FDA Safety and Innovation Act (FDASIA):
GMP Inspection Impact

Presented by:
David L. Chesney,
Vice President, Strategic Compliance
PAREXEL Consulting
Waltham, MA USA
781-434-4092
dave.chesney@parexel.com
Agenda

- Overview of the FDASIA Legislation
- GMP-specific Provision
  - Guidance Documents Issued to Date
- Changes to FDA Inspection Authority – Sanctions for Delay or Refusal of Inspection
  - Guidance Document
  - Warning Letters Issued to Date
- Changes Needed to Company SOPs
  - For Supplier Management
  - For Managing FDA Inspections
Overview of FDA Safety and Innovation Act (FDASIA)

• Signed into law on July 9, 2012
• Amends several drug and device provisions of the FD&C Act
• 11 Titles
  • First 4 concern medical device user fees: PDUFA, MDUFA, GDUFA, BSUFA
  • Title 5 relates to pediatric drug issues
  • Title 6 makes improvements to the device regulatory process
  • Title 7 makes major changes to enhance FDA control over the drug supply chain
  • Title 8 creates incentives for development of antibiotics for resistant strains
Overview of FDA Safety and Innovation Act (FDASIA)

• 11 Titles – continued

• Title 9 enhances the accelerated approval process by expanding the scope of eligible products

• Title 10 addresses current drug shortages, requires notification of shortage situations that are anticipated

• Title 11 – several miscellaneous provisions
  – provides for the regulation of medical gases
  – provisions on prescription drug abuse,
  – 180-day generic drug marketing exclusivity,
  – citizen petitions,
  – controlled substances
  – Nanotechnology
  – Other miscellaneous issues
Key GMP Provision of FDASIA

• Title 7 – Drug Supply Chain
• Significant changes to enhance FDA’s inspection authority and the drug supply chain
• Data base for registered firms world wide
• Drugs from unregistered foreign firms regarded as misbranded under the Act
• A drug will be deemed adulterated if it has been manufactured, processed, packed, or held in any factory, warehouse, or establishment by an owner or operator who has delayed, denied, or limited an inspection, or has refused to permit entry or inspection
Key GMP Provision of FDASIA

- Specifies that GMP includes the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products
  - Section 501 (21 U.S.C. 351) is amended by adding at the end the following flush text: "For purposes of paragraph (a)(2)(B), the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

- Inspection frequency for drug firms changed from biennial to “risk based”

- Authorizes FDA to enter into agreements with foreign governments to recognize inspections of FDA-registered foreign establishments to facilitate in risk-based inspections
Guidance for Industry

Contract Manufacturing Arrangements for Drugs: Quality Agreements

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to Docket Management Branch (HFA 365), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments must be identified with the docket number listed in the notice of availability that publishes the draft guidance.

For questions regarding this draft document contact Paula Katz (CDER) at 301-796-8972; or (CDER) the Office of Communication, Outreach, and Development at 301-825-4709 or 301-8271800, or (CVS) Communications Staff at 210-276-9300.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVS)

May 2013
Current Good Manufacturing Practices (CGMP)
“This guidance describes our current thinking on defining, establishing, and documenting the responsibilities of each party (or all parties) involved in the contract manufacturing of drugs subject to Current Good Manufacturing Practice (CGMP). In particular, we describe how parties involved in the contract manufacturing of drugs can utilize Quality Agreements to delineate their responsibilities and assure drug quality, safety, and efficacy. This guidance applies to the commercial manufacturing of Active Pharmaceutical Ingredients (APIs or drug substances, or their intermediates), finished drug products, combination products, and biological drug products.”

“Because the Agency considers contractors an “extension of the manufacturer’s own facility,” both Owners and Contracted Facilities are responsible for ensuring that their products are not adulterated or misbranded (21 CFR 200.10). As amended, the Act also specifies that current good manufacturing practice (CGMP) includes the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. See FDCA, as amended by the Food and Drug Administration Safety and Innovation Act.” (emphasis added)
Impact of this Guidance

• A Guideline is not a regulation, and by definition, the specifics of a guideline are not enforceable. This guideline, like all FDA guidelines, contains the following disclaimer: “This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.”

