Expedited Programs: Phase Appropriate Regulatory Expectations for Microbial Control and Sterility Assurance

Virtual CMC Strategy Forum:
Phase Appropriate Development from a GMP Perspective

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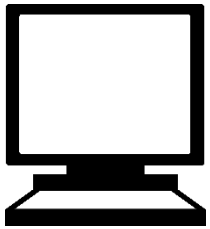
Pharmaceutical Quality

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



Pharmaceutical Quality

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

Drugs are no different.


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

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


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

Topics

- Regulatory framework for expedited programs
- Phase appropriate microbial control and sterility assurance information and data
- Phase-appropriate CGMPs
- Strategies to expedite CMC program development and readiness for a BLA submission
  - Use of novel manufacturing technologies for aseptic processing and use of rapid microbial methods

REGULATORY FRAME WORK FOR EXPEDITED PROGRAMS

IND Regulations

- Any use of a drug not previously authorized for marketing in the US requires an Investigational New Drug (IND) submission to the FDA.

21 CFR 312.22 and .23

General principles

- The primary objective in all phases of an IND investigation is
  - To assure the safety and rights of subjects, and
  - To assure the quality of the scientific evaluation during phase 2 and 3.
    - The amount of information that must be submitted depends upon:
      - the novelty of the drug
      - the extent to which it has been studied previously
      - the known or suspected risks
      - the developmental phase of the drug.

Type of CMC information

- Regulations allow for a graded nature of manufacturing and controls information.
- An IND submission should contain:
  - A description of the composition, manufacture, and control of the drug substance and the drug product.
  - Sufficient information to assure the proper identification, quality, purity and strength of the IND drug.
  - The initial Phase 1 CMC information should allow evaluation for safety.

21 CFR 312.23(a)(7)

Type of CMC information (cont.)

- CMC amendments must be submitted during the IND CMC development phases.
  - The amount of information varies with phase of investigation, dosage form and the amount of information generally available.

21 CFR 312.23(a)(7)

CMC Microbiology Quality: What should amendments include?

- For sterile products, the updates should include:
  - Changes to a sterilization process (e.g., from terminal sterilization to aseptic processing).
  - Information related to the validation of a sterilization process need not be submitted at this time.
  - Changes in microbiological tests (e.g., sterility and pyrogen or bacterial endotoxins for sterile products, antimicrobial preservative for multiple-dose sterile and nonsterile dosage forms and microbial limits for nonsterile dosage forms) need to be submitted. Include:
    - References the USP <51> APET or a description of an equivalent procedures with associated test validation for sterile preserved products in multiple-dose containers or nonsterile-preserved products
    - In-use storage conditions after reconstitution or dilution of the drug product (e.g., microbial challenge studies to support storage conditions).

Reference: Guidance for Industry: INDs for Phase 2 and 3 Studies: Chemistry, Manufacturing, and Controls Information (2001)

CGMP Requirements

- Section 501(a)(2(B) of the FD&C Act requires that drugs, including IND products, comply with current good manufacturing practice (CGMP).
  - CGMP are intended to ensure safety and quality of the IND products.
- Regulations 21 CFR 210 and 211 further elaborate on the CGMP requirements.
    - Certain parts of 211 (e.g., 211.110(a) and 211.142) may not be appropriate to the manufacture of most investigational drugs used for phase 1 clinical trials:
      - 211.110(a) validation of the manufacturing process
      - 211.142 warehousing

CGMP Requirements for Phase 1

- The 2008 FDA Guidance for Industry "Current Good Manufacturing Practice for Phase 1 Investigational Drugs for Phase 1 Studies" provides recommendations for complying with CGMP.
  - Phase 1 investigational drugs, including biological drugs are exempt from complying with all the 21 CFR part 211 under 21 CFR 210(c).
  - However, appropriate CGMP must be applied to ensure subject safety.
    - Intended to facilitate the initiation of investigational clinical trials in humans.

