Excipient Company Experience with Implementation of ICH Q3D

4th PQRI Workshop on ICH Q3D Elemental Impurities Requirements
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Priscilla Zawislak
Immediate Past-Chair, IPEC-Americas
Global Regulatory Affairs Advocacy Manager, DuPont Nutrition & Biosciences
priscilla.zawislak@dupont.com

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ICH Q3D Risk Assessments

Component Approach
Options 1, 2A, 2B

Finished Product Approach
Option 3

Risk Assessments

- **Options 1, 2A or 2B: Component Approach**
  - Assess potential elemental impurities from each component of the drug product (API, excipients, container closure system)
  - Assess each component for potential sources of elemental impurities
  - Identify known or likely elemental impurities
  - Determine the contribution of each component or source of elemental impurity to the levels in the final drug product

Abs = absorbed

FDA results

Component	Category	Quantity (mg/tablet)	Dose "x" tablets (mg/day)
		x =	2
Tablet core:			
Active	Synthetic	100	200
Mannitol	Synthetic	120	240
calcium phosphate	Mineral	65	130
modified starch	Plant derived	10	20
cellulose	Plant derived	10	20
Magnesium stearate	Synthetic	3	6
Titanium dioxide	Mineral	2	4
Talc	Mineral	1	2
Polyethylene glycol	Synthetic	1	2
Ferric Oxide Red	Mineral	0.1	0.2
Purified water			
Total Tablet weight		**312.1**	**624.2**
Total element			

Risk Assessments

- **Option 3: Finished Product Analysis**
  - Assessment of potential elemental impurities in the finished drug product
    - Identify potential elemental impurities and their source(s)
    - Initially analyze for elemental impurities in finished drug product
    - Decide whether to routinely test for elemental impurities in finished product

ICH Q3D Risk Assessments – Which Option is Most Commonly Used?

