REPORT:
Breakout Session A

Risk-based Assessment and Control Strategy Development
1A. What will be the impact of metals classifications and applying ICH Q3D PDE requirements to existing drugs vs. new drugs?

1B. What additional difficulties (beyond ICH Q3D) might occur when implementing the USP requirements to all drugs and what impact could this have on the implementation timeline and roll-out plan?
New drugs essentially ok
  - But problems arise because new drugs will still contain existing excipients
Existing products may be an issue
  - Is it possible to ask FDA for exemption because of longevity
  - Use complaint files defend with safety studies
Reformulations might be necessary
  - This adds time and complications as alternatives may not be readily available
Need to ensure this does not increase drug shortages
Q1A: Responses: New vs. Existing (2)

• USP does not differentiate between new and existing.
  – USP implementation timeframe needs to be sufficiently long enough to address this concept

• New API’s will provide better info

• USP is to post update soon – includes guidance and position
Many concerns regarding implementation and application to existing products/materials

- If current drug product is found to be out of limit, what does one do?
- What will companies have to do if product doesn’t meet limits?
- Petition FDA “can’t comply but product needed as is”?

- Above may be easier to apply to critical drugs and parenterals more so than OTC

USP proposed option to raise the limits in the monograph
Q1B: Additional Difficulties

1. Industry needs sufficient time to incorporate existing excipients
2. Need reasonable implementation time
   - Consider modeling timeframe after previous issues
     - EXAMPLE: Opioid impurities, interim specs’ (6-7 years)
3. Global issues need to be factored in
• Work with FDA. Plan for large number of exceptions
• USP works with FDA to resolve revision time at least 1 year
• Qualify at different level with FDA
• If you have problem with product consult FDA
• Europe – work with EMA and EMEA
• OTC must comply with USP Chapter exception, consult FDA
• Cost of reformulation includes review of all aspects. High probability the product will go off the market.
ICH Q3D should have certain categories of risk. i.e. catalysts metals vs environmental

- Max daily dose – must be kept
- 1 year is not enough to implement
- we have been aware for 10 yrs about need to avoid problems similar to residual solvents issue.

- Can high Fe interfere with trace? Well-trained, good methods, performance criteria will resolve analytical problems.
Q1B: Additional Difficulties (2)

- If ICH limits are safety, how can monograph be higher:
- USP Flexible Monograph Process
- Safety concern or not a particular level.
- Low limits
- Methods are there
- Microwave HF needed
- Container silicas extracted
- ICH should reconsider limits based on risk of exposure
A. What is the acceptability of periodic (skip lot) testing in US, EU and Japan to justify compliance?

B. What manufacturing process and raw material information is needed to use this technique in each region?

C. Does test data need to be submitted on ALL metals to demonstrate compliance?

D. How many batches would be needed to determine compliance?
Q2A: Acceptability – Reduced Testing (1)

- Acceptability already exists
- Testing practices should be addressed within a company’s control strategy (and/or internal policies)
  - Suppliers of materials already apply this principle and indicate as such on COA
- Issue is more appropriate for internal control strategy – and therefore should not go back as an issue for EWG
- Only testing!
- PQRI recommends periodic testing
Q2A: Acceptability – Reduced Testing (1)

- Skip lot testing NOT acceptable without data first.
- Depends on same lot;
- Depends on number of different materials in drugs
- Skip lot testing based on level of predictability
- Data (per audience) is still a big issue based on 3-5 years potential product development.
Q2B: Justification & Q2C: Submission of All Data?

2B:
- Justification – customer needs to know
- Control strategy & internal company procedure should address

First step: make argument there is nothing present.
Second step: Set up test plan to assure absence of metals

2C:
- No – unless there is a potential risk
- May not be a reason to ever test everything
- If you know your product / materials well you may not even need to do full testing
- Risk assessment is necessary to determine what metals should be tested. Documented results, assessment etc. document needs to be robust enough to satisfy internally and externally.
Q2D: Number of Batches?

