A Generic Industry Perspective on Establishing Impurity Limits
And a Corresponding Control Strategy

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Disclaimer

The information within this presentation is based on the presenter's expertise and experience and represents the views of the presenter for the purposes of stimulating discussion at this workshop.
The Question of Definitions

- **Purity** – “Freedom from adulteration or contamination (Oxford Dictionary)
- **Purity** – “The quality or state of being pure” (Merriam-Webster Dictionary)
- **Impurity** – “Any component of the new drug substance that is not the chemical entity defined as the new drug substance.” (Q3A(R))
- **Impurity** – “Any component of a drug substance that is not the chemical entity defined as the drug substance and in addition, for a drug product, any component that is not a formulation ingredient. (USP)
• **Control** – “A means of limiting or regulating something” (Oxford Dictionary)

• **Control Strategy** - A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)
Important Fact #1

There is nothing in the world that is absolutely pure.

- Any specifications regarding purity must always recognize this fact.
Important Fact #2

Control of Impurities in the Pharmaceutical World is a Complicated Problem

- Both for Industry and Regulator
- Many Possibilities
- Risk Management Principles are Required
- International Regulatory Harmonization (Convergence?)
Important Fact #3

You cannot and do not improve the quality of a drug substance or product by tightening a specification.

- This can only be done by changing the production process
Types of Impurities

• Drug Substance Impurities can be conveniently classified into 3 categories:
  – Organic Impurities – ICH Q3A and M7
  – Inorganic Impurities – Q3D
  – Residual Solvents – Q3C

Ref: ICH Q3A(R2) and USP <1086>
FDA Guidance: “ANDAs: Impurities in Drug Substances”

• Notable exclusions: Biologics/biotech, peptides, fermentation products, others
• States that much of Q3A(R) is applicable to ANDAs
• States specification should include a list of each class of impurity where applicable
• Unique importance of USP in setting acceptance criteria

△ Applicability is function of the control strategy
Organic Impurity Specifications

Should Include:

• Specified Identified Impurities
• Specified Unidentified Impurities
• Unspecified, Unidentified Impurities
• Total Impurities
Acceptance Criteria for unspecified impurities in ANDAs should be set not to exceed the identification threshold in Q3A even when higher acceptance criteria are listed in USP.

- Will this change in future with adoption of General Chapter <476>?
Important Fact #4

The Generic Industry is Different than the Innovator Industry

- Original NDA (NCE) sets the bar for subsequent ANDAs. However, regarding impurities, the level “qualified” by innovator may not be representative of intrinsic safety but driven more by their process capability at time of submission.
- Most generic companies do not develop or manufacture the drug substance used in their drug products.
- Product Development stage of Product Lifecycle is generally much shorter than that of Innovator.
FDA Guidance: “ANDAs: Impurities in Drug Substances”

This guidance introduces several important means of impurity qualification outside of what is included in Q3A:

- Comparison to RLD – Generally most useful
- Significant Metabolites – Less useful
- Toxicity Studies – Least preferred by FDA and Industry
- Scientific Literature – Rarely useful

QSAR are not good enough for qualification purposes
Acceptance Criteria

• “An applicant is not expected to tighten the limits based on process capability, provided that the elemental impurities in drug products do not exceed the PDEs”. (Q3D)

• An applicant is not expected to tighten the limits based on process capability, provided that the impurities in drug products do not exceed the qualified level

❖ Is this enlightened philosophy consistently followed by FDA re: organic impurity limits in ANDAs?
In 2010 this Guidance replaced 1998 draft Guidance partially in recognition of ICH Q3B

Scope includes impurities in drug products that are classified as degradation products

States that much of Q3B(R) is applicable to ANDAs

Unique importance of USP in setting acceptance criteria
In considering the production of a drug product, there are broad categories of potential sources of impurities:

- Residual impurities resulting from components intentionally added in the formation of the drug substance, excipients or other drug product components.
- Impurities that are potentially introduced into the drug substance and/or drug product from manufacturing equipment.
- Impurities that have the potential to be leached into the drug substance and drug product from container closure systems.
- Degradation products of the drug substance.
- Reaction products of an excipient with the drug substance.
- Microbial contamination from environment.

A properly developed control strategy must take all of these into account. Finished product specifications are not the answer. You cannot test quality into a product.
Important Fact #5

The relevance of the acceptance criteria for any impurity specifications is no greater than the quality of the analytical procedure(s) used to measure the impurity(ies).

Is it really worth arguing that the acceptance criteria for an unspecified impurity should be 0.1% versus 0.2%, if the actual level of the impurity is 0.01% or 1.0% when measured by a more accurate analytical procedure?
An Invitation for Trouble

• An ANDA applicant proposes/establishes a limit for an impurity that is outside of the control limit of the process capability.

  ❖ For a generic company this is often done unintentionally due to incomplete understanding of product and process capability
We all want to do the right thing, but…
Areas of Concern

- Complex Drug Substances
- Complex Drug Products
- Compliance
- Supply Chain Complexity
- Economic and Political Pressure
Progress in Quality Guidance

• ICH M7
• ICH Q3D
• ICH Q12 (under development)
The Question of Genotoxic Impurities

• ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

• A Complementary Guideline to Q3A and Q3B, which treat such impurities only superficially

❖ Modern guidance that takes into account risk-based assessment in evaluation of impurities
The Question of Elemental Impurities

• ICH Q3D: 17 pages of Guideline + 56 pages of Appendices. Official December 2014
• Implementation date of ICH Q3D: December 2017
• USP <232> becomes official Jan. 1 2018
• USP <231> goes away
• Q3D Training package is now available at www.ich.org
• Specific FDA Guidance is under development

❖ Implementation for generics may be difficult?
ICH Q12 is currently under development
Concept of Established Conditions is already proposed by FDA in draft guidance
Opportunity would be huge for generics to adapt control strategy based on significantly greater dataset and process/product knowledge

Will Regulators and Industry collaborate on development and implementation of Q12 to realize benefits to the patient?
DISCUSSION, ANYONE?

Questions????

Comments???
Thank You

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