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

Scope of this Presentation

- 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.
- Joint IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients- 2006
- 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 (sometime 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

Control of Elemental Impurities (EIs) Risk Assessment Considerations – ICH Q3D

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

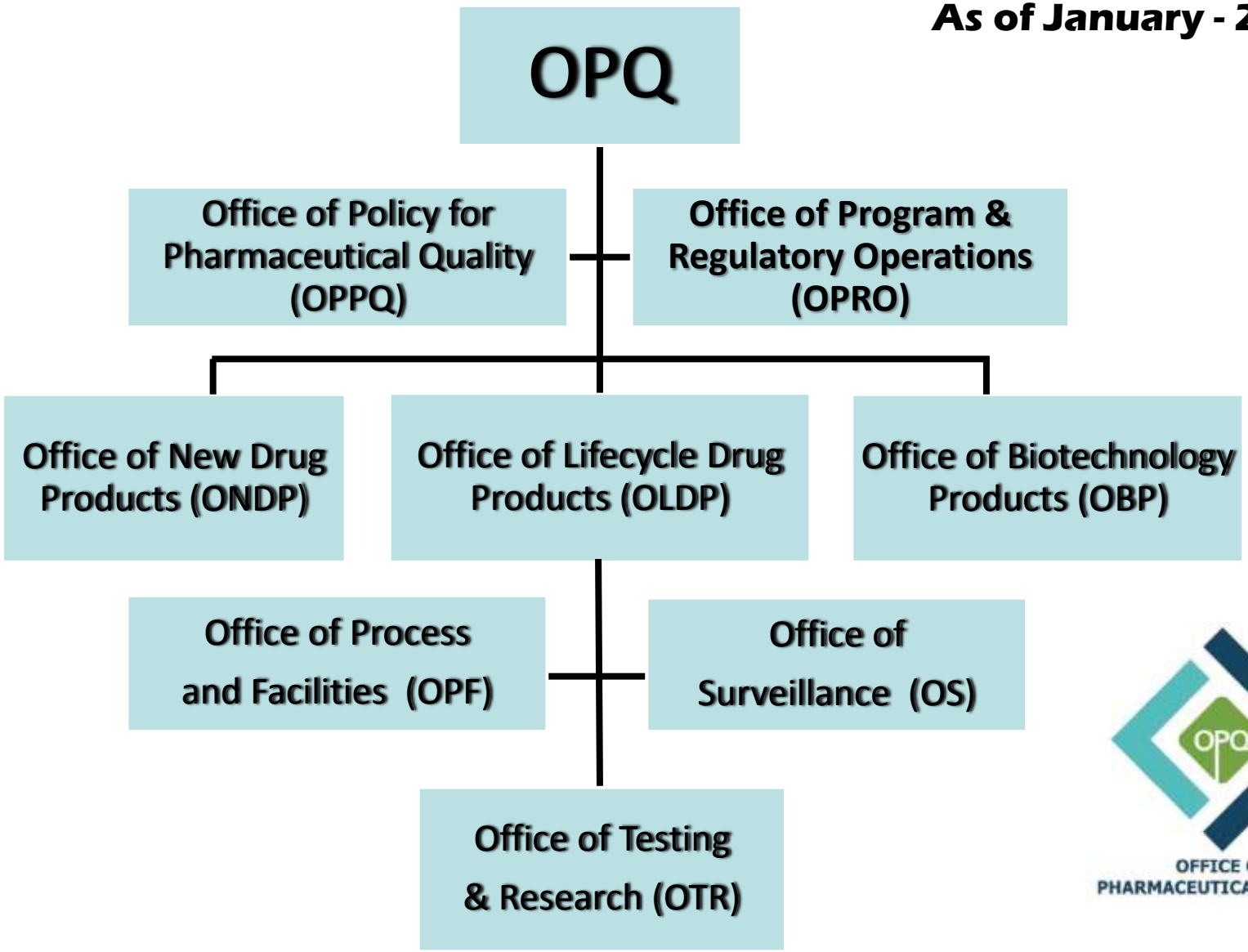
Must be approved by firm's Quality System

- 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 PHARMACEUTICAL QUALITY

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

Office Of Pharmaceutical Quality(OPQ)
Regulating Drug Quality

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

OPQ
OFFICE OF PHARMACEUTICAL QUALITY

Quality Assurance Under CMC & GMP

Quality Assurance Under CMC & CGMP

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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