Reference: Current Good Manufacturing Practice for Phase 1 Investigational Drugs (2008)

CGMP Requirements for Phase 1 (cont.)

- Some of the recommendation in the 2008 Guidance include:
  - Use of established or standardized QC procedures and following appropriate CGMP, such as:
    - Well-defined, written procedures.
    - Adequately controlled equipment and manufacturing environment.
    - Accurately and consistently recorded data from manufacturing (including testing).
  - There should be an assessment of the risks from a manufacturing environment, such as risks associated with:
    - Manufacturing in laboratory facilities.
    - Manufacturing a phase 1 investigational drug that is susceptible to **contamination or cross contamination** with other substances (e.g., chemicals, biologicals, adventitious agents).

CGMP Requirements for Phase 1 (cont.)

- Additional recommendations from the guidance include:
  - Use of technologies that can facilitate the conformance with CGMP and streamline product development, such as:
    - Use of disposable equipment and process aids to reduce cleaning burden and chances of contamination.
    - Use of commercial, prepackaged materials (e.g., WFI, pre-sterilized containers and closures to eliminate the need for additional equipment for demonstrating CGMP control of existing equipment).
    - Use of closed process equipment to alleviate the need for stricter room classification for air quality.
    - Use of contract or shared CGMP manufacturing facilities and testing laboratories.

CGMP Requirements for Phase 1 Specific to Biological Products

- The guidance provides the following recommendations :
  - Control and documentation of a manufacturing process to ensure the production of a comparable product through IND development and to support licensure.
  - Retention of samples for comparative analysis at a later date and to provide links in reproducing comparable product.
  - Establishment of equipment and manufacturing controls to ensure performance of unit operations with safety-related function (e.g., viral clearance, virus/toxin attenuation, pasteurization).
  - Implementation of specific testing may add to the safety assurances.
    - Use testing for safety-related purposes such as viral loads, bioburden, detoxification of bacterial toxins, virus clearance (i.e., removal or inactivation), and removal of residual substances (e.g. antibiotics, chemicals), as appropriate.

CGMP Requirements for Phase 1 Specific to Biological Products (cont.)

- The guidance recommends that adventitious contamination risks be identified and mitigated:
  - Containment of phase 1 products made from pathogenic microorganisms, transgenic animals and plants, live viral vaccines, and gene therapy vectors.
  - Establishment of cleaning and testing procedures to ensure prevention and/or detection of contamination by adventitious agents.
  - Use of dedicated equipment and/or disposable parts (e.g., tubing) is recommended.
  - Establishments of procedures that prevent cross-contamination and that remove previously manufactured product from shared equipment and work surfaces.

CGMP Requirements for Phase 1 Sterile Products

- Product sterility is a critical element for human subject safety.
  - The 2008 guidance provides detailed recommendations for the manufacture of a sterile phase 1 product.
    - Main recommendations will be covered in this presentation.
  - Phase 2 and 3 clinical materials must comply with 21 CFR 211 and specific 600-680 regulations for biological products and follow recommendation provided in the 2004 Aseptic Processing Guidance for marketed products.

CGMP Requirements for Phase 1 Sterile Products (cont.)

- Regarding aseptic processing operations the following is recommended:
  - Use of unidirectional air flow for all aseptic manipulations of sterile products and materials.
  - Trained personnel involved in manual aseptic operations.
  - Microbial control of components.
  - Execution of process simulations (media fills).
  - Environmental monitoring, including microbial monitoring by settling plates and by active air monitoring of the aseptic area during processing.
  - Disinfection of the aseptic work stations (before and between different operations), gloves or frequent change out, surfaces of nonsterile items with sterile disinfectant before placement in the laminar flow hood.

CGMP Requirements for Phase 1 Sterile Products (cont.)

- Documentation of procedures intended to maintain sterility of components, in-process materials and final drug.
  - Verifying that the equipment is suitable for its intended use (i.e., autoclave/depyrogenation oven for component sterilization).
  - Sterilization of sterile components and disposable equipment (e.g., filters, bags, containers/stoppers).
- Release of a phase 1 product by the Quality Unit after a review of documentation.
- Release of a phase 1 product only with acceptable results of sterility testing.