- Companies need to define their testing model/practice and justify
  - Examples: Guidance by ANSI, ISO,
- Type of excipient might need to be considered in determining strategy
- 3rd party audits will not address the level of acceptance for demonstrating data levels for metals
- Number of batches depends on assessment.
- Manufacturing process and sources of metal contamination are considered
- Manufacturing equipment change may lead to change of metals contamination
Q3

A. What information (based on raw material sources and/or manufacturing process) could be used to justify not requiring additional testing?
B. What will regulators need to justify this claim?
C. Will ingredient suppliers be willing to share this type of information given confidentiality concerns?
Q3A: How to justify

- Whether a material Synthetic vs. natural and whether or not there is further processing
- If enough knowledge of process can justify
  - Use of common research/public data on bioavailability.
- Risk assessment is necessary to determine what metals should be tested. Documented results, assessment etc. document needs to be robust enough to satisfy internally and externally.
- API manufacturing controls might look for step that removes metals
- Milling change may cause metal changes e.g., finely milled powder.
Q3B: What do regulators need?

Q3C: Willingness to share?

3B:
- Regulators will need to see the data
- Regulators must be willing to engage with supplier/producers
- Need to get all functional people involved
- Food GMP may not be suitable to track/notify change. Food FMP focus is on food safety. Unlike drug GMP

3C:
- If it is in DMF it would be OK (but this does not resolve issues in countries without DMF system
- Not without a way to protect confidential information
- Concern for reliable quality agreements
Q4

A. Can a common format/template be developed for carrying out a risk assessment on individual excipients and APIs?

B. What could this look like?
Q4A: Template?
Q4B: Content?

4A:
- Develop points to consider and highlight them.
- We could develop a process/format.
  - EX: where, how processed, purified, catalyst, mined Team has to be knowledgeable

4B: Ask the right questions. Have knowledgeable source for the information needed.
- Supplier needs to reply with available data. Include variability
- Mined or plan/animal sourced.
  - Needs to be tailored to situation.
  - IPEC could develop
  - A template would be desirable – mechanics may be problematic
ADDITIONAL DISCUSSION:

- Specifications for ICH:
- Set based on tox publication
- Carcinogen data were included or not included?
- Likelihood of contamination
- Most comments found
- Speciation
- Limits should be vetted publically
REPORT
Breakout Session B
Methodology & Bioavailability Issues
• Although USP and EP are developing proposals for general chapters on metal impurity testing, our understanding is that JP is not.
• 1A: Can the development of an ICH Q4B pharmacopeial harmonized general chapter be expedited to prevent dis-harmonization on methodology?
• 1B: What impact could not including a general chapter on metals impurities in the JP have?
• 1C: What implications might result from specific monograph requirements trumping general chapter requirements since excipients only need to comply with the limits listed in the monographs which may not always be harmonized.
Q1A: Q4B
Q1B: JP

1A:
- Q4B completed its remit and has been decommissioned.
- Will be a company decision as to which pharmacopeia will be used.
- Methods Chapter for PDG is coming
- No. Discuss any validated suitable method
- Harmonization difficult because of matrices

1B:
- USP said JP would like methods chapter but not limits.
  - May not be an issue because MHLW/PMDA will adopt the Q3D limits
- ICP is already listed as the method for the standard.
- May need two tests. Can have 1 cp-ms data but report UP levels.
- May need 3 tests? Or validate monographs with lower + spec and use that
Q2

2A: Very low metal detection limits may require ICP-MS – are their sufficient instrument manufacturers and independent testing labs to cope with demand and are their limits of detection capable to meet ICH Q3D limits?

2B: What types of additional testing costs may be incurred and how will these costs be passed on?

