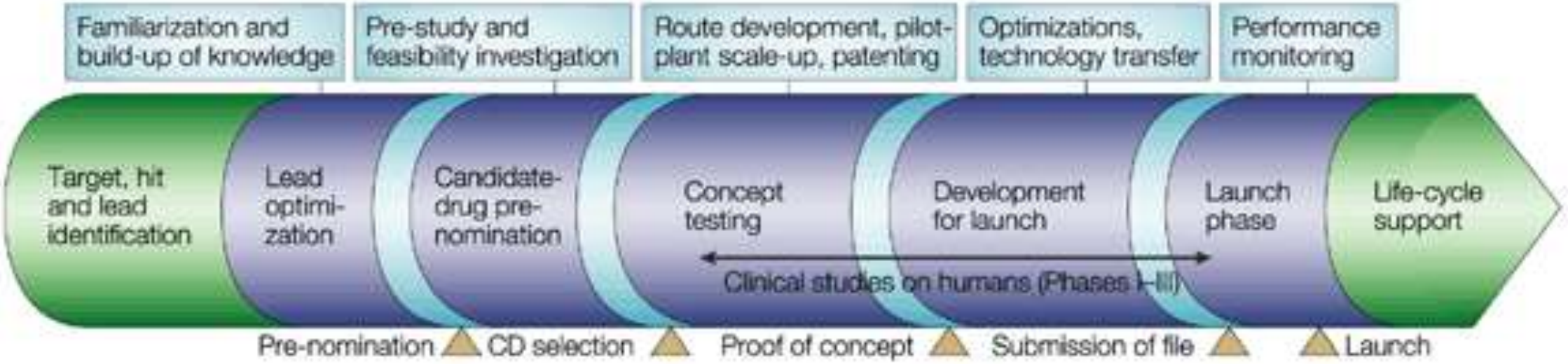

It is what gives patients confidence
in their *next* dose of medicine.

CMC Review Process

- Inclusive of drug substance, drug product, manufacturing, and facilities expertise
  - Inspection, Surveillance and Post-market reviewers as needed
- Uses science- and risk based approach that is patient-focused



Drug Development Process



Nature Reviews | Drug Discovery

www.fda.gov

Drug Approval Process-Overview

- Discovery
- Development- Chemistry/Biology/Feasibility
- Non-Clinical
- Pre- IND
- IND- Phase I

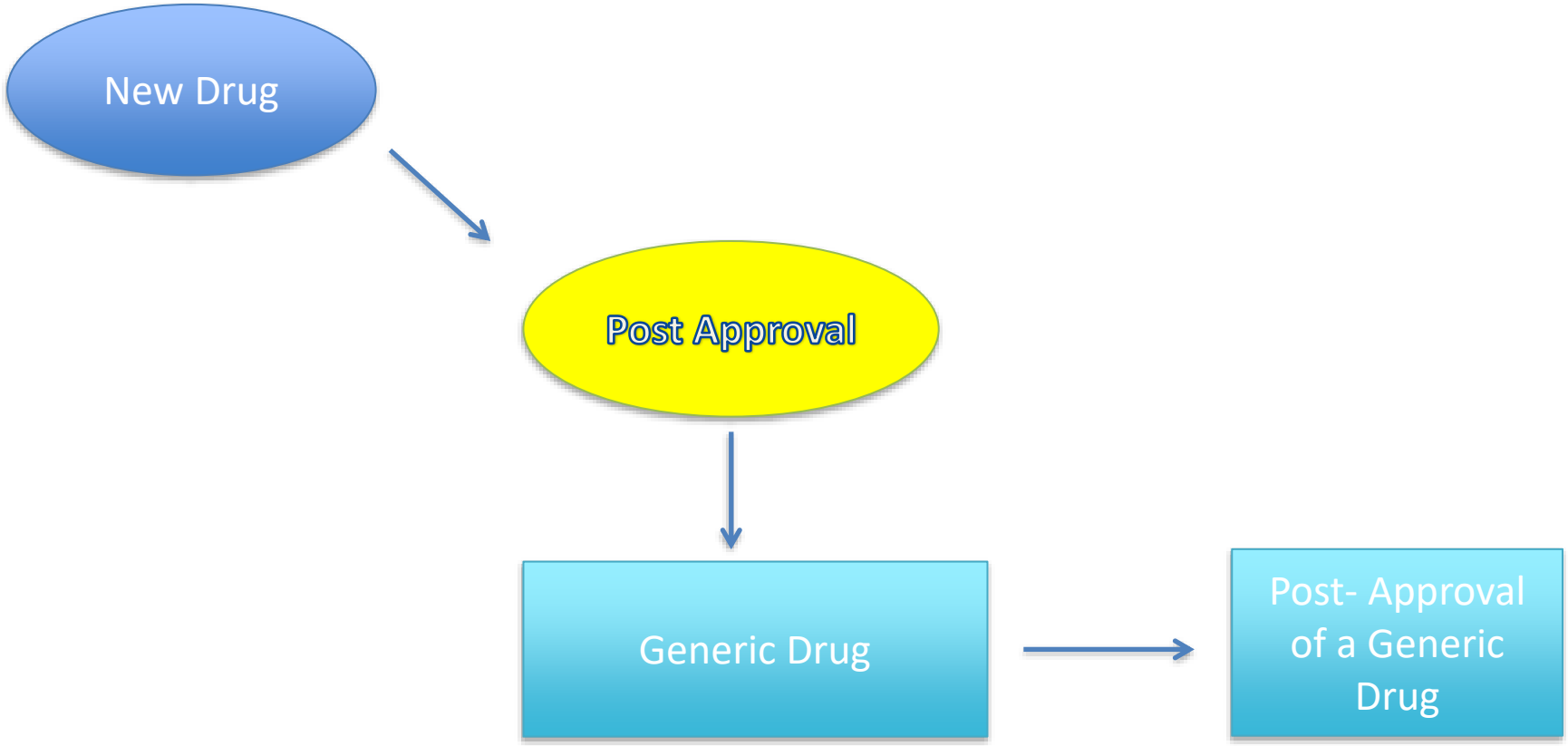
Drug Approval Process-Overview (cont.)

