Lifecycle Changes to Chemistry, Manufacture, and Controls in NDAs

- FDA Perspective

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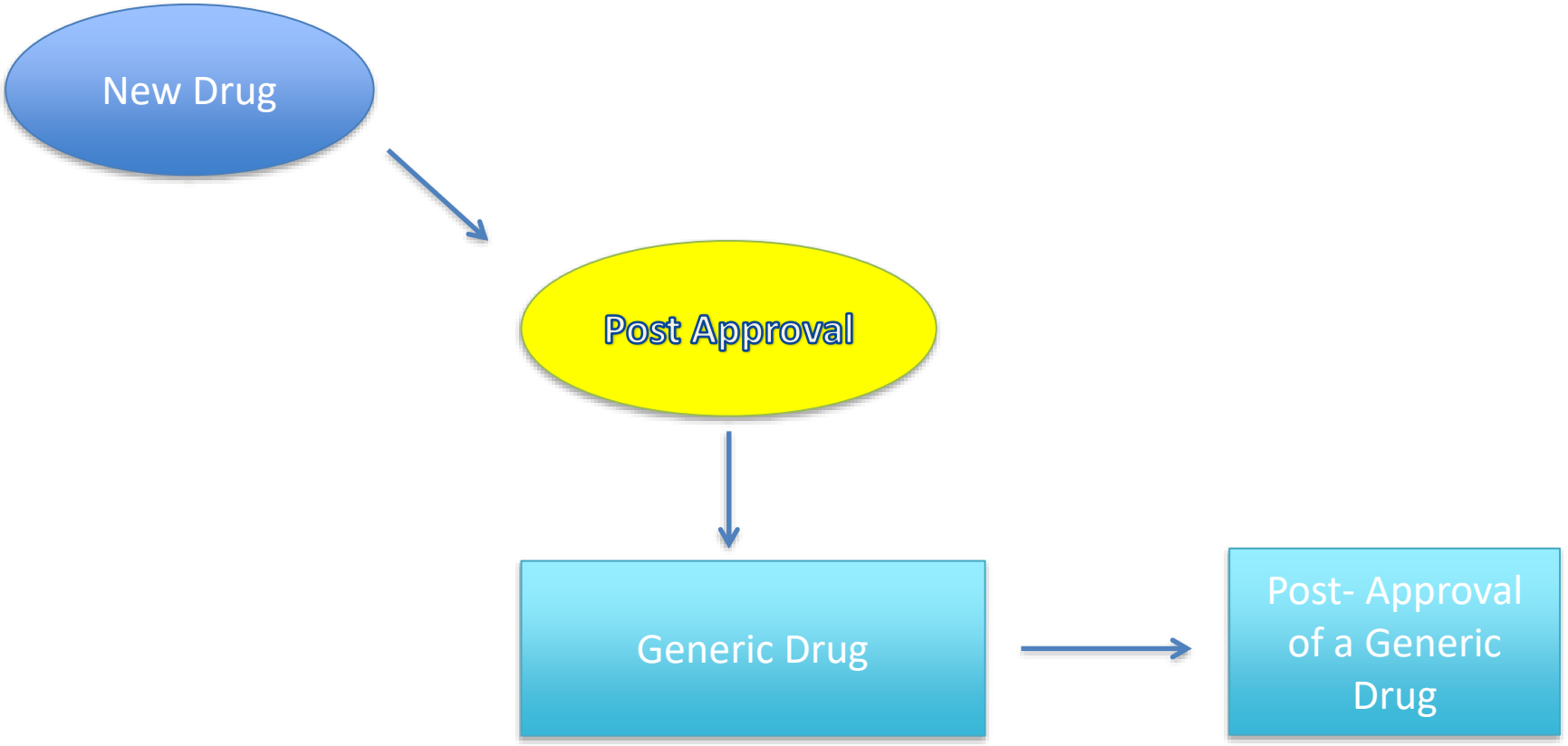
Defining the Lifecycle

