Arnold & Porter

Regulation of Drug Manufacturing

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Howard Sklamberg

Partner, Life Sciences & Healthcare Regulatory Practice

Agenda

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3. Scope of Pre-Approval Inspections
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Establishment Registration and Listing

Registration and Listing Requirements

- Manufacturers of drug products must:
  - Register their establishments
    - This includes submitting the names of the owner and operator, trade names, address, and telephone numbers
    - Foreign establishments must designate a United States agent
  - List all manufactured products in commercial distribution
    - This includes submitting, as applicable, National Drug Codes ("NDCs"), established and proprietary names, and current labeling
- "Manufacturer" means a person who owns or operates an establishment that manufactures, prepares, propagates, compounds, or processes a drug, including, control laboratories, contract laboratories, contract manufacturers, contract packers, and contract labelers
  - Manufacturers must register each physical establishment engaging in such activities
- Failure to comply with these requirements renders a drug product manufactured at the facility misbranded

Submission Timing and Updates

- Establishment Registration
  - Initial Registration: No later than 5 calendar days after commencing manufacturing activities
  - Renewal: Annually between October 1 and December 31
  - Updates: Generally captured during renewal except for the following updates which must be submitted no later than 30 calendar days after their occurrence:
    - Closure/sale of an establishment
    - Change in an establishment's name or physical address
    - Change in the name, mailing address, telephone number, or email address of the official contact or the United States agent
- Product Listing
  - Initial Listing: At time of establishment registration
  - Review and Update: Every June and December

Standards of Inspections

Purpose and Standards

- Ensure drug products are manufactured in accordance with Food and Drug Administration ("FDA" or the "Agency") requirements, the New Drug Application ("NDA"), and internal policies and procedures
- Applicable standards that FDA will use to inspect drug manufacturing establishments include current Good Manufacturing Practice ("cGMP")
  - Codified in 21 C.F.R. Parts 210 & 211
- FDA has released several cGMP guidances that interpret the above regulatory requirements, including:
  - Sterile Drug Products Produced by Aseptic Processing
  - Data Integrity and Compliance with Drug cGMP
- International Council for Harmonisation ("ICH") Guidelines may also be relevant:
  - Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
  - Q11 Development and Manufacture of Drug Substances

Adulteration

- Deviations from cGMP and other applicable standards may render a drug adulterated under the Federal Food, Drug and Cosmetic Act ("FDCA")
- The FDCA also considers a drug to be adulterated under 21 U.S.C. § 351 where:
  - It consists of any filthy, putrid, or decomposed substance
  - It has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth or rendered injurious to health
  - Its container is composed of any poisonous or deleterious substance which may render the contents injurious to health
  - It purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standard set forth in such compendium
  - Its strength differs from, or its purity or quality falls below, that which it purports or is represented to possess
  - It has been manufactured or held in any establishment of which the owner, operator, or agent delays, denies, or limits an FDA inspection, or refuses to permit entry or inspection

Warning Letter Trends

- Over the past several years, FDA has increasingly issued Warning Letters to active pharmaceutical ingredient ("API") manufacturers for cGMP violations and finished drug manufacturers for failing to effectively monitor their supply chains
- Warning Letter citations of API manufacturers included:
  - Quality system not adequately ensuring the accuracy and integrity of data to support safety, effectiveness, and quality of manufactured API
  - Failing to exercise sufficient controls over computerized systems to prevent unauthorized access or changes to data and failure to have adequate controls to prevent omission of data
  - Failing to establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel
  - Quality unit failing to ensure that quality-related complaints are investigated and resolved
  - Failing to maintain complete data derived from all laboratory tests conducted to ensure API and intermediates comply with established specifications and standards

Warning Letter Trends (cont'd.)