- IND- Phase II
- IND-Phase III
- NDA Submission to FDA for Approval
- Phase IV-Post Marketing Surveillance

CMC Essentials

- The Main Body of Data
  - Drug Substance
  - Drug Product
  - Packaging and Stability
  - Placebo Information (applicable only for INDs/clinical trials)
  - Labeling

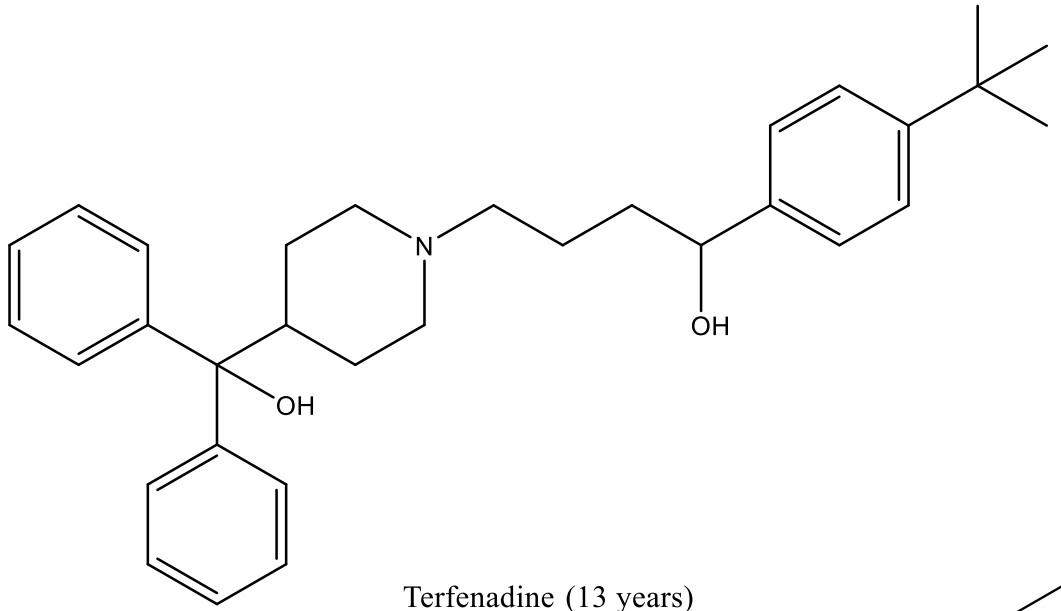
Defining the Lifecycle



