



## Change Control within a Supplier: Understanding and Knowing your Suppliers and Their World

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### Overview

- n Extractables/leachables
- n Supplier Inputs to Extractable/Leachable Profile – As Delivered
- n Normal Variations Impacting Extractables/Leachables – Supplier Perspective
- n Changes Outside Normal Variation for n-1 Suppliers
- n Supplier Managing Changes
- n Change Control Management Overview
- n Conclusion

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## Extractable and Leachable Definitions

- n **Extractables** – Chemical species that migrate from packaging or other components under appropriate solvent, temperature and time conditions
  - “Exaggerated conditions”
- n **Leachables** – Chemical species that migrate from packaging or other components under normal conditions or use or during stability studies
  - “Normal conditions”

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## Supplier Inputs to Extractable/Leachable Profile – As Delivered

- n **Raw Materials**
  - Multiple sources: risk management
- n **Equipment**
  - Duplicate Equipment
  - Types:
    - n Injection vs. compression
    - n Calendar vs. extruder
    - n Etc.
  - Work input
  - Equipment lubricants

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## Supplier Inputs to Extractable/Leachable Profile – As Delivered

### n Manufacturing Process

- Time
- Temperature
- Pressure
- Speed
- Etc.

### n Processing Aides

- Partitioning agents
- Mold release
- Detergents
- Silicone

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## Supplier Inputs to Extractable/Leachable Profile – As Delivered

### n Residual/Reaction Products

### n Finish Goods Packaging Materials

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## Customer Inputs to Extractable/Leachable Profile – As Used

### n Equipment

- Wear: work input
- Equipment lubricants
- Type
  - n Washer/Dryer
  - n Sterilizer

### n Manufacturing Process

- Time
- Temperature
- Pressure

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## Customer Inputs to Extractable/Leachable Profile – As Used

### n Processing Aides

- Detergents
- Silicone

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## Normal Variations Impacting Extractables/Leachables Supplier Perspective

- n **Raw Material (ingredients, processing aides)**
  - Multiple sources (n-2 Suppliers)
    - n Different starting materials
    - n Different processing steps
    - n Manufacturing approved process windows
    - n Specification tolerances
  - RM (n-1/n-2) non-pharmaceutical grade
- n **Equipment**
  - Multiple equipment
    - n Same type – age, rebuild
    - n Different type – size, configuration

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## Normal Variations Impacting Extractables/Leachables Supplier Perspective

- n **Equipment (continued)**
  - Different types
  - Work Input
    - n Age and type
      - Stress
      - Strain
      - Shear
      - Heat
      - Time
  - Equipment lubricants
    - n Seal wear

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## Normal Variations Impacting Extractables/Leachables Supplier Perspective

### n Manufacturing Process

- Parameters not strict set-point
- Process windows
  - n Plus/minus time
  - n Plus/minus temperature
  - n Plus/minus pressure
  - n Plus/minus speed
  - n Plus/minus change over time

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## Normal Variations Impacting Extractables/Leachables Supplier Perspective

### n Processing Aides

- Partitioning agents
  - n Strippable films
    - Slip agents
    - Plasticizers
  - n Stearates, talc, etc.
    - Plus/minus quantity
    - Uniformity
  - n Mold release
    - Quantity
    - uniformity

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## Normal Variations Impacting Extractables/Leachables Supplier Perspective

### n Processing Aides (continued)

- Partitioning agents
  - n Detergents
    - Plus/minus quantity
    - Dwell time
    - Solubility
    - Adhesion
  - n Silicone
    - Plus/minus quantity
    - Dispersion
    - Dwell time
  - n Absorption
  - n Transfer

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## Normal Variations Impacting Extractables/Leachables Supplier Perspective

- n Residual/Reaction Products
  - Interaction of all of the above results in a normal "dynamic" extractable/ leachable profile as packaged.
- n Finish Goods Packaging Materials
  - Antioxidants
  - Antiozonants
  - Slip agents
  - Ink components
  - Label Adhesives

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## Normal Variations Impacting Extractables/Leachables Customer Perspective

- n Same as those for supplier
- n Compounded by each component in the container/closure system that contacts the drug product
- n Drug product itself
- n Reaction of the drug product with the container/closure component

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## Changes Outside Normal Variation for n-1 Suppliers

- n External
  - Suppliers' mergers
  - Suppliers' product rationalization
  - Suppliers' lean activities
    - n Efficiency,
    - n Waste reduction,
    - n Elimination of non-value added steps
    - n Etc.
  - Force majeure
  - Suppliers' quality improvements
  - CAPA

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## Changes Outside Normal Variation for n-1 Suppliers

### n Internal

- Rationalization
- Capacity issues
- Risk mitigation
- Lean activities
  - n Efficiency,
  - n Waste reduction,
  - n Elimination of non-value added steps,
  - n Etc.
- Quality improvements/Six Sigma programs
- CAPA

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## Changes Outside Normal Variation for n-1 Suppliers

### n Changes outside normal variation in the suppliers' operation, have the potential to change the extractable/leachable profile of a supplier's component

- Raw materials suppliers
- Raw materials suppliers' processes
- Raw materials
- Sub-contractors
- Facilities/Utilities
- Manufacturing sites

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## Changes Outside Normal Variation for n-1 Suppliers

- n Manufacturing processes
- n Manufactured components
- n Manufacturing/testing equipment
- n Laboratory processes/procedures
- n Test methods
- n Components' documentation  
(specifications, filings, drawings, etc.)
- n Computer hardware/software packages  
affecting product

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## Supplier Managing Changes

- n OINDP manufacturers and suppliers  
should discuss, understand, and agree on:
  - What is the extractable profile specification
  - What method(s) are to be used to determine  
the extractable profile
  - What constitutes a significant change
  - What type of changes require notification
  - What type of changes require notification and  
approval
- n Terms agreed should be reflected in a supply  
agreement and/or quality agreement

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## Supplier Managing Changes

- n Changes need to be adequately controlled through a change control process
  - Proceduralized
    - n Identification,
    - n Documentation,
    - n Appropriate review
    - n Approval of changes
  - Independent group, such as the quality unit, should have responsibility and authority for management/approval of changes

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## Change Control Management Overview

- n Define change
  - Title
  - Type
  - Class
  - Description
  - Affected process
  - Initiator
- n Change request reviewed for approval to proceed
  - Affected area(s)
  - Quality Assurance

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## Change Control Management Overview

- n Change requested routed to defined reviewers for assessment and approval including:
  - Route to additional reviewers/approvers
  - Addition of needed supporting action items and/or change control "children"
    - n Include assessment of extractables/leachables
  - Feedback mechanism
    - n Document changes
    - n Rejection of change

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## Change Control Management Overview

- n Quality assurance reviews completed review request and provides final disposition to execute/not execute changes
- n Change control execution
  - Implement change
  - Complete defined action items
  - Complete defined change control children

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## Change Control Management Overview

- n Completed change control and associated documentation forwarded for final disposition
  - Others
  - Quality Assurance - last

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## Conclusions

- n Normal manufacturing operation inclusive of raw materials is variable in itself
  - Multi-manufacturing steps with defined processing windows adds complexity to the extractable/leachable profile due to numerous matrix window combinations
- n Multi-component OINDP container/closure system in combination with OINDP raw materials and manufacturing process adds additional layers of complexity to extractable/leachable profile

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## Conclusion

- n Changes throughout the supply chain must be documented and managed by the initiator and recipient
- n Each recipient in the supply chain adds layers of complexity to the overall extractable/leachable profile

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## Questions

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