EAS CONSULTING GROUP

Specializing in FDA Regulatory Matters

FOREIGN DRUG INSPECTION/AUDITS FROM THE FDA PERSPECTIVE

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Statistics

- About 80% of world supply of APIs from India and China
- Some API produced in Korea, but little if any shipped to US
- About 600 drug manufacturing facilities in each of India and China registered with FDA
- Most of the facilities are API manufactures
- In 2015 FDA conducted about 200 inspections in India and about 130 in China
- Most of the inspections were of API facilities

FDA Foreign Drug Inspection Compliance Program

A foreign API drug inspection is likely a pre-approval inspection conducted under these compliance programs.

- CP 7346.832 Pre-Approval Inspections

Program Objectives:

- 1. Readiness for Commercial Manufacturing
- 2. Conformance to Application
- 3. **Data Integrity Audit**
- CP 7356.002F API Process Inspection

FDA Foreign Drug Inspection Compliance Program (Cont'd)

- CP 7346.832

"Domestic and international pre-approval inspections are conducted for generic and innovator drug applications, and may cover all facilities associated with a submission including drug component manufacturing (such as Active Pharmaceutical Ingredients***"

CP 7356.002F API Process Inspection

- System based inspection-systems included

1. Quality System.
2. Facilities & Equipment System.
3. Materials System.
4. Production System.
5. Packaging & Labeling System.
6. Laboratory Control System.

CP 7356.002 Drug Manufacturing Inspections (Cont'd)

- Inspection Types
- Full Inspection Option
- -First inspection, no history, compliance F/U
- -All Systems Covered
- Abbreviated Inspection Option
- -No history of compliance issues
- -At least two systems covered – must include Quality System and one other

FDA Quality Standards

- 21 CFR Parts 210 and 211, Good Manufacturing Practice Regulations for Drugs

- ICH (International Conference on Harmonization) Q7A, Active Pharmaceutical Ingredients

India & China Specific Concerns

(Based on my audit experience in India & China-No clients in Korea)

- Communications-document translation

- Overall country sanitation &hygiene

- Details of documentation-highly educated staff-trust me attitude-data integrity concern

India & China Specific Concerns (Cont'd)

- Data Integrity-number of FDA Warning Letters

- Sometimes may not understand Data Integrity expectations (raw data, audit trails)
- Serious consequences if there are data integrity issues

FDA Findings

- At least 8 Warning Letters to API manufacturers in India and China in 2015
- About 45 India manufacturers on FDA Import Alert
- About 40 China manufacturers on FDA Import Alert
- Most facilities on Import Alert are API manufacturers

2015 Warning Letter Issues

- Data Integrity-8 of 8 Warning Letters
- Inadequate Quality Unit oversight and documentation-8 of 8 Warning Letters
- Inadequate investigations (complaints, product failures, OOS)-5 of 8 Warning Letters
- Facility and equipment maintenance (qualification and cleaning/sanitation)- 4 of 8 Warning Letters

Data Integrity Definition

- Accurate-no errors or editing without documented amendments
- Attributable-who acquired the data or performed the action and when
- Available-for review and audit or inspection over the lifetime of the record
- Complete-all data are present and available
- Consistent-all elements of the record, such as the sequence of events, follow on and are dated or time stamped in expected sequence

Data Integrity Definition Cont'd

- Contemporaneous-documented at the time of the activity
- Enduring-on proven storage media (paper or electronic)
- Legible-data can be easily read
- Original/Reliable-written printout or observation or a certified copy thereof

API Purchaser Responsibility

- Knowledge of manufacturers facility, quality system and regulatory status
- System for on-site evaluations/audits
- Conduct on-site GMP audits every 2/3 years
- Sampling/testing of incoming APIs

Possible FDA Actions

- Inspection finds no significant problems and application is approved
- Significant problems are found and application approval is withheld until corrections are made and verified (probably with another inspection)
- Import Alert-Automatic Detention
- Issue Warning Letter

Thank You