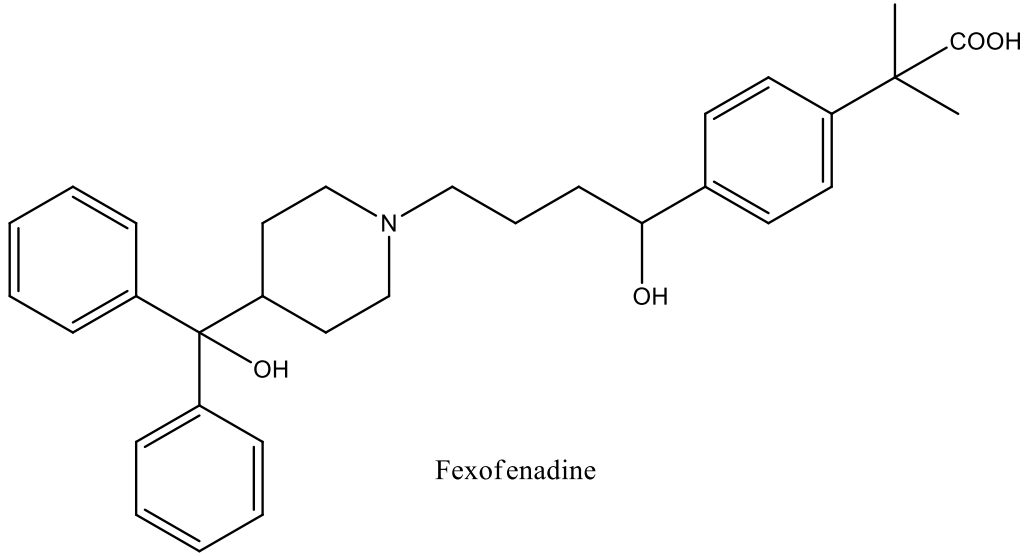
Lifecycle Examples

- Learnings from clinical trials define the pathway
- Post-marketing experience
- The Following four slides provides a short lifecycle history of some unusual drug entities as examples!

Seldane and Allegra

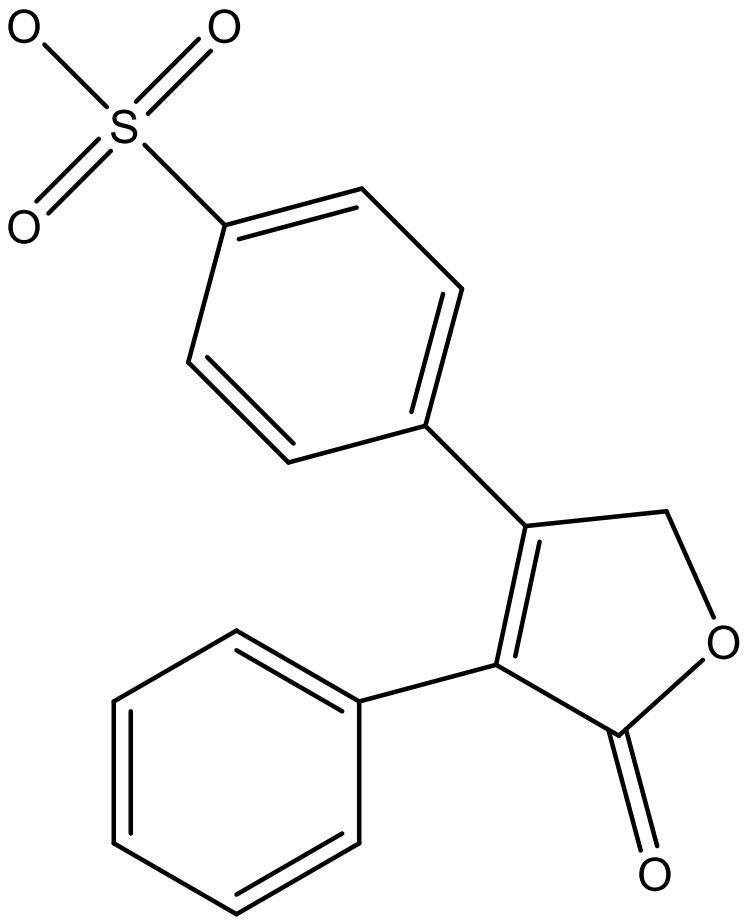


Terfenadine (13 years)



