Elemental Impurity Requirements in a Global Environment
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Elemental Impurities in APIs and Excipients - GMP Expectations

Vibhakar Shah, Ph.D.
Office of Policy for Pharmaceutical Quality (OPPQ)
Office of Pharmaceutical Quality (OPQ)
CDER, USFDA
Vibhakar.shah@fda.hhs.gov

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FDA perspective, in particular the GMP expectations, for implementing the recommendations provided in

- ICH Q3D: Guideline for Elemental Impurities
- USP <232> Elemental Impurities – Limits
- USP <233> Elemental Impurities – Procedures

in controlling Elemental impurities (EI) in the

- Active Pharmaceutical Ingredients (APIs)/ Drug substances
- Excipients
Statutory Requirement
Drug Quality

- **Sec 501(a)(2)(B) of the FD&C Act** – requires **conformity** with **Current Good Manufacturing Practice (CGMP)** for the manufacture of drugs.

**FD&C Act Section 501(a)(2)(B)**

“A drug shall be deemed to be *adulterated* if...

the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with *current good manufacturing practice*...... to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”
Statutory Requirement
Drug Quality

➢ **Sec 201(g)(1) of the FD&C Act** defines **drug** as any article
  ◊ recognized in USP, NF, HP
  ◊ intended for use in the *diagnosis, cure, mitigation, treatment, or prevention* of disease or other condition
  ◊ affecting structure or function
    ■ chemical action/metabolized in/on body
  ◊ that is a component of any of the above

➢ **No distinction** between **API** and **finished product**

➢ **Like APIs, excipients** are drug components impacting
  ◊ manufacturability, drug release, bioavailability, stability etc.

➢ **From a statutory standpoint** they are all required to be manufactured in **conformity** with **Current Good Manufacturing Practice**
Regulatory Requirements
DPs, APIs and Excipients

- **Finished Drug Products (DPs):** Regulations codified in 21 CFR parts 210, 211, and 600, 601, 610 establish Current Good Manufacturing Practice (CGMP) requirements for finished DPs, including biologicals (CBER/CDER)
  - **Contract manufacturers** are an extension of the manufacturer's own facility (21 CFR 200.10)

- **Active Pharmaceutical Ingredients (APIs):** Recommendations in ICH Q7A establishes CGMP requirements for the APIs

- GMP regulations require that the DP manufacturers **ensure** that the excipients **reliably** meet the **desired quality and performance characteristics** for their **intended use**
  - through an **effective** and **efficient** vendor/supplier qualification
  - FDA recommends an audit program
NGO* Guidelines and Voluntary Consensus Standards For Excipient GMPs

- Over last several years, Agency has actively encouraged all stakeholders to develop voluntary consensus standards for excipient GMPs that meet statutory requirements and allow self-regulation to ensure quality with minimum regulatory oversight as an incentive.
  - OMB Circular A-119 directs government agencies to use voluntary consensus standards in lieu of government-unique standards if appropriate.
- USP <1078> Good manufacturing Practice for Bulk Excipients
- GMP for Pharmaceutical excipients NSF/IPEC/ANSI 363-2014

*NGO – Non Government Organizations
Accredited 3rd Party Auditors

Excipient GMP Auditing and Certifications

Available 3rd Party Auditing Schemes and Bodies (for example):

- NSF (formerly IPEA)
- EXCiPACT
- Rx-360
- USP
Complying to GMP Requirements...

- Quality must be *built into*, rather than *tested into*, the product.

- Establish **systems** approach to *assure* proper design, monitoring, and control of manufacturing processes and facilities

- **To prevent** contamination, mix-ups, deviations, failures, and errors

- **To assure** that drug products meet their quality standards
  - Identity, Purity
  - Quality, Strength
Complying to GMP Requirements...

- **Quality is built in by design** and at every manufacturing step
- **Facilities** are designed for intended use and maintained properly
- **Equipment** is suitable for its purpose, calibrated, cleaned and maintained properly
- **Employees** are qualified and fully trained
- An effective **quality management system** is established
- **Raw materials** of appropriate quality are procured and verified before use
- **Robust processes** are established and maintained under state of control
- Reliable testing laboratories are maintained
- **Product quality deviations** are detected, reported, investigated, documented properly and followed-up with Preventive actions
- **Change control management** is established and managed effectively
Elemental Impurities (EIs)  
Why Control?

