Introduction of New Manufacturing Sites in a Regulatory Submission

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Then and Now – Some History
December 12, 2011 (which was later extended to June 12, 2012), if the PET drug is produced for commercial distribution and used in humans for clinical practice to diagnose a patient, the maker of the PET drug must have submitted a new drug or abbreviated new drug application for that drug. A PET drug marketed prior to December 12, 2011 can continue to be marketed after the application is submitted.

All PET producers must be operating under an approved NDA or ANDA, (or an effective IND) by December 12, 2015.
What does this mean for the introduction of a brand new site into an ANDA or NDA?

If a company submitted an ANDA for a new site that was manufacturing before June 12, 2012, the facility was allowed to manufacture while awaiting approval.

After that date, the company had to await approval before manufacturing, which had no specific timeframe. It could take as long as 3-4 years before approval.

With GDUFA, the FDA has assigned a 10 month clock for review and approval of a new drug and a PAS (vs. CBE-30) if it’s a new facility that hasn’t been inspected. If the site is inspected and has satisfactory history, the clock can be 6 months.

Example text from a PAS acknowledgment letter from FDA:

This prior approval supplement is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). The GDUFA goal date for review of this standard supplement is August 21, 2023. If FDA determines that this standard supplement requires an inspection or the use of a time- and resource-intensive alternate facility assessment tool, the goal date will be December 21, 2023. Two possible goal dates are provided because FDA is unable to determine if a supplement requires an inspection or the use of a time- and resource-intensive alternate facility assessment tool at the time of submission. FDA will make this determination during the assessment of the supplement. For information, see FDA’s guidance for industry, ANDA Submissions–Amendments to Abbreviated New Drug Applications Under GDUFA.

THE NEED FOR ADDITIONAL SITES

- PET manufacturing generates products with short-lived radionuclides.
- Product shelf-life ranges from 4 to 12 hrs for most Ga-68 and F-18 based PET agents. N-13 products are limited to 45 - 70 mins shelf life. Access is restricted by limitations of conventional transport (auto, air, or co-located).
- Ensuring access to diagnostic agents nationally and globally requires PET manufacturers to invest in the development and qualification of a broad networks of manufacturing facilities.
- Commercial PET manufacturing faces two major risks on a daily basis:
  - Manufacturing Failure prior to product release.
  - Breakdown of logistics and transportation beyond product release.
- Without a broad network of manufacturing sites, patients are forced to travel for diagnostic access.
REGULATORY SUBMISSIONS

Pharmaceutical NDA and ANDA amendments to introduce new facilities fall under two supplement submissions:

CBE-30
Utilized when the additional pharmaceutical manufacturing facility (PMF) is functionally identical in quality, operational structure and aseptic operations to comparator site, in addition to having a satisfactory FDA inspection history.
Response typically granted within 30 days of supplement submission. Full approval decision provided 6 months from initial submission.

PAS
Utilized for initial NDA or ANDA submissions of first PMF or a new facility.
Utilized when additional PMF is discernibly different in quality, operational structure or aseptic operations from the initial comparator facility.
Utilized if the PMF has no recent FDA inspection history.
Approval decision generally granted within 6 months of submission. This timeline is extended to 10 months if inspection is required prior to approval. Priority review can expedite these timelines significantly.

TIMELINE OF SITE PREPARATION – GAP ASSESSMENT

• Facility Gap Assessment
  • Personnel
  • Quality system
    • Exception Report Management (DEV, OOS, CAPAs, etc.)
    • Material Specifications and Equipment Qualification Plans
    • Data Integrity Governance
  • Administration and Operational systems
    • Recent History of Inspections & Audits
  • Aseptic Practices & Environmental Monitoring
• Any gaps identified must be addressed via CAPA plans or applicable remediations prior to submissions.
TIMELINE OF SITE PREPARATION – EQUIP. QUALIFICATION