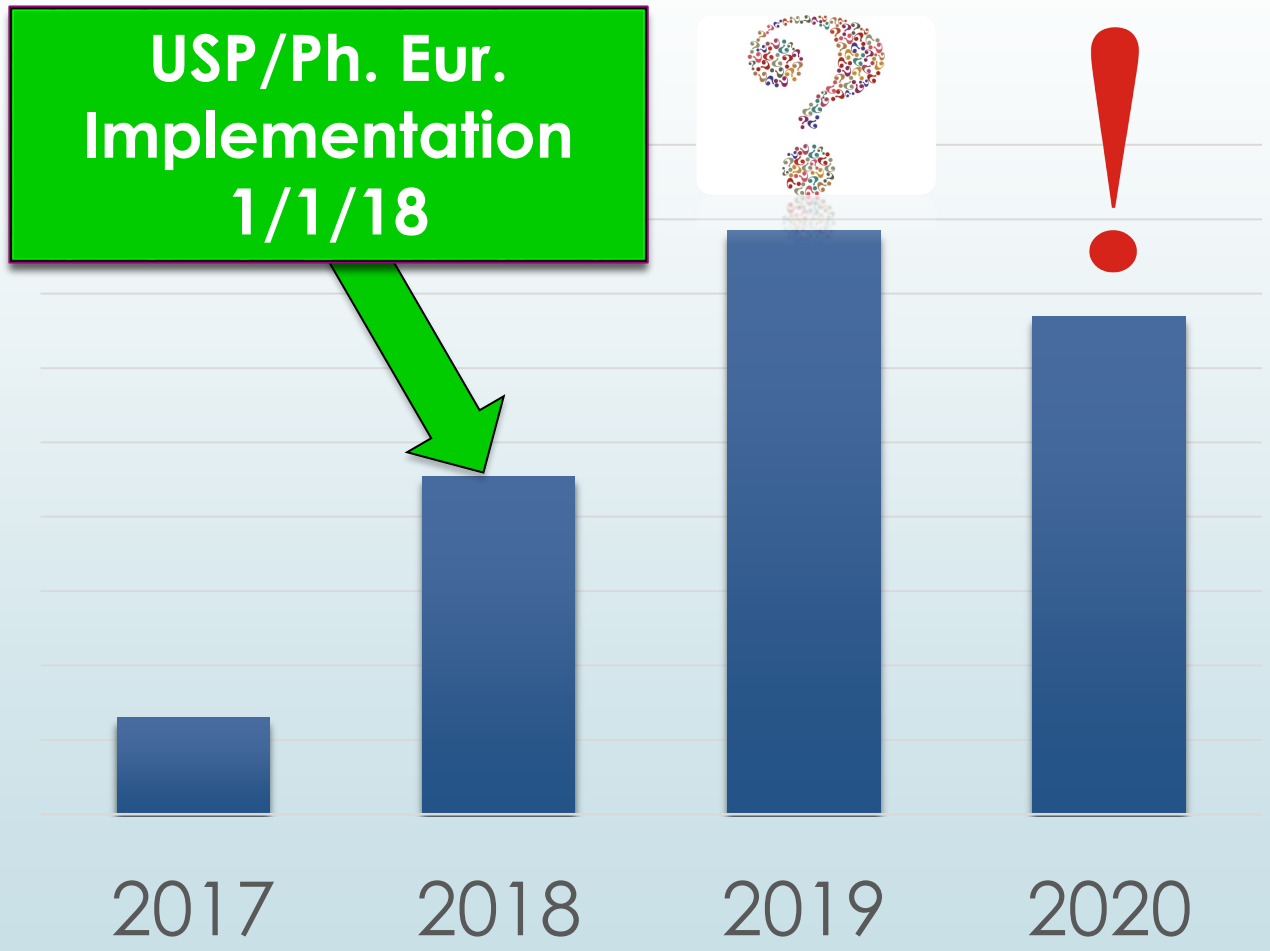
Component Approach
Options 1, 2A, 2B

Finished Product Approach
Option 3

We are seeing more of this approach – mainly from generic pharma companies

Trends in Information Requests

Requests for Elemental Impurities Information

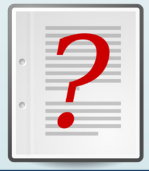


Limited Supplier EI Information

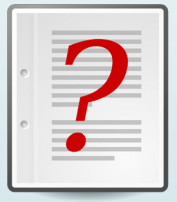
- **Business decisions, not regulatory requirements** - the level of excipient supplier engagement depends on whether the pharmaceutical uses of the excipient make up a significant share of their business or not
- Most suppliers **do not** plan to do any additional routine testing for elemental impurities and will not agree to new specifications
- Some suppliers have designed studies on a limited number of batches to improve their knowledge of potential EI in their products so they can provide some risk assessment assistance to their customers or they may have data driven by other market needs (i.e. food)

What are suppliers seeing from FDA via pharmaceutical companies?

Letter from FDA reviewer to pharma company re: missing information in risk assessment



Pharma company sends same request to supplier



Typical customer request: This is regarding the FDA query we received for our ANDA and we need your help to answer the Agency within the stipulated time limits…..

Pharma company communication to supplier

Please understand that **FDA overrule all ICH guidelines**. ICH is guidance and does not need to be followed strictly. **FDA has clearly demanded documents** and **mentioned that these documents can be obtained from the [excipient] manufacturer**. If **FDA is asking for documents then we have to provide them** and we cannot give any reference to other customer and [FDA or trade association] presentation etc.

The following are excerpts from FDA letters sent to pharma companies after reviewing the EI information provided in submissions

Excipient analytical methods & validation reports

- "Since you adopted **option 2b** approach for risk assessment, please **confer with your suppliers and provide information on the verified/validated methods used for** determination of EI levels in the APIs and **excipients**."
- "**Provide the analytical method(s) used** to quantify the identified EI in both the drug substance and the excipients…Please note that **this information may be obtained from** the DMF holder and **excipient manufacturers**."
- "We acknowledge that you provided the EI analysis per **Option 2b**, however, we could not locate the **analytical method or validation reports used by the…excipient manufacturers** justifying the numerical data used in your calculations. Please **contact…the respective excipient manufacturers to obtain the analytical method**. "
- "**Please contact the manufacturers of the excipients...and provide the analytical method used for the EI analysis and the supporting method validation reports**."
- [for the excipients]"…If the method is not per USP <233> please also **provide the corresponding validation report**."