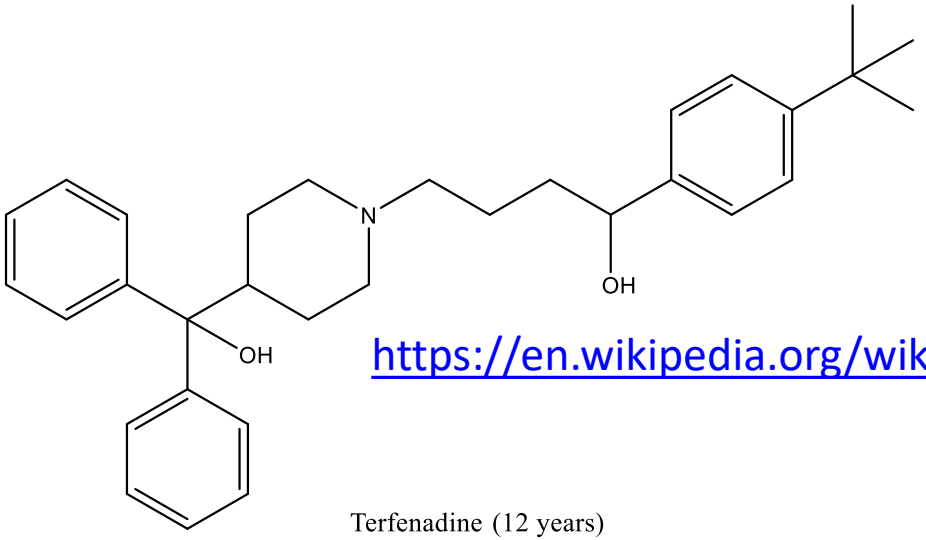


What Determines the Lifecycle

After approval of a new drug:

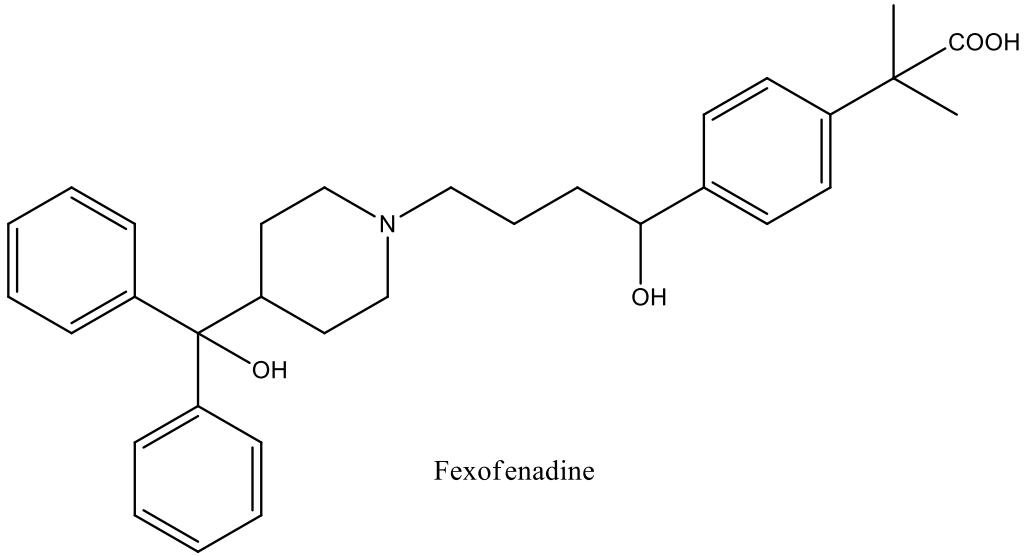
- Indication
- Efficacy in Patients
- Safety in Patients
- Manufacturability
- Quality
- Continuous Improvement
- Economics and Business decisions