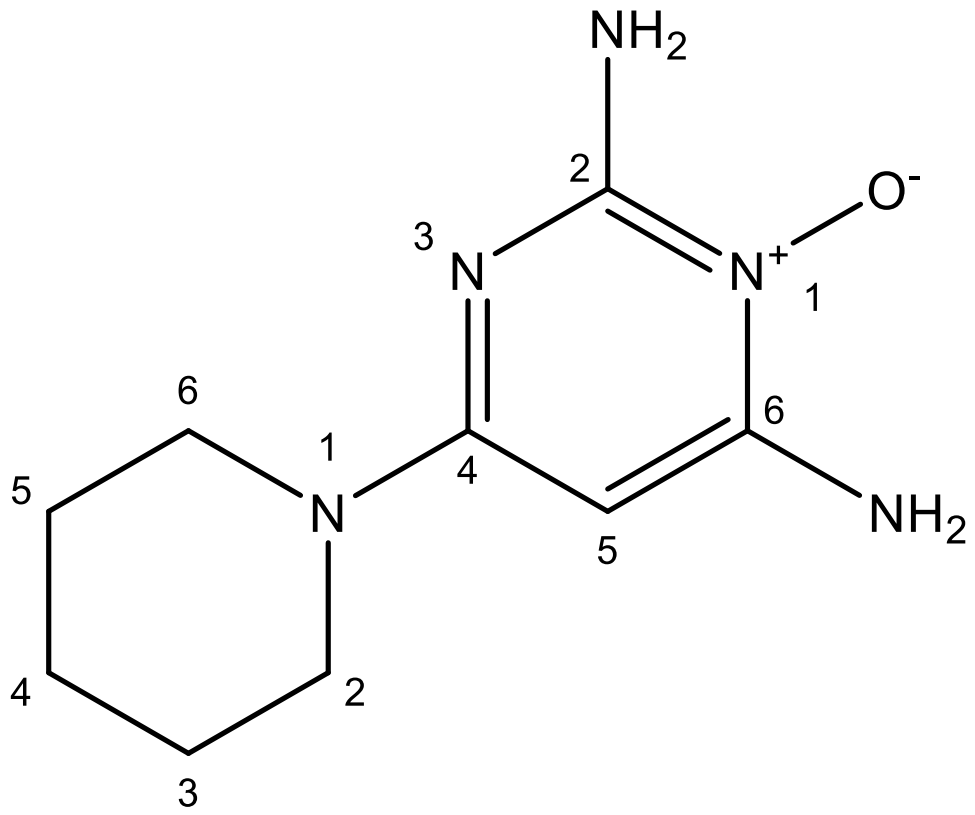
Fexofenadine

Vioxx

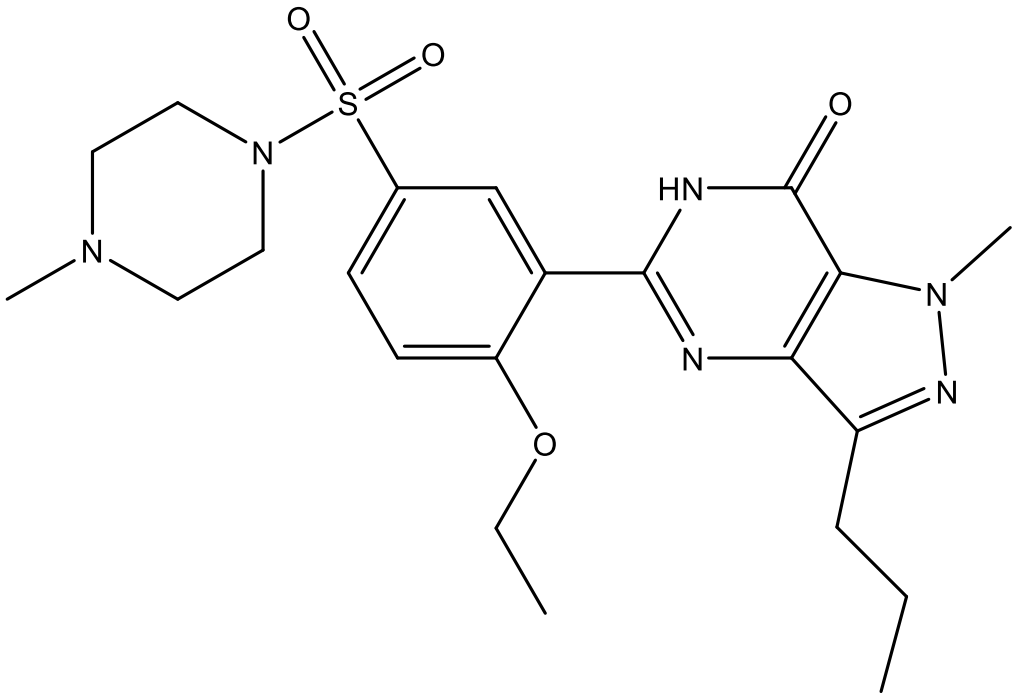


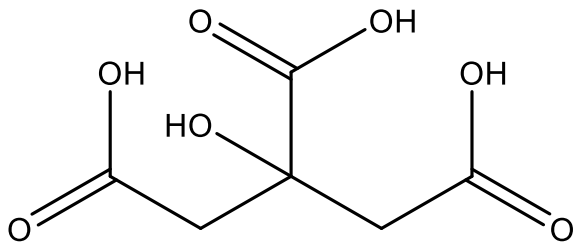
Vioxx (5 years)

Minoxidil



Viagra (sildenafil citrate)





Why Post-Approval CMC Changes?