- Warning Letter citations of finished product manufacturers included:
  - Failing to validate and establish the reliability of its component supplier's test analyses at appropriate intervals
  - Failing to conduct at least one test to verify the identity of each component of a drug product
  - Quality control unit failing to exercise its responsibility to ensure drug products manufactured are in compliance with cGMP, and meet established specifications for identity, strength, quality, and purity
  - Failing to establish adequate written procedures for production and process control designed to assure that the manufactured drug products have the identity, strength, quality, and purity they purport or are represented to possess, and to follow its written production and process control procedures

Select Complete Response Letters

- Complete Response Letter (“CRL”) #1 – July 2020
  - FDA issued a CRL because it was seeking additional information regarding certain aspects of the chemistry, manufacturing and controls (“CMC”) process
- CRL #2 – December 2019
  - FDA issued CRL for reasons related to CMC
- CRL #3 – November 2019
  - CRL raised questions that generally related to CMC matters and the company planned to expand on CMC testing to resolve such questions
- CRL #4 – May 2019
  - FDA was unable to approve the NDA based on the need for additional CMC and non-clinical data

Scope of Pre-Approval Inspections

When Required

- Pre-Approval Inspections (“PAIs”) are not always required before approving a NDA
- Rather, the Center for Drug Evaluation and Research (“CDER”) will evaluate certain factors to determine whether a PAI is required
- Generally, CDER will require a PAI where:
  - The manufacturing facility has never been inspected/has no compliance history
  - The facility is named in an application for the first time
  - The product is manufactured by a significantly different process at the facility than previously reviewed in an application
- Other factors that may be considered include:
  - Whether the product is a new molecular entity
  - Whether the facility is using a substantially different manufacturing process
  - Whether the application is the first filed by the applicant
  - Whether there is a high risk of API deviation

Scope of a PAI

- The purpose of a PAI is to ensure commercial readiness, regulatory compliance, and the accuracy of data submitted to the Agency
- Investigators will generally review systems, policies, procedures, and operations relating to:
  - Quality
  - Production
  - Facilities and equipment
  - Laboratory controls
  - Materials
  - Packaging and Labeling

Scope of a PAI (cont'd.)

- Specific areas that may be the focus of a PAI include:
  - Verifying data submitted to the NDA are accurate and complete
  - Batches or lots that did not meet specification and verifying out-of-specification investigations are completed
  - Stability data and verifying they meet specifications
  - Raw materials and components testing
  - Shipping validation for drug substance and drug product
  - Procedures for reporting adverse event reports
  - Facility and equipment controls in place to prevent contamination
  - Procedures exist for batch release, change control, investigating failures, deviations, and complaints
  - Verifying that the processes, manufacturing and testing, and compare with the description and/or batch record submitted in the CMC section

Inspections During COVID

- Generally, most inspections, especially those overseas, are suspended
- FDA will proceed with “mission-critical” inspections on a case-by-case basis
  - FDA will consider several factors relating to the public health benefit of U.S. patients having access to the product subject to inspection, including whether the product:
    - Received breakthrough therapy designation
    - Is used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute
- FDA will use “all available tools” to evaluate NDAs when it cannot physically inspect a manufacturing facility
  - These tools include:
    - Facility compliance history
    - Information from trusted foreign regulatory partners
    - Requesting records “in advance of or in lieu of” facility inspections
  - FDA will use this information to apply a “holistic approach” to evaluate the application

Inspection Process

Preparation

- Inspections are typically unannounced with the general exception of PAIs
- Manufacturers aware of an impending inspection should take certain preparatory actions, including:
  - Clean internal and external areas
  - Review applicable policies and procedures regarding regulatory inspections
  - Establish and practice a tour route
  - Review past inspection findings and outstanding items
  - Prepare a list of commonly requested items (*e.g.*, policies and procedures, corrective and preventive actions ("CAPAs"), deviation logs)
  - Reserve conference/meeting rooms
  - Determine roles of team members, including the lead
  - Review production schedules

Initiation

- FDA will generally send a team consisting of an investigator and an analyst/specialist although larger teams may be warranted based on the size and complexity of the facility and manufacturing process
- The investigator will present his/her credentials upon arrival as well as a Notice of Inspection (FDA Form 482)
- Manufacturers should have policies and procedures in place governing how to respond to FDA inspections
  - Generally such policies and procedures may designate responsible personnel for interacting with the Agency, designate areas where investigators can meet and review documents, and detail notification procedures

Conduct

- FDA must conduct inspections “at reasonable times and within reasonable limits and in a reasonable manner” (21 U.S.C. § 374)
- Inspections will typically last for more than one day
  - At the end of each day, the investigator will usually summarize any potential observations
  - Manufacturers should indicate whether they disagree with such findings and, where possible, take mitigating/corrective actions
- Investigators will review and collect records, review physical equipment and facilities, take environmental and product samples, and interview facility personnel
  - Facility personnel should accompany FDA investigators to respond to questions and take notes

Conduct (cont'd.)