REGULATORY OVERSIGHT - EXPEDITED PROGRAMS

Expedited Programs

- Described in the FD&C Act and 21 CFR part 312, Subpart E regulations
  - Intended to expedite the development, evaluation, and marketing of certain new therapies.
  - Allows FDA to exercise regulatory flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness.
- Guidance for Industry – Expedited Program for Serious Conditions – Drugs and Biologics (2014)
  - The guidance describes four FDA programs
    - Fast Track Designation
    - Breakthrough Therapy Designation
    - Accelerated Approval
    - Priority Review

Fast Track Designation

- Section 506(b) of the FD&C Act:
  - "… if it is intended,….. for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such disease or condition."
    - Intended to facilitate development and expedited review for rapid availability on the market.
    - Provides increased opportunities for frequent interactions with the review team, including pre-IND, EOP-1, EOP-2 to discuss clinical development studies. Product may be available for priority review.
    - Allows for a rolling review of the BLA – for example, complete CMC sections of a submission are reviewed before the complete application is submitted.

Breakthrough Therapy Designation

- Section 505(a) of the FD&C Act:
  - "… if the drug is intended, …….to treat a serious or life threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints,……."
  - Allows preliminary clinical evidence to support designation.
  - Requires full data review to support marketing approval.
  - Contain provisions to rescind designation if program criteria are not met.
  - Allows a rolling review of the BLA – complete portions of a submission are reviewed before the complete application is submitted.

Accelerated Approval

- Section 506(c) of the FD&C Act:
  - "…. A product for a serious or life-threatening disease or condition…upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier …….taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

Priority Review Designation

- Prescription Drug User Fee Act of 1992:
  - Given to a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.
  - Qualifying criteria:
    - Serious conditions
    - Significant improvement in safety or effectiveness

Emergency Use Authorization (EUA)

- Issued for the use of an unapproved medical product or unapproved uses of approved medical product in an emergency:
  - Serious or Life-threatening Disease or Condition
  - Evidence of effectiveness ("may be effective", lower standard of evidence than "effectiveness" standard for drug approvals)
  - Risk-Benefit Analysis
    - Benefits outweigh risks; based on threat level by CBRN
  - No alternatives

Reference: Emergency Use Authorization of Medical Products and Related Products and Related Authorities: Guidance for Industry and Other Stakeholders (2017) (https://www.fda.gov/media/97321/download)

Expedited Programs: Challenges

- Clinical and CMC programs not aligned and do not advance in a coordinated fashion:
  - Expedited clinical programs may advance very rapidly and CMC is often rate limiting.
    - Difficult to project manufacturing scale and supply requirements.
    - Hesitancy by sponsors to committing sufficient resources with uncertain clinical outcomes early in the IND process.
    - Delays in BLA preparation and submission with market supply challenges.

FDA Meetings
During an Expedited IND Program

- To accelerate CMC development programs, FDA recommends the following based on the 2014 Guidance for Industry:
  - Timely and early communications during all phases of the IND development program must occur.
    - Responses to inquiries between industry and FDA should be timely and focused on important issues.
    - Sponsors should have a clear understanding of the CMC expectations for product licensure (BLA) early in the IND program.
      - This should help in the timely planning all CMC activities during IND development and for licensure.

FDA CMC Meetings

- Sponsors should request to meet with product quality review groups (OBP and OPMA).
- CMC meetings should focus on complex and rate limiting CMC issues, such as:
  - Product characterization
  - Process design and scale-up requirements
  - Early identification of manufacturing facilities
    - Inspection planning
    - Site changes may impact BLA submission timelines.
  - Process validation strategies for DS and DP
  - Comparability of clinical and commercial lots.
  - Analytical method validation
  - Drug delivery systems
  - Stability program, stability data and proposed shelf-life.
  - Product availability for BLA approval, market demand and supply post-approval.

