It's a Bird, It's a Plane, No Wait, It is Finally Multi-Center Current Thinking on Parametric Release of Drug Products Terminally Sterilized by Moist Heat

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Topics

- Who are those CDER Product Quality Microbiologists
- What is the big deal about parametric release (definition and utility)
- Parametric release and PAT-is there a connection?
- Filing issues—not heaps of paper!!
- Submission content for Parametric Release-current thinking

Product Quality Microbiology in CDER

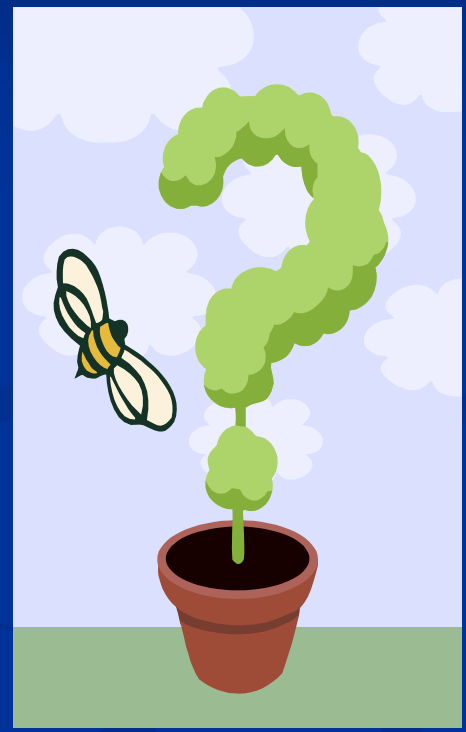
- 1973-First microbiology reviewers-LVP products only
- 1988-Review of generic drugs
- 2005-16 product quality microbiology reviewers divided between OPS (INDs/NDAs) and OGD (ANDAs)
- Approximately 20% of all generic drug applications will be reviewed by an OGD microbiologist—for year 2005 over 800 original submissions received

This Presentation

- What it will cover
  - Moist heat
  - ANDAs and NDAs
- What it will not cover
  - Other terminal sterilization processes
  - Design and validation

What is Parametric Release?

- Replacement of the end-product sterility test as a release criterion→ no sterility test for finished product
- Critical process parameters identified for the terminal sterilization cycle
- Critical parameters are measured in real time; material attribute effects determined during development



Why do You Care?

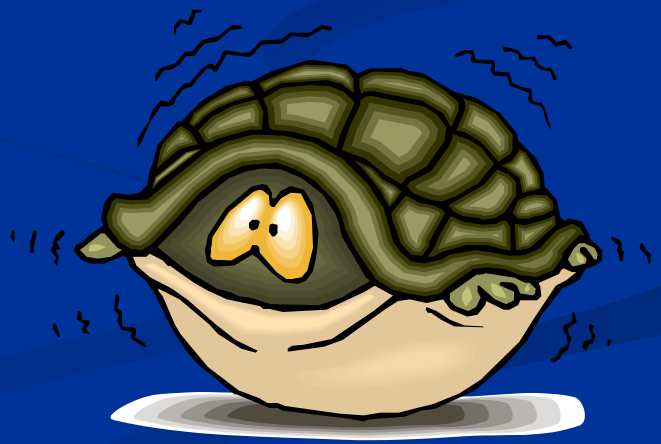
- Faster Release
- No waiting for 14 or more agonizing days (for sterility test results)!!!
- Saves you $$$
- Process understanding →better sterility assurance

What do You do in Return?

- Certain commitments with regard to batch disposition →in cases of cycle failure →batch rejection
- Commitments in submission
- Commitments in Finished Product Release Specifications

Some History

- Approval of the first submission by the FDA in the US using parametric release submission was in 1985
- Not again until 1996
- Expectations at that time→ extensive production history with the product
- This resulted in reluctance by industry to embrace the practice



Is it a painful process?

- Currently several manufacturers of generic and innovator drugs release CDER regulated products by parametric release
- 2 decades of success
- It is all about Process Control and Knowledge of the manufacturing process

How is Parametric Release related to PAT?