- Manufacturers should provide complete and accurate responses to FDA inquiries and document requests during an inspection
  - FDA's authority to request documents is quite broad although it has limited authority with respect to certain financial, commercial, personnel, and research documentation and data
  - In light of these limitations, it is a best practice to maintain Quality Agreements as separate documents from the underlying supply/manufacturing agreement
- Investigators may also take photos or videos
  - There is no clear FDA authority for this practice and certain manufacturers view this as FDA overstepping
  - However, if a manufacturer chooses to refuse or prevent FDA from taking pictures or videos, there is a risk FDA may invoke its authority under Food and Drug Administration Safety and Innovation Act ("FDASIA") § 707 absent a reasonable explanation for the refusal
    - This authority allows FDA to deem a drug manufactured at the facility to be adulterated

Conduct (cont'd.)

- Other actions that may lead FDA to consider using its FDASIA § 707 authority include:
  - Failing to agree to, or delaying, a scheduled inspection date without a reasonable explanation
  - Delaying access to an area of the facility to the investigator without a reasonable explanation
  - Failing to produce documentation within the requested timeframe without a reasonable explanation
  - Refusing to allow the investigator to begin the inspection
  - Refusing to allow the investigator to inspect the facility because certain staff members are not present without a reasonable explanation
  - Discontinuing all manufacturing for the duration of the inspection without a reasonable explanation
  - Limiting direct observation of portions of the manufacturing process without a reasonable explanation
  - Providing some, but not all, requested records that FDA has authority to inspect
  - Providing unreasonably redacted records that FDA has authority to inspect

Conclusion

- Inspections often end with a close out meeting during which the investigator will discuss any observations of objectionable or violative practices
- Such observations will be detailed in an FDA Form 483 (“483”)
- Manufacturers should carefully listen and respond to the investigator’s observations noting where the investigator is mistaken or an observation has been remedied in the course of the inspection

Conclusion (cont'd.)

- As discussed on the following slides, FDA will eventually classify the inspection as one of the following:
  - No Action Indicated ("NAI"): No objectionable conditions or practices or any objectionable conditions found do not justify further regulatory action
  - Voluntary Action Indicated ("VAI"): Objectionable conditions or practices were found but the Agency is not prepared to take or recommend any further action
  - Official Action Indicated ("OAI"): Further action will be recommended
- At the closeout meeting, the investigator may indicate the potential classification as well as whether they recommend approval of a NDA in the case of a PAI although such statements are non-binding

Responding to FDA Form 483

Initial Actions

- Although 483s do not necessarily establish violations of the FDA, manufacturers should promptly and thoroughly address each observation in a 483
- Manufacturers have 15 working days to respond to a 483 in writing
- The response should detail CAPAs undertaken by the manufacturer
  - The response should indicate which CAPAs remain open and their timeline for completion
- Importantly, manufacturers should attempt to confirm and demonstrate to the Agency that the observations do not impact the quality or safety of any already-released product

Written Response

- Generally, a 483 response should include the following:
  - An overarching commitment to quality and compliance
  - Acknowledgement of each observation and a point-by-point explanation of CAPAs taken in response
    - This should include appropriate supporting documentation, which can be attached
  - Any overarching quality system remedial actions and assurances
  - Description of root cause analyses/investigations
  - Confirmation that there has been no effect on released product quality and safety
- It is important to not over-promise on the types of CAPAs or timelines for completion
  - The failure to meet such commitments may result in further action (*e.g.*, Warning or Untitled Letter)