• However the law does mandate control over the supply chain. Therefore it is best to follow the guideline as if it was a binding regulation, realizing that it is not. If you choose not to follow it you must be prepared to show how what you are doing is equal to or better than the approach in the guideline.
What can we expect next?

• Finalization of the guideline
• Possible change to Part 211 to reflect new requirements
  • Comprehensive 211 rewrite or piecemeal approach?
  • What about supplier management programs and audit approach?
Other Inspection Related Provisions of FDASIA

• Under FDASIA, a drug will be deemed adulterated if it has been manufactured, processed, packed, or held in any factory, warehouse, or establishment by an owner or operator who has delayed, denied, or limited an inspection, or has refused to permit entry or inspection.
Authority to Request Records Remotely

- Section 706 of FDASIA specifies the authority of FDA to demand production of records remotely by adding the following text to the wording of the Food, Drug and Cosmetic Act:
  - "(4)(A) Any records or other information that the Secretary may inspect under this section from a person that owns or operates an establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a drug shall, upon the request of the Secretary, be provided to the Secretary by such person, in advance of or in lieu of an inspection, within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form, at the expense of such person. The Secretary's request shall include a sufficient description of the records requested.

  - "(B) Upon receipt of the records requested under subparagraph (A), the Secretary shall provide to the person confirmation of receipt."

©2013 PAREXEL Consulting
Inspection Refusal or Partial Refusal

- Section 707 of FDASIA adds 501(j) to the Food, Drug, and Cosmetic Act (FD&C Act) to deem a drug adulterated that “has been manufactured, processed, packed, or held in any factory, warehouse, or establishment and the owner, operator, or agent of such factory, warehouse, or establishment delays, denies, or limits an inspection, or refuses to permit entry or inspection.”

- Previously, a company or person refusing could be criminally prosecuted (though no one has been for decades) or be served with an administrative inspection warrant (if in the United States), but this approach was not feasible for international firms, and had no impact on the status of the product(s) being made at the facility where the refusal took place.

- FDASIA Changes that and makes it possible for FDA to proceed against the product(s)
What does the Guideline say about delay or refusal?

- Examples of delay in scheduling a pre-announced inspection that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:
  - A facility will not agree to a proposed inspection start date and does not give a reasonable explanation for its failure to do so.
  - After scheduling an inspection, a facility requests a later start date without giving a reasonable explanation.
  - A facility fails to respond following FDA’s attempt to contact the facility’s designated contact(s).
What does the Guideline say about delay or refusal?

- Examples of delays during an inspection that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:
  - A facility does not allow the FDA investigator access to an area of the facility until a specific future date or time even though the area is operational and is an area of the inspection site that FDA has authority to inspect.
  - A facility leaves the FDA investigator in a conference room without access to necessary documentation or responsible individuals for an unreasonable period of time that interferes with the investigator’s ability to complete the inspection.
What does the Guideline say about delay or refusal?

• Examples of delays in producing records that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:
  
  • During an inspection, the FDA investigator requests records FDA has authority to inspect within a specific, reasonable timeframe, but the facility fails to produce the requested records within the timeframe requested by FDA, without adequate justification.
  
  • FDA requests records pursuant to section 704(a)(4) of the FD&C Act, but the facility fails to produce the requested records in a timely manner, without adequate justification.
What does the Guideline say about delay or refusal?

Examples of behavior that may constitute a denial that may cause drugs to be adulterated under section 501(j) of the FD&C Act include, but are not limited to:

- A facility rejects FDA’s attempt to schedule an inspection.
- A facility does not allow the FDA investigator to begin an inspection of a facility, even if it has been pre-scheduled.
- A facility does not allow the FDA investigator to inspect the facility because certain staff members are not present.
- A facility does not allow the FDA investigator to inspect the facility by falsely alleging the facility does not manufacture drugs.
What does the Guideline say about delay or refusal?