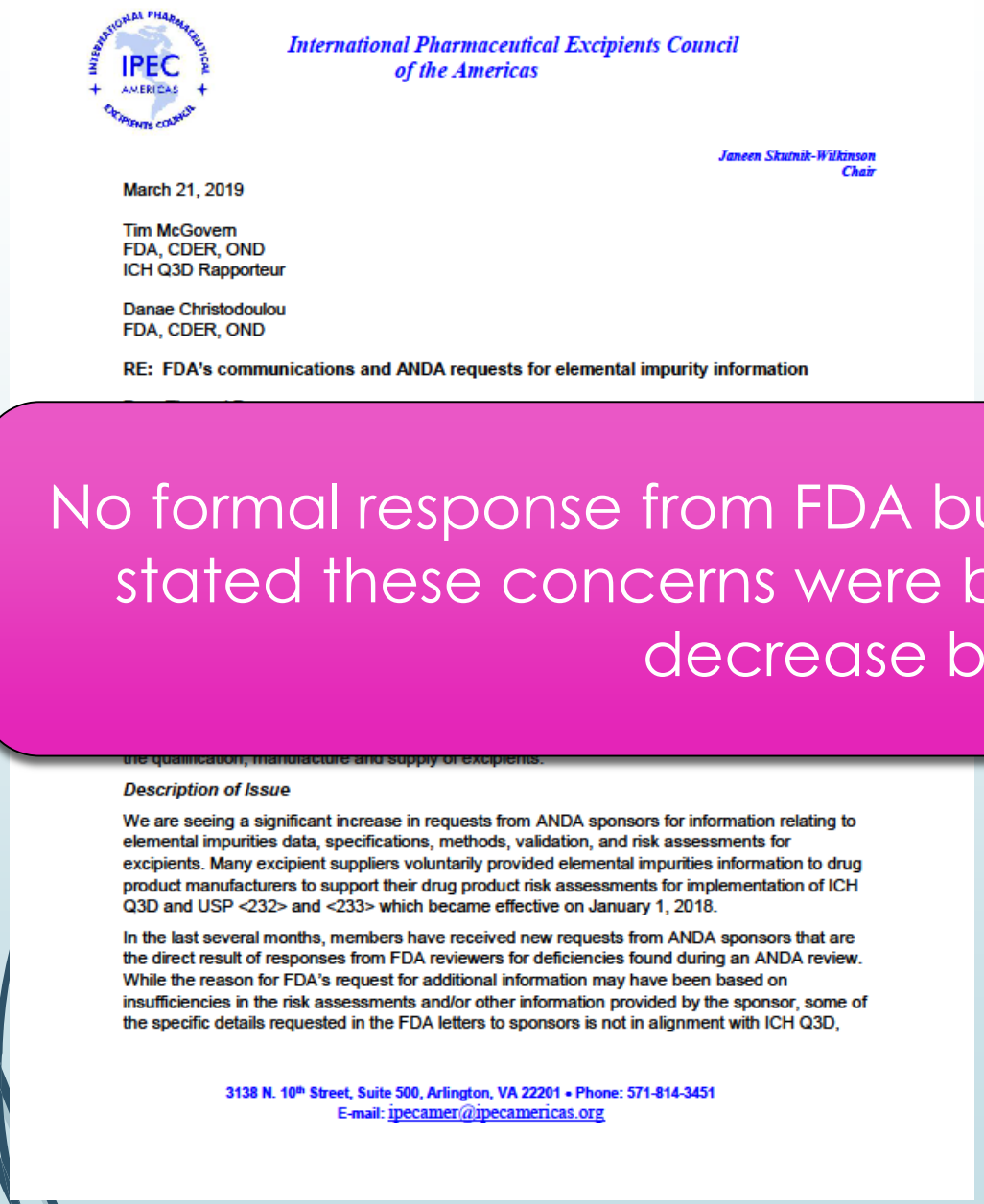
Specification limits, EI data, compliance to USP <233> & supplier risk assessments

- "Your EI Risk Assessment…indicates **Option 2a** was chosen. Thus, **the suppliers of the excipients need to specify a limit for all target elements identified in the risk assessment…they need to submit actual EI data to confirm the proposed limit**…they need to **confirm whether their methods comply with USP <233> or not**."
- "Please **submit the actual analysis results of each Class 1 and 2A EI generated by each supplier for all excipients**…"
- "**Please consult the suppliers of [excipient] to confirm whether their methods comply with USP <233>."**
- "…**Option 2b** was chosen. Thus the **suppliers of each excipients should indicate elemental limit for each Class 1 and 2A EI in their statements…they need to submit actual EI data to confirm the proposed limit**."
- "It is not clear how zero level of most EI in most excipients was retrieved. Please clarify why the EI content as reported in the risk assessment was not transcribed into your EI risk assessment for the drug product. Please **re-evaluate the EI statements provided for excipients and request updated statements from each manufacturers as needed**. Please ensure updated documentation includes EI risk assessments to show compliance with ICH Q3D."