Follow Up Actions

- 483 responses may be supplemented following initial submission to FDA
  - FDA may also ask questions or comment on responses and their supplements
  - Manufacturers should continue to keep FDA informed of the status/progress of any open CAPAs in accordance with timelines/frequency set forth in its 483 response and supplements
- FDA will issue an Establishment Inspection Report ("EIR") following the inspection
  - An EIR is more detailed than a 483 and may include the following, as applicable:
    - Summary of findings
    - Administrative data
    - History
    - Interstate commerce and jurisdiction
    - Individual responsibility and persons interviewed
    - Training
    - Manufacturing and design operations
    - Manufacturing codes
    - Complaints and recall procedures
    - Objectionable conditions and management's response
    - Supporting evidence
    - Discussions with management
    - Refusals
    - Additional information
    - Samples collected
    - Voluntary corrections
    - Exhibits collected
    - Results of any analyses conducted by the Agency

Follow Up Actions (cont'd.)

- Following the EIR, FDA will classify the inspection as NAI, VAI, or OAI
- Under the Concept of Operations agreement between CDER and the Office of Regulatory Affairs ("ORA"), inspection classifications will be made within 90 days following the end of an inspection

Potential Outcomes

- FDA may accept the 483 response and close the inspection
- FDA may verify CAPAs detailed in a 483 response in a follow-up inspection
- FDA may issue a Warning or Untitled Letter if the observations are not adequately remedied or are repeated issues
- FDA may delay or withhold approval of the NDA and issue a Complete Response Letter
- Depending on the manufacturer's cooperation and risk of patient harm, FDA may seek administrative and judicial remedies, such as import alerts/detention without physical examination, seizure, injunction, and criminal prosecution

Post-Approval Manufacturing Issues

Post-Approval Changes

- CMC changes to an approved NDA generally fall into one of the following categories:
  - Prior Approval Supplement ("PAS"): Changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as they may relate to safety or effectiveness ("Major Change") require a NDA supplement, which must be approved prior to distribution of the product manufactured using the change
  - Changes Being Affected:
    - 30 Days: Changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as they may relate to safety or effectiveness ("Moderate Change") require the change to be reported in a supplement at least 30 days prior to distribution of the product made using the change
    - Immediate: FDA has identified certain Moderate Changes for which the product made using such change may be distributed immediately upon the Agency's receipt of a complete supplement
  - Annual Report: Changes that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as they may relate to safety or effectiveness ("Minor Change") must be captured in an annual report

Examples of Major, Moderate, and Minor Changes

- Major
  - Changes in sterilization method
  - Fundamental change in the manufacturing process or technology from that currently used
  - Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet approved specifications
- Moderate
  - Redefinition of an intermediate, excluding the final intermediate, as a starting material
  - A change in methods or controls that provides increased assurance that the drug substance or drug product will have its purported characteristics of identity, strength, quality, purity, or potency
  - Filtration process changes that provide for a change from single to dual sterilizing filters in series
- Minor
  - A minor change in an existing code imprint for a dosage form
  - Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved drug products
  - A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations

Field Alert Reports

- Field Alert Reports (“FARs”) must be submitted for distributed drug products upon receiving:
  - Information concerning any incident that causes a drug product or its labeling to be mistaken for, or applied to, another article; or
  - Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application
- FARs must be submitted within 3 working days of receipt of the above information
- NDA/Abbeviated New Drug Application (“ANDA”) holders are responsible for submitting FARs

Field Alert Reports (cont'd.)

- NDA/ANDA holders may submit follow up FARs to supplement the information contained in an initial FAR
- If it is unclear whether a reportable event has occurred, it is generally prudent to err on the side of reporting to avoid missing the required deadline
- This determination is separate and apart from whether a recall or other corrective actions are required
- Examples of events that may require a FAR if they meet reporting criteria include:
  - Use of a vial stopper that could result in contamination
  - Validated out of specification results
  - Occurrence of a media fill validation failure

Questions?

Howard Sklamberg

Partner, Washington, DC

howard.sklamberg@
arnoldporter.com
+1 202.942.5075