- Continuous improvement
  - Product Optimization
  - Incorporating new technologies
  - Process improvement (based on historical knowledge)
- Regulatory Requirements/Commitments
- Product quality issues
- Business Reasons
  - Supply & Demand

Types of Supplements

- Efficacy supplements
  - Claim for a New Indication in the Labeling
  - Changes in the dosing regimen
  - Safety Changes (precautionary statements/Blackbox warning/new contraindications)
  - Addition of dosing information for special population
- Labeling supplements
  - Changes in the approved labeling, including package insert, immediate container and carton labels, or medication guide
- CMC Supplements
  - Changes in the drug substance and/or drug product manufacturing, analytical changes, site changes etc..

Regulatory Review Times

- Investigational New Drugs- Phase I -30 days
- NDA
  - Standard 10 months
  - Priority- 6 months
- Post- Approval Supplemental applications
  - Prior Approval (4 months)
  - CBE-30 or CBE-0 (6 months)

Typical Post-Approval CMC Changes

- Drug Substance
  - New manufacturing site
  - New supplier for regulatory starting materials
  - Changes to the route of synthesis
  - Changes to the manufacturing process
  - Changes to the in-process controls and/or drug substance specifications
  - Changes to the shelf life or retest period….

Typical Post-Approval CMC Changes

- Drug Products
  - New manufacturing site
  - Changes to the manufacturing process and/or equipment
  - Changes to the formulation
  - Changes to the container closure system
  - Changes to the specifications
  - Changes to the shelf-life (extension or reduction)
  - Introduction of new strengths
  - Introduction of a new presentation ....

Regulatory Basis for Post-Approval Changes

- 21 CFR 314.70

  § 314.70 Supplements and other changes to an approved application.

  – The applicant must notify FDA about each change in each condition established in an approved application.

Regulatory Basis- FDA Guidances

- Changes to an approved NDA or ANDA
- Scale-up and post-approval change (SUPAC)
- SUPAC-IR, SUPAC-MR, SUPAC-SS
- SUPAC: Manufacturing equipment addendum
- CMC post-approval manufacturing changes to be documented in annual report
- Comparability protocol – Chemistry, Manufacturing, and Controls information
- PAC-ATLS: post-approval changes – analytical testing laboratories sites

Guidance for Industry

Changes to an Approved NDA or ANDA

U.S. Department of Health and Human Services Food and Drug Administration

Center for Drug Evaluation and Research (CDER) April 2004

CMC

Revision 1

Regulatory Basis- ICH Guidances

- All relevant ICH Guidances
  - ICH Q1A to Q14

  https://www.ich.org/page/quality-guidelines

Regulatory Basis- FDA Guidances

- FDA Guidances

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents

ICH Q12

Fundamental tools and enablers to support harmonized lifecycle management:

- Established Conditions (EC)
- Product Lifecycle Management (PLCM)
- Post-Approval Change Management Protocols (PACMP)
- Pharmaceutical Quality Systems (PQS)

Comparability Protocols

- A Comparability Protocol (CP) is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC post-approval change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product as these factors may relate to the safety or effectiveness of the product (i.e., product quality).
  Agency definition in draft guidance published April 2016

Emerging Technology

Guidance:

- Guidance for Industry: Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization
- Guidance for Industry: Quality Considerations for Continuous Manufacturing

Classification of CMC Changes

- Major changes (Prior Approval Supplements)
  - High impact to the product quality
  - Cannot be implemented until approved
  - Four months review clock
- Moderate changes (Changes Being Effected in 30 Days Supplements)
  - Moderate impact to the product quality
  - Can be implemented 30 days after submission at the applicant's own risk
  - Six months review clock
- Minor changes (Changes Being Effected in 0 Days Supplements or Annual Reportable)
  - Minimal risk to product quality
  - Can be implemented immediately after submission
  - Six months review clock for supplements

Meetings with FDA

- Types of meeting
  - Type A
    - Granted within 30 days
  - Type B
    - Granted within 60 days
  - Type C
    - Granted within 75 days

www.fda.gov

Source: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM466486.pdf

Conclusions

- Post-Approval changes are essential for the process improvement of the Drug Product
- Patient response and potential for repurposing
- Market demands
- Continuous Improvement & Essential to maintain Product Quality and Patient Safety

THANK YOU!