- Limiting Access to Facilities and/or Manufacturing Processes
- Examples include, but are not limited to:
  - A facility orders the discontinuation of all manufacturing for the duration of the FDA inspection without a reasonable explanation.
  - A facility states that direct observation of the manufacturing process, in whole or in part, must be limited to an unreasonably short amount of time, thus preventing FDA from inspecting the facility as is usual and customary.
  - A facility limits direct observation of portions of the manufacturing process.
  - A facility unreasonably restricts entry to a particular facility without adequate justification.
  - Staff at a facility cause the FDA investigator to leave the premises before the inspection is completed.
What does the Guideline say about delay or refusal?

- Limiting Photography

- Not allowing photography by an FDA investigator may be considered a limitation if such photographs are determined by the investigator(s) to be necessary to effectively conduct that particular inspection. Examples of conditions or practices effectively documented by photographs include, but are not limited to: evidence of rodents or insect infestation; faulty construction or maintenance of equipment or facilities; product storage conditions; product labels and labeling; and visible contamination of raw materials or finished products.
What does the Guideline say about delay or refusal?

• Limiting Access to or Copying of Records

• Examples of records limitations include, but are not limited to:
  • A facility refuses to allow the FDA investigator to review the facility’s shipping records that FDA has authority to inspect.
  • A facility provides some, but not all of, the records requested by the FDA investigator that FDA has authority to inspect.
  • A facility provides the FDA investigator the requested records that FDA has authority to inspect, but the records are unreasonably redacted

• Limiting or Preventing Collection of Samples

• Examples of sample limitations include, but are not limited to, declining to allow FDA to collect the following types of samples: environmental samples, finished product samples, raw material samples, in-process material samples, and reserve samples in bioequivalence and bioanalytical studies.
What does the Guideline say about delay or refusal?

• Complete refusal to permit entry or inspection

• Examples include, but are not limited to:
  • The facility bars the FDA investigator from entering the facility or certain areas of the facility, for example, by not unlocking the areas or taking other necessary actions that would permit access by the investigator(s).
  • Following FDA’s attempt to contact the facility’s designated contact(s), the facility fails to respond.
  • The facility does not answer calls from the FDA investigator who is present at the facility, despite clear evidence of the presence of employees engaged in job-related functions.
Warning Letter Citing Unreasonable Delays and Obstruction of an Inspection

Warning Letter July 13, 2013 to Wockhardt Ltd., Aurangabad, India; selected quotes:

“… an FDA investigator identified the presence of unlabeled and partially labeled vials in the laboratory glassware washing area. When the investigator asked a QC Analyst to describe the contents of these vials, the QC Analyst immediately began dumping the contents of the vials into the drainage sink. The QC Analyst stated that the content of the vials could not be determined. Because you limited the direct observation by the FDA investigator and prevented any determination of the contents of the unlabeled vials, you limited the inspection.”

“The FDA investigator was impeded at the inspection site from properly performing the inspection in a reasonable manner. Because you directed the FDA investigator away from (the aseptic) production area, you obstructed the direct observation of the manufacturing process to an unreasonably short amount of time, and you limited the inspection. Because the investigator only later discovered the existence of the area, you delayed the inspection.”
Changes Needed to Company SOPs

• Companies should re-evaluate their Supplier Management programs against the draft FDA Guidance, as well as applicable Canadian, EU or other venue requirements that apply to their operations

• SOPs for management of FDA inspections should be reviewed and revised to ensure they will prevent unreasonable delays in the conduct of FDA inspections, as detailed in the pertinent FDA guidance document
  
  • In particular, this may entail reconsideration of company policy regarding photography during FDA inspections, as many company SOPs have an outright prohibition of photography; FDA position has long been that photographs are sometimes necessary to a reasonable inspection, and FDA personnel will consider refusals to permit photography as a serious matter
Bottom Line

• FDASIA is a highly complex, voluminous piece of legislation
• Conventional wisdom is it is the “user fee renewal” bill, which it is
• But it is much more, including sweeping implications for supply chain management, stronger authority for FDA in many areas, and impact on inspection management
• Companies need to understand all these provisions and integrate them into their inspection management training and approach