Assumptions

- Primary driver - the sponsor likely did not provide all of the necessary risk assessment summary information specified in ICH Q3D, USP <232> and FDA Guidance
- Possible areas of misunderstanding:
  - Most issues are related to use of Option 2b
  - Incomplete information on all ingredients
  - Confusion about <30% of PDE provisions

IPEC-Americas letter to FDA March 2019 regarding concerns with FDA reviewer responses



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Janeen Skutnik-Wilkinson
Chair

March 21, 2019

Tim McGovern
FDA, CDER, OND
ICH Q3D Rapporteur

Danae Christodoulou
FDA, CDER, OND

RE: FDA's communications and ANDA requests for elemental impurity information

Description of Issue

We are seeing a significant increase in requests from ANDA sponsors for information relating to elemental impurities data, specifications, methods, validation, and risk assessments for excipients. Many excipient suppliers voluntarily provided elemental impurities information to drug product manufacturers to support their drug product risk assessments for implementation of ICH Q3D and USP <232> and <233> which became effective on January 1, 2018.

In the last several months, members have received new requests from ANDA sponsors that are the direct result of responses from FDA reviewers for deficiencies found during an ANDA review. While the reason for FDA's request for additional information may have been based on insufficiencies in the risk assessments and/or other information provided by the sponsor, some of the specific details requested in the FDA letters to sponsors is not in alignment with ICH Q3D,

3138 N. 10th Street, Suite 500, Arlington, VA 22201 • Phone: 571-814-3451
E-mail: ipecamer@ipecamericas.org

- The FDA requests are impacting ANDA submissions.

No formal response from FDA but they acknowledged the letter and stated these concerns were being addressed. Have seen some decrease but issues still exist.

- Q&A document for Elemental Impurities in Human Drugs to FDA modeled after the draft guidance published by FDA CVM but specific to the types of questions we are seeing from pharmaceutical companies.

Clarification is still needed to address FDA & pharma industry understanding

- ICH Q3D applies only to the finished drug product
- Components (i.e. excipients & APIs) are **NOT** subject to the limits in ICH Q3D
- It is the responsibility of the drug product manufacturer to verify the vendor information
- There are **NO** requirements for the excipient or API manufacturers to perform any testing for EI, to provide any batch data or method validations
- As with any method validation, the drug product manufacturer must conduct their own method validation and cannot use a vendor's validation
- Some suppliers may have historical data but the test methods may not have been validated and may not be one in <233>
- Suppliers are **NOT** required to conduct an EI risk assessment of their product(s). If a supplier conducts a risk assessment, they are **NOT** required to share the details of the assessment with the drug sponsor, but may choose to share a summary or the results.

Clarification is still needed to address FDA & pharma industry understanding

Pharma company request: For elemental impurity calculation for finished product, we required excipient specification or limit for elemental impurities

Drug product manufacturer's responsibilities

In cases **where a specific risk factor has been identified** based on the risk assessment, the **drug product manufacturer** is expected to **establish a test method and limit** for EI in either the raw material or the drug product to ensure they are adequately controlled.

When using the component approach, daily exposure to the elements should be calculated based on the amount and composition of the excipients or drug substances in the drug product and the maximum daily dose.

The drug product manufacturer should **NOT** expect the supplier to establish or agree to specifications for the raw material!

Sometimes the Component Approach isn't the best option!

Do not ask every supplier to meet lower or the same specifications for components that are not contributing to the higher levels or to justify using the <30% of the PDE to avoid testing!

- Many companies are trying to use the <30% of the PDE option and this may not always be feasible

Sometimes the ONLY option is to test the drug product!

- If possible, apply controls to those with the highest levels, NOT all components

Understand how to use supplier information

All above the ICH limit

Supplier spec, max. expected level, LOD or LOQ	ICH Q3D Option 1 limit (oral)
Cd 1 ppm	Cd NMT 0.5 ppm
Pb 3 ppm	Pb NMT 0.5 ppm
As 2 ppm	As NMT 1.5 ppm

Customer request: Considering above, until we get a declaration that this material will comply with our proposed limits, our product will not comply with ICH Q3D

It is important to understand:

- Intended use, limitations and reliability of supplier provided information
- How to evaluate "Likely to be present: No" when accompanied by an LOD or LOQ
- How to use supplier specs or max. expected levels in calculations

Conclusions

- Surprising that the number of customer requests for information remains high 2 yr+ after implementation in US & EU
- Strong interest in using the Component Approach and wanting to apply the <30% of the PDE option
- Training re: ICH Q3D & compliance options is still important for industry and FDA reviewers

Thank You!