2C: Is the current compendia Heavy Metals test still viable in certain situations?
• 2A
  - Sufficient test labs are out there.
    - There are difficulties now but that may resolve with experience.
    - Labs are doing environmental testing mostly. May not meet needs for metals.
    - Can universities be used?
      - Concerns over whether or not full method validation is needed vs. GLP
      - Instruments are available, matrix + sample prep is still an issue independent and contract labs have to be good audited/qualified. Turn around time will be an issue

• 2B
  - Labs may charge for validation
  - Cost saving if in house
  - Some problems with results, skills, experience.
  - Methodology may result in different costs. Costs will be passed on downstream.
  - Testing may result in product holds until material approved. These are costs as well and must be discussed w/user.
  - Validation 20K, audit, visit lab get qualified. Excipient company may simply leave the pharma business if cost of testing is high
Q2C: Usage of the current method?

• 2C: Current method is to be replaced, and it is unlikely to be used due to the fact that it cannot be validated.
• No. LOD’s are higher than limits set.
• Not selective.
Q3

3A: How can method interferences, leading to false test results for certain excipients and APIs, be handled?

3B: What type of method validation may be required to ensure interferences do not exist for each excipient or API?
Q3A: Method Interferences and Alternatives?

Q3B: Validation and necessary elements?

• 3A:
  – ICP-EOS might be a good alternative easier but maybe not for all metals.
  – Xray Fluorescence another possibility. Individual instruments must be evaluated for achieving results before purchase.
  – Knowledge of interferences – false risks are more difficult to validate. Contamination needs to be controlled
  – Validate method for each matrix specificity, linearity, examine interferences

• 3B
  – Spiking very important. Need good lab person who is familiar w/environmental methods.
  – Addressed in validation.
4A: The safety implications of metal impurities depend on the bioavailability of each metal in a dosage form. Many metal impurities found in inorganic excipients are bound inside of an insoluble excipient particle and are not bioavailable. Should the ICH Q3D guideline specify that only bioavailable metal impurities (i.e., acid extractable, etc.) be measured to determine compliance to proposed limits?

4B: Although ICH Q3D is currently targeted at oral and parenteral products, how might establishing these metal impurity limits impact dermal products?
Q4A: Emphasis on bioavailability or amount absorbed?
Q4B: impact on other dosage forms

• 4A:
  – Lab personnel would need good guidance for running simulated gastric testing for bioavailability.
  – Define routes of administration / dosage form / guidance for implementing bioavailability incorporate a guideline time span to come up with info.
  – Bioavailability – yes, makes sense to audience
  – FDA No difficulty of getting bioavailability data. Total gives benchmark
  – Burden of proof is up to the drug product maker
  – Acid leach work for Ag only

• Collecting bioavailability data can be done independent of checking for limits. Offering patents to support lack of bioavailability. Rats & humans study
  – patent # US 2008/0026079 A1
  – patent # US 2008/0008763 A1
• 4B:
  – Dermal – maybe sometime in the future.
• Yes – one opinion. How to define bioavailable? USP monograph can address bioavailability.
• ICH Q3D not likely and change in absence of limits need data. Follow USP.
What types of sample preparation methods are appropriate to ensure metals data reflect only the bioavailable metal and not total metal impurity content?
Q5: Sample Preparation

• Route, dose, methodology
• Take time to develop plan timeline
• There are simulated fluids that may be of use.
• FDA handles as special case
• Run metals test on leached.
• Total metals 1st
• Acid leachable (define media) There is media for applicant
• Bioavailable (simulate bioavailable)
REPORT
Breakout Session C
Excipient Realities & Communication Tools
Session will discuss the sharing of information about metal impurities between makers, users and regulators. Includes discussion of the realities of what can be expected from suppliers and the timing needed for implementation of ICH Q3D.
1A: Will excipient and API manufacturers proactively identify and test key excipients for metals, either routinely or periodically, depending on their control systems?

1B: Will they provide a detailed justification (based on manufacturing process and raw material sources) to help users understand the range of potential metal variability present in excipient products?