Terfenadine & Fexofenadine



https://en.wikipedia.org/wiki/Terfenadine

Terfenadine (12 years)

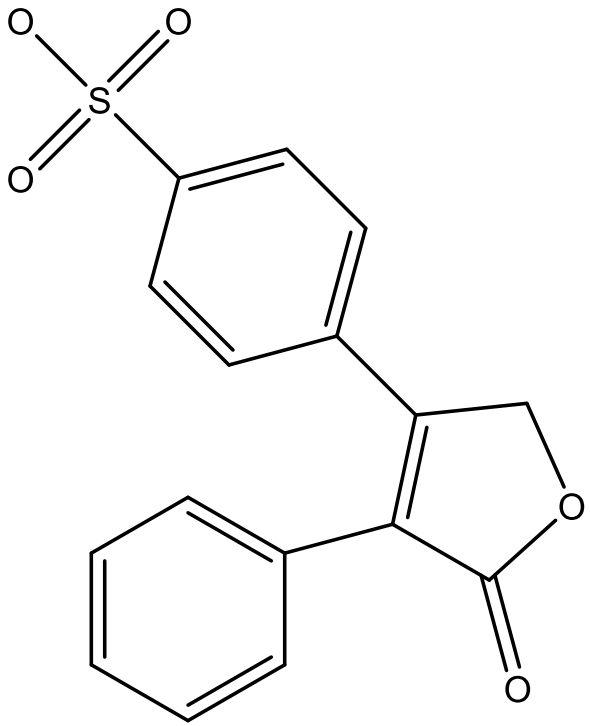


Fexofenadine

https://en.wikipedia.org/wiki/Fexofenadine

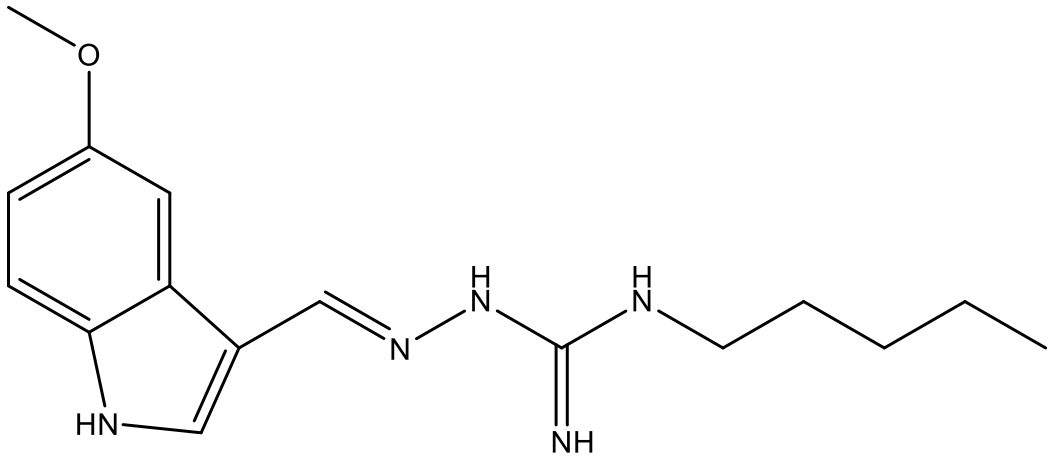
Rofecoxib

- Vioxx (5 years)



https://en.wikipedia.org/wiki/Rofecoxib#:~:text=Rofecoxib%20is%20a%20COX%2D2,conditions%2C%20migraine%2C%20and%20dysmenorrhea.

Tegaserod



Zelnorm (5 years)

https://en.wikipedia.org/wiki/Tegaserod

What Happens in a Lifecycle?

- Effects of the drug in (real) patients start only after an approval
  - Real efficacy
  - Long term safety
  - Stability issues related to the formulation
  - Potential for alternate dosage forms
  - Challenges in maintaining high standards of Quality

During the Lifecycle....