Regulatory Flexibility: Rolling Submissions

- CMC sections of the submission may be submitted earlier than the rest of the BLA.
  - Allow for a timely review and resolution of CMC review issues.
- Manufacturing facilities must be ready for inspection during the review of the application.
  - Inspections are typically conducted after a BLA is filed. However, inspections before the filing date may be planned to expedite the BLA review process, especially in cases where multiple facilities must be inspected.
  - Communications with FDA on inspection planning is critical.

Regulatory Flexibility : BLA Planning and Content

- All BLAs must meet regulatory standards set in the PHS Act and in the applicable regulations for licensure.
- Flexibility may be provided for the timing of certain information and data:
  - The BLA may be updated during the review timeframe with simple stability updates and with additional process validation data, as agreed in the IND CMC or pre-BLA meetings.
  - Pre-license inspections (PLIs) must be planned when commercial scale manufacturing operations are in progress.
  - All required inspections must be completed for licensure.

Regulatory Flexibility : BLA Planning and Content

- The level of flexibility provided for an expedited product is typically determined on a case by case basis considering:
  - Product characteristics
  - Seriousness of the condition and medical need
  - Manufacturing processes
  - Robustness of sponsor's quality system
  - Strength of sponsor's risk-based quality assessment.
- These aspects must be discussed during the IND development phase with the Agency.

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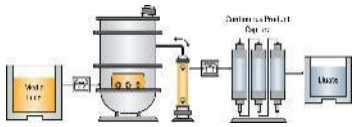
Role of Advanced Manufacturing Technologies in the Expedited Programs



Expedited Programs: Aseptic Processing

- Manufacturers face challenges in manufacturing sterile products under expedited programs.
  - Traditional aseptic processing involves the use of complex facilities for high risk manufacturing operations that can impact product quality and patient safety.
  - Sterile product development timelines can be impacted.

Expedited Programs: Aseptic processing (cont.)

- These challenges may be alleviated by adopting advanced technologies involving the use of automated/robotic equipment in simplified facilities.
  - Lead times required to adopt some of the advanced technologies can be significantly shorter than traditional aseptic processing methods.
    - Scale-out options may streamline scale-up operations (e.g., by addition of the same robotic units in the same simplified facility).

Expedited Programs: Aseptic Processing (cont.)

- Technologies that may mitigate some of the challenges and provide flexibility while maintaining sterility assurance include the use of
  - Single-use systems
    - Improved sterility assurance, especially when coupled with other advanced technologies
  - Automated and gloveless isolators
    - Completely robotic units eliminate direct human interactions with the product and support sterility assurance.
  - Simplified facilities
    - Including mobile and modular units (PODS).
  - Rapid microbial methods

Rapid Microbial Methods

- Use of rapid microbial methods may provide for more timely assessments of the state of microbial control and provide for timely and useful results.
  - The USP <71> sterility test takes for 14 days.
    - May be rate limiting in the release of clinical batches.
  - In-process microbial tests for bioburden, including mycoplasma, do not provide for real time results and may delay the resolution of deviations.
- Efforts to implement rapid microbial methods to streamline operations should begin early in the IND development phases:
  - Rapid environmental monitoring (EM) in fill finish facilities for continuous particle monitoring and viable particle monitoring.
    - e. g., use of Bio-fluorescent Particle Counters (BFPCs) for viable particles.
  - Use of rapid methods for sterility testing of finished product.
    - e.g., use of membrane filtration coupled with detection with ATP-Bioluminescence.
  - Use of PCR based methods for mycoplasma testing.

Conclusions

- Potential pathways to align clinical and CMC development programs for expedited programs:
  - Communications between industry and FDA:
    - Early and often
  - Graded implementation of CGMP in the manufacturing environment.
  - Use of innovative manufacturing platforms:
    - Include more advanced manufacturing technologies early in the development phase to streamline CMC development process.
  - Use of rapid microbial methods:
    - Real time process monitoring
    - Timely release of drug product batches

THANK YOU!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