• Equipment Qualification & Analytical Method Verification
  • All critical equipment must be installed with applicable IQ/OQ & PQ documentation.
  • All analytical methods must be validated or verified according to ICH Guidance and USP <1225> or USP <1226>. Demonstration of method suitability for final product and final product formulation.
    • Chemical Purity & Radiochemical Purity Methods (HPLC, TLC)
    • Residual Solvent Methods (Gas Chromatograph)
    • Endotoxin Methods
    • Impurity Limit Methods

TIMELINE OF SITE PREPARATION – TECH TRANSFER & VALIDATION

• Technology Transfer
  • Demonstrates feasibility and robustness of manufacturing and batch analysis procedures.
  • Demonstrates proficiency of onsite personnel and effective transfer of all processes from comparator site
  • Identify areas of concern prior to formal validation
• Validation (vary by product and Industry vs. Academic)
  • Replicates of demonstrative process validation batches
  • Validation of Sterility test methods and suitability of test media
  • Stability Studies – Product Shelf-life evaluation
  • Bioburden Studies – process sterility by design
TIMELINE OF SITE PREPARATION – SUBMISSION

• Submission (Comparability Protocol, if applicable)
  • Introduction of NDA or ANDA Holder
  • Executive Summary of new PMF and General Facility Information/Overview
  • Description of Quality Systems
  • Process Comparisons to Comparator Site
  • Evaluation of manufacturing components and materials
  • Executed Validation and Stability Records
  • Aseptic Practices Summary
  • Analytical Method Validation/Verifications
  • Deviations

WHAT TO INCLUDE IN ADDING THE NEW SITE

• Form 356h  Application to Market a New or Abbreviated New Drug or Biologic for Human Use
• Form 3794 GDUFA Cover Sheet or... Form 3397 PDUFA Cover Sheet
• Cover Letter
• 2.3.P (drug product summary)
• 2.3.S (drug substance summary)
• 3.2.S.2.1 (manufacturer, drug substance)
• 3.2.P.3.1 (manufacturer, drug product)
• 3.2.P.3.3 (manufacturing, process and controls)
• 3.2.P.3.5 (process validation and/or evaluation)
• 3.2.P.8.1 (stability summary)
• 3.2.P.8.3 (stability data)
• 3.2.A.1 (Facilities & Equipment) (Appendices as needed)
• 3.2.P.5 (Control of Drug Product) (As needed)

Note: these are the common submission components within the commercial manufacturing space. Additional items may be added/removed for different spaces depending on the nature of the product, any process changes or classification of regulatory submitter. Further changes could occur to this list in the future at FDA's discretion. See the most recent FDA guidance on the assembly of the Common Technical Document for additional information.
NEXT STEPS AFTER SUBMISSION

- CBE-30 or PAS is submitted through the Electronic Submissions Gateway (ESG) – 3 receipts generated

- Receive Letter within 30 days of submission
  - Acknowledgment letter with GDUFA or PDUFA dates listed (with and without inspection)
  - Refuse to Receive (ANDA) or Refusal to File (NDA) if application deficiencies are found

QUESTIONS FROM THE PET INDUSTRY

What is FDA’s current thinking regarding adding a new manufacturing site (that manufactures currently approved PET drugs) to an ANDA or NDA post approval under an agreed upon comparability protocol as CBE-30?

Are there any instances where a brand new manufacturing site can be added to an approved NDA or ANDA under a comparability protocol as a CBE-30 if the company has good inspectional history?

What are FDA’s expectations when providing a complete response 6 months after a CBE-30 is approved?

For networks considering a novel NDA or ANDA submission, is it the FDA’s preference that an initial meeting be scheduled to discuss the details of the initial and subsequent submissions?
REFERENCES


https://www.fda.gov/media/89258/download

https://www.fda.gov/media/162263/download

https://www.fda.gov/media/82370/download

https://www.fda.gov/files/drugs/published/Changes-to-an-Approved-NDA-or-ANDA.pdf