- When the drug is approved:
  - May become a block buster
  - May have unintended adverse events not seen during the clinical trials
  - May be withdrawn due to serious adverse events
  - May prove to be more effective for other indication(s)

Managing Approved Products

- Better risk management
  - Understanding the past experiences
  - Evaluating the present situation
  - Planning for a better future with all the lessons learnt
- Changes necessary to avoid pitfalls

Post- Approval Changes- Why?

- After approval changes are inevitable
  - Optimization of process
  - Production scale
  - Fine tuning the controls
- Changes are global
- Quality changes tied to economics of the company
- Multiple changes at multiple levels

Lifecycle Changes
21 CFR 314.70

- Prior Approval Changes (PAS) – High Risk
  - Review clock 4 months, Efficacy 10 months or 6 months
- Changes Being Effected in 30 days (CBE-30) - Moderate Risk
  - Review clock 6 months
- Changes Being Effected in 0 days (CBE-0) – Moderate Risk
  - Review clock 6 months
- Annual Reportable Changes- Low Risk changes

PAS Changes (Examples)

- New Formulation (including changes to excipients)
- Labeling Changes
- Additional strengths
- Primary Container Closure System changes
- Comparability Protocols
- Manufacturing Facility changes to sites for which no CGMP history is available
- Stability Protocol

CBE-30 Changes (Examples)

- Manufacturing Facility changes to sites for which CGMP history is available
- Change in Testing Facility sites for which CGMP history is available
- Manufacturing process changes
- Analytical method changes

CBE-0 Changes (Examples)

- Additional Specification to controls
- Method modifications
- Editorial changes
- Corrections
- Missing data
- Commitments (depending upon the risk)
- Changes that do not impact Quality/Safety/Efficacy in any way

Annual Reportable Changes

- Changes that would not impact quality of the drug product- low risk changes
  - e.g. -Extension of expiry dating period with an agreement with the Agency during an approval of an NDA based on a real time long term data

ICH Q12

- A guidance for Lifecycle management
- Risk based approach to changes
- Regulatory Flexibility
- Case by Case basis

Objectives ICH Q12

- Management of post-approval changes
  - Increased emphasis on risk based approach
- Regulatory Flexibility
- Increased transparency and predictability
- Innovation and continuous Improvement

Common Changes

- Formulation
- Dosage form
- Introduction of a strength
- Changes in Testing Facility
- Changes in Manufacturing Process
- Changes to the Manufacturing Facility

Case Study -1

- An ‘Immediate Release’ Tablet drug product was approved five years ago. The manufacturing process was a batch process.
- Now the applicant wants to change the process to an efficient continuous manufacturing process.
- What should they do?

Case Study -1

- This is a novel technology.
- The applicant should request a “Type C Meeting Request’ from the Agency
- Submit a meeting package with the exact plan and with relevant questions- expectations from the Agency
- Usually the ‘Emerging Technologies Team’ will get involved
- Before submission a ‘Pre-Operational Visit’ from the Agency’s review team is recommended

Case Study -2

- A liquid sterile product in a polymeric primary container closure system
- The applicant wants to change the resin due to discontinuation of the currently used polymeric resin.
- What should the applicant do in terms of implementing the change?

Case Study -2

- This Change involves a higher risk hence a ‘Prior Approval Supplement’
- The stability data of the product in the proposed resin is important
- Extractable & Leachable data is also Necessary
- Pharmacology/Toxicology evaluation of Leachables under stability conditions based on the proposed expiry dating period.

Case Study -3

- After approval of an extended-release solid oral drug product the applicant wants to change the analytical method without changing the specification.
- What kind of Submission is required?