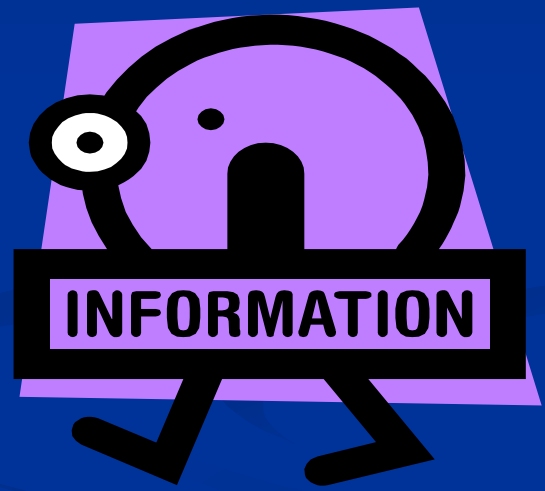
- PAT and "*Real Time Release*"
- Parametric release is the foundation for "*Real Time Release*"
- HOWEVER→ Parametric Release submissions will not follow PAT

Filing a Parametric Release Submission

- Prior Approval supplement
  - Existing TS cycle
- Original application
  - Existing TS cycle
- Original application
  - New TS cycle

Contents for a Parametric Release Submission

- Reflects our current thinking
- Information needed based on accumulated knowledge of product and process
- Additional Center recommendations



Contents for a Parametric Release Submission

- Original submission: Sterility assurance info *"Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"*
- PA supplement: Current Program
  - Application no.(s) and approval date(s)
  - Drug product; container/closure system
  - Terminal sterilization process
  - Differences: current process vs. approved process

Contents for a Parametric Release Submission

- PA supplement: Current Program cont.
  - Microbiological monitoring plan:
    - Bioburden levels of packaged product or components prior to sterilization
    - Procedures for spore detection and screening (when applicable)
    - General response plan for exceeded levels

Contents for a Parametric Release Submission

- Knowledge of Process Control: Production History
  - To demonstrate understanding of the process
  - Depends upon product, process, and previous submissions providing for sterility assurance

Contents for a Parametric Release Submission

- Production History
  - Sterility test excursions
  - Bioburden excursions and spore characterization
  - Terminal sterilization cycle excursions
  - Corrective actions for any above excursions

Contents for a Parametric Release Submission

- Specific Information for the Parametric Release Process: Documentation
  - Critical parameters for cycle and acceptance criteria
    - Acceptance criteria must be met for release
  - Sterilization Load Monitor (21 CFR 211.167a)
    - Characterization
    - Considered a Critical Parameter
  - Evaluation and Disposition decisions

Contents for a Parametric Release Submission

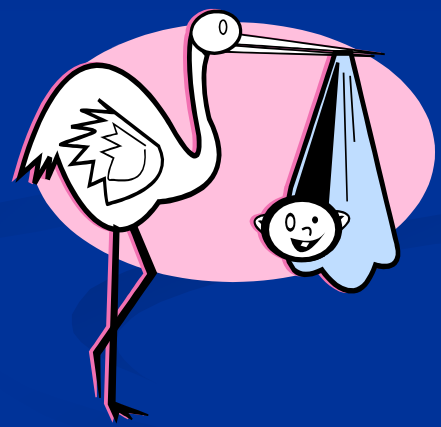
- Specific Information: Commitments
  - Parametric Release replaces sterility test
  - Cycle failure and rejection defined
  - Use of the sterility test is prohibited as a backup if cycle fails

Contents for a Parametric Release Submission

- Specific Information: Finished Product Release Specifications
  - Parametric release in lieu of sterility test
  - No sterility test back up
  - "*Method*" → "parametric release process" or SOP title/number for the process
  - "*Specification*" → list of critical parameters and acceptance criteria or "must meet requirements" and reference to SOP that contains the information
  - Statement: All acceptance criteria for all critical parameters must be met for product release or rejection occurs

We are about to give Birth to a Draft Guidance!!

- In-Progress→ draft Guidance for Industry: *"Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Process"*



Lost and Confused

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Thank You

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