1C: Will users be willing to pay excipient manufacturers a premium for this testing?
Q1A: Suppliers

1A

- It is unlikely that excipient suppliers will be able to do this – considering that pharmaceuticals is a very small potion of their market
- It is more likely that risk assessment will be done especially for synthetic materials
- Drug product manufacturers don’t need detailed information from suppliers (regarding their confidential processes) they will want to work with supplier to understand the potential for metals
- Supplier audit; C of A may not be good enough, may have to do more audits.
- Excipient Manufacturers should have qualified suppliers.
  • But currently doesn’t require 27 metals.
- The Q3D limit is for finished product so applying those limits to excipients and API doesn’t make sense since it depends on how much of the ingredient is used and the overall percentage in formulation
- Determine awareness of what metals they might have
Q1B: Providing Justification & Q1C: Costs

1B:
- This gets into proprietary issues. Company A/B or C has cadmium information. This is what they supply don’t want the whole process.
- Tremendously helpful to know what is proprietary if safety issue then may need an agreement with suppliers.
- Analysis should be done first and early on to gather some info

1C:
- There will be cost increases associated with the implementation of Q3D
  - Testing (equipment, method development and validation)
  - Potential for re-formulation
  - Filing costs
  - Excipient producers will likely charge a premium
Q2A: Will excipient and API manufacturers be willing to establish tighter than compendia specification limits for customers requiring lower raw material metal impurity levels to meet their finished dosage form PDE?

Q2B: What excipients are likely to have long-term excursions from normal levels which could impact specification compliance if tighter limits are established?
Q2A: Specifications &
Q2B: Types of excipients & variability of levels

2A:
- Willing but not able. But depends on excipient because some get premium for pharma grade excipients.
- Depends on relationship w/ vendor.
- No - avoid specification creep where levels get lower and lower if safety issue it is one thing but don't want to change spec just to meet most GRAS…used for years.

2B
- Natural products. Mined excipients.
- Variability in levels may cause drug shortages!
- Need to address the situation of Atypical actives (for currently marketed)
  *If cannot comply should be able to use history of use, complaint data etc to justify exemption
- Excursions are not predictable.
  - Mined materials would be expected, but still unpredictable
  - Users will have to explore not only which metals are present/expected. But also low many data points, frequency, etc.
  - Validated methods are not currently being used widely
What options do users have when they cannot get any information on the Q3D metal impurity levels from their excipient supplier?

Test their finished products or incoming materials

- Testing is the option
  - Calculated worst case scenario
  - Discontinue use of excipient
  - Negotiate w/FDA that product (drug) is not fully “USP”
Q4

Should a standardized template be created for drug manufacturers to request metal impurity information on excipients and APIs from their suppliers?

Should IPEC incorporate a standard approach into the Excipient Information Package (EIP) guideline for metal impurities to help ensure transfer of metal impurity information from the suppliers to their customers?
Q4: template?

• Standardized form from IPEC would be helpful.
  – Cannot have 500 different ways of providing this information
• Incorporation into EIP guidance would be best.
• Recommend that there be Q&A rolled out with Q3D guidelines.
• Include method information
• -Where in process is metal introduced
• -Don’t draft a questionnaire until the draft guidelines are finalized
• -Who will be answering questions?
• -IPEC handles APIs? SOCMA?
• -What about raw materials for APIs?
• -Maybe 2 templates
  - 1. Request for excipients
  - 2. APIs request to applies
• -Include method validation
Q5

• Q5A: Given the existence of current unknowns pertaining to actual excipient and API metal levels, what implementation timeline is reasonable for industry to properly prepare?

• Q5B: What impact could Q3D requirements have if implemented too quickly (before appropriate long-term variation levels/data are available for excipients and APIs)?
Q5A: Implementation timeline?
Q5B: Impact of hasty implementation

5A:

- Timeline = willing to implement ICP or get data quickly.
- Validated methods how long will it take?
  - 2-3 mo. /method x 27 metals for each material.
- Realistically could take 5 years to implement even for just new products (since they will be using/relying on existing excipients)
- A statistical model (for method validation) might reduce time (lumping product types)
- If we can use as a screening method is GLP sufficient?

- 2 years to be official for new products, 2 years not be enough
- 7 years for existing products from time Q3D goes to step 2
• Can’t delete <231> until <232>, <233> finalized
• Produce ID/MS can take at least 1 year to produce them more to get up and running
• 5B
  – Drug shortages
  – Drug delays