Case Study -3

- It Depends upon the analytical method and the filing category is risk based
- For example: When you change the dissolution method for an extended release oral dosage form it is a PAS
- Changes to assay and content uniformity by LC would be CBE-30
- In general it is CBE-30 or PAS

Case Study -4

- An applicant submits a supplement for a change in the supplier for the ‘Active Pharmaceutical Ingredient’. References to a brand new DMF (Drug Master File). Also the manufacturing facility has been previously inspected by FDA and has an ‘acceptable’ CGMP Compliance. However, no changes in the process or impurities were reported. The Specification is exactly as it was approved in the Original NDA.
- What would be filing category?

Case Study -4

- Brand New DMF means, it has to be reviewed for its Adequacy.
- Hence it must be a ‘Prior Approval Supplement’
- Even if the facility is in good standing, ‘Prior Approval Inspection’ may be required depending upon the process.

Case Study -5

- A Prior Approval supplement references

  DMF# A for a new Drug Substance Manufacturer. DMF# A references DMF# B.

  DMF# B references DMF# C. During the review it was determined that the facility used in the manufacture of the drug substance was recommended for approval, data provided in DMF# A and DMF# B were adequate and however DMF # C is deficient. What would be the outcome of the review?

Case Study -5

- Since DMF # C is referenced by DMF # B. All DMF's A, B & C will be inadequate (deficient).

  Hence the entire application will receive a 'Complete Response' letter.

Pulmonary Delivery Devices

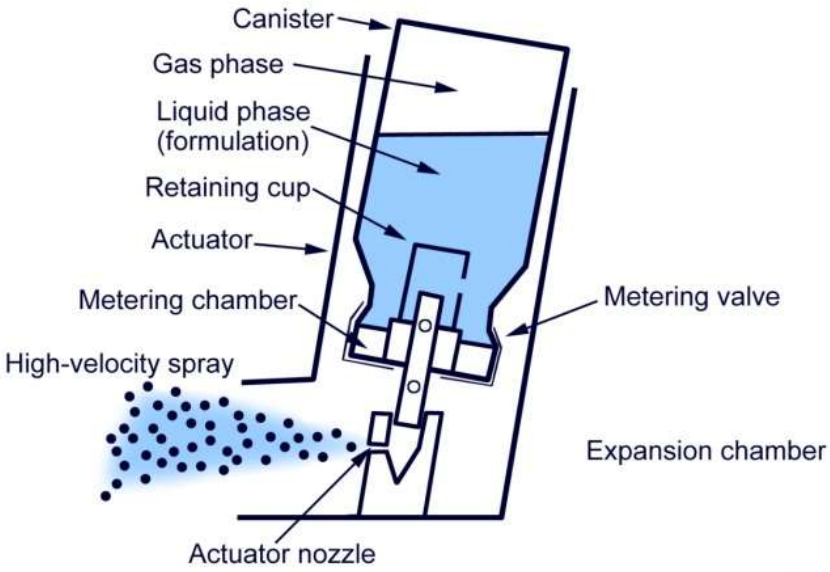
- **Metered Dose Inhalers (MDIs)**
  - also known as *inhalation aerosols*
- **Dry Powder Inhalers (DPIs)**
  - also known as *inhalation powders*
- Inhalation solutions/suspensions
  - Use CDRH cleared general-use nebulizers (devices)
- **Inhalation Sprays**