- Any impurity (inorganic or organic) including elemental impurity (EI) in APIs or excipients are
  - undesired contaminants (sometimes unavoidable)
  - Some are relatively toxic
  - presence in the drug product **do not offer** any **therapeutic benefit** to the patient

- From a risk/benefit perspective, it is **sensible** to expect that any EI when present should be removed if possible or **controlled**
  - reliably to a **reasonably achievable level** that is
  - unlikely to **exceed** its known/established safe (PDE) level
Acceptable level/limit of an EI should be established based upon risk assessment and risk-mitigated controls

- Source(s) of the EI: where and how it finds its way
  - Intentionally added during manufacture (e.g., catalyst, reagents)
  - Potentially present (e.g., from process aid – ground water, mining)
  - Introduced during process (by wear and tear of Mfg. equipment)
  - Leached from the container-closure on storage

- Probability of occurrence and natural abundance of the EI
- Innate toxicity of the element and its established PDE
- Source-specific prior knowledge of conc. range for the EI
- Observed levels based on removal efficiency of work-up/purification steps – process average & variability estimate
- Intended route of administration/exposure
GMP expectations
For EIs in APIs & Excipients

- Availability of the Risk Assessment Report at site in accordance with the ICH Q3D recommendations or
  - an alternate approach that may be equal to or better than ICH Q3D and deemed acceptable
- Scientific data supporting
  - inclusion and/or deletion of EI from the Specification
  - limit(s)/specifications for the EIs of concern based on process knowledge
- Method validation data demonstrating suitability of the test methods for intended use
- Product/process data demonstrating capability and reliability of the mfg. process steps to remove or control EIs consistently at or below specified levels
- Change control management for potential impact on EI profile
Qualification and audit program
APIs & Excipients

Must be approved by firm’s Quality System

- Criteria for qualification and maintenance of qualified status
- Routine vs. full testing and frequency of full testing
- Audit frequency
- Supply chain integrity (who does what)
- Quality agreement elements (as example)
  - Roles and responsibility
    - elements of control strategy (e.g., who will do testing as needed)
  - Commitment for timely communication and disclosure of
    - product/process deviations, OOS, investigation outcome, CAPAs and necessary process/equipment/SOPs/test methods changes impacting EI limits
Implementation under Recent CDER Reorganization
Office Of Pharmaceutical Quality (OPQ)
Regulating Drug Quality

As of January - 2015

- Office of Policy for Pharmaceutical Quality (OPPQ)
- Office of Program & Regulatory Operations (OPRO)
- Office of New Drug Products (ONDP)
- Office of Lifecycle Drug Products (OLDP)
- Office of Biotechnology Products (OBP)
- Office of Process and Facilities (OPF)
- Office of Surveillance (OS)
- Office of Testing & Research (OTR)
Office Of Pharmaceutical Quality (OPQ)  
Regulating Drug Quality

- New office within CDER – January 2015
  - Creates a single unit dedicated to product quality.
  - Expected to provide better alignment among all drug quality functions at CDER, including review, inspection, and research.
  - Combine non-enforcement-related drug quality work into one super-office, creating one quality voice and improving oversight of quality throughout the lifecycle of a drug product.
  - Creates a uniform drug quality program across all sites of manufacture, whether domestic or foreign, and across all drug product areas – new drugs, generic drugs, and over-the-counter drugs.

- OPQ organization along with new processes and policies
  - will support CDER mission to ensure that safe, effective, high quality drugs are available for the American public.

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm418347.htm
Changes include:

- Realignment of functions and personnel from the Office of Pharmaceutical Science to OPQ
- Realignment of preapproval and surveillance inspection activities from the Office of Compliance (OC) to OPQ
- Realignment of inspection-related activities for bioequivalence/bioavailability and non-clinical studies from OC’s Office of Scientific Investigations to the Office of Translational Sciences (OTS)

Foster and institute One Quality Voice and improve oversight of quality throughout the drug product lifecycle

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm418347.htm
Office of Policy for Pharmaceutical Quality (OPPQ)

What We Do:

- Establish, implement, and update drug product quality policies and standards, including quality review and CGMP/inspection policies
- Evaluate Agency findings such as deficiencies and inspectional citations for conformance to policy
- Lead CDER interactions with compendial, national, and international quality standard-setting organizations
- Provide executive leadership for the CDER Council on Pharmaceutical Quality
In *theory*, there is no difference between theory and practice. But, in practice, there is.
Abbreviations used

**ANSI:** American National Standards Institute

**CMC:** Chemistry, Manufacturing and Controls

**ExCiPACT:** International Excipient Certification

**GMP:** Good Manufacturing Practice

**ICH:** International Conference on Harmonization

**IPEC:** The International Pharmaceutical Excipients Council

**IPEA:** International Pharmaceutical Excipients Auditing Inc.

**NSF:** National Sanitation Foundation International

**OMB:** Office of Management and Budget

**PQG:** The Pharmaceutical Quality Group

**PQRI:** Product Quality Research Institute

**Rx-360:** An International Pharmaceutical Supply Chain Consortium

**USP:** United States Pharmacopeial Convention
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Thank You for Your Attention

Questions

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