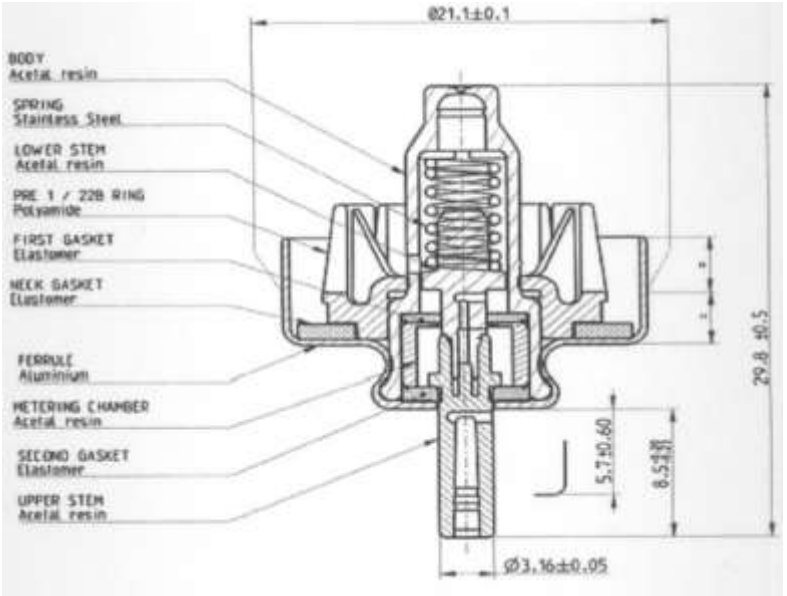
- All of these are Combination Products as per 21 CFR 3.2

Issues in Inhalation Products

- Delivered Dose
- Aerodynamic Particle Size Distribution (APSD)
- Plume Geometry (in case of Aerosol activated and sprays)
- Extractable and Leachable Information
- Human Factors

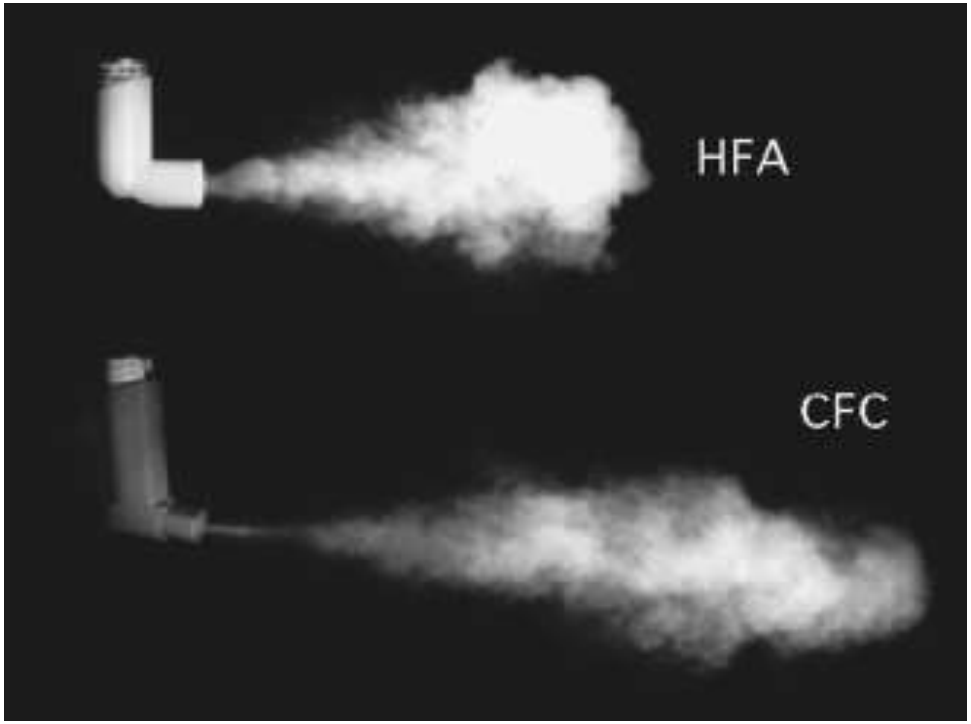
Metered Dose Inhalers -Aerosol





Plume Geometry

http://basicmedicalkey.com/quality-of-inhalation-products-specifications/



Conclusions

- Life of Drug Product starts only after it's approval by the Agency
- Changes to drug product after approval are essential for multi-various reasons
- Maintaining the Quality is essential throughout its lifecycle
- Focus on the Patient