

Variability of Extractable / Leachable Components of Flexible Packaging Materials

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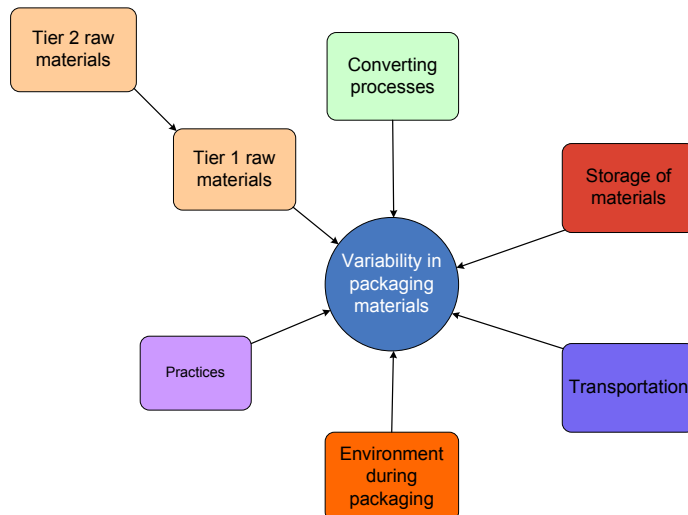
Variability of E/L Components

1. Sources of variability within flexible packaging materials
2. Models for interaction between drug manufacturers and component suppliers for setting extractable limits
3. Upstream Investigation of extractables for packaging manufacturers
4. Strategies for Dealing with Upstream Suppliers



Sources of Variability

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Sources of Variability

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Possible Contaminants within Flexible Packaging Materials

- Residual solvents (processing, storage, transportation)
- Un- or under-reacted polymeric components (Tier 1 or 2 suppliers)
- Antioxidants (Tier 1 or 2 suppliers, processing)
- Processing aids (Tier 1 or 2 suppliers, processing)
- Lubricants (Tier 1 or 2 suppliers, processing)
- Degradants (Tier 1 or 2 suppliers, processing, storage, transportation)
- Reaction products (Tier 1 or 2 suppliers, processing)



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Models for Interaction with Suppliers

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Model 1: Minimal interactions with packaging suppliers

1. Select materials for packaging application based on functionality.
2. Packaging materials screened for extractables, identifying all possible
3. Quantitative investigations conducted, extraction methods identified
4. Tox (safety) investigations conducted to identify risk compounds
5. Targeted analyses for several lots of material to establish base lines
6. Establish variability for risk materials within components
7. Negotiate limits for risk compounds with the FDA
8. Begin testing to limits



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Models for Interaction with Suppliers

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Model 1: Minimal interactions with packaging suppliers

Issues with this model:

- 1) No control of risk compounds other than go / no go criteria
- 2) No actual leachable studies performed
- 3) No collaboration with packaging upstream suppliers, thus limited to no understanding of roles for risk materials
- 4) All responsibility lies on drug manufacturer for policing materials



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Model 2: Partnering between Drug and Packaging Manufacturers Using Unknown Materials (simplified)

1. Pharma company and packaging manufacturer discuss application and select packaging materials based on functionality – perform risk assessment together
2. Screening studies done to identify extractable compounds (with amounts) and match these to raw material sources (working with upstream suppliers).
3. Leachable studies performed on packaged drug product and placebo, correlation with extractables.
4. Tox (safety) assessments done on potential risk compounds; decide which should be monitored on an ongoing basis, which materials have unacceptable materials or limits (reduce to safe levels?).
5. Tailor or change raw materials if necessary to minimize risk by working with upstream suppliers, repeat steps above, if necessary
6. Establish acceptance criteria for L/E



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Model 2: Partnering between Drug and Packaging Manufacturers Using Unknown Materials

Issues:

- 1) Extended investigation times and costs: establishing which analytical methods are suitable
- 2) Variability in test materials: important compounds might be below AET in test materials, but variability puts them above AET in subsequent materials
- 3) Possible need to modify or change raw materials downstream after initial studies done



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Model 3: Partnering between Drug and Packaging Manufacturers Using Known Materials

- 1) Packaging manufacturer performs controlled extraction studies on materials to construct database for materials selection.
- 2) Packaging supplier works with upstream vendors to establish high/low limits on extractables.
- 3) Packaging materials are selected based not only on material functionalities, but also on extractable content.
- 4) Depending on package design, selected extractable/leachable studies are conducted to verify content and look for leachables for the given drug/placebo.
- 5) Tox (safety) assessments performed, decide which should be monitored on an ongoing basis, which materials have unacceptable materials or limits (reduce to safe levels?).
- 6) Tailor or change raw materials if necessary to minimize risk by working with upstream suppliers, repeat steps above, if necessary
- 7) Establish acceptance criteria for L/E



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Models for Interaction with Suppliers

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Model 3: Partnering between Drug and Packaging Manufacturers Using Known Materials

Issue:

Even with more upfront work by packaging suppliers (prior to selection of materials), entire L/E protocol needs to be followed.



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Upstream Investigation of Extractables for Packaging Manufacturers

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- Most customers (pharma manufacturers) have their own extractable / leachable protocol, making it difficult to generate data that is universally acceptable.
- Different customers have a) different interpretations of extractable data, b) safety concerns, and c) opinions about the rigor needed for extraction
- Extractable studies must be carried out on both completed structures and also raw materials.
- Extractable studies are expensive and time-consuming.
- Investigation of variability within components can either be based on historical data or on high/low batches from upstream vendors



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Strategies for Dealing with Upstream Suppliers

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- **Awareness** – Make your suppliers aware that their materials will be used in sensitive applications.
- **Partnership** – Devise strategies for control of possible risk materials upstream with the raw materials suppliers, not in spite of them.
- **Correlation** – Understand the relationship between what is added to the raw materials and what possible extractable amounts are.
- **Limitation** – Explore high and low extractable limits based on the addition of compounds with upstream suppliers.
- **Control** – Develop control limits for the risk compounds after analysis correlation with extractables



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Strategies for Dealing with Upstream Suppliers

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Reality when Dealing with Raw Materials Suppliers

- Many will not cooperate because they say their products are not designed with sensitive applications in mind, mainly because of liability issues.
- Some suppliers will not share information, even for regulatory purposes.
- Some suppliers will not participate in upstream materials studies.
- There are materials that simply cannot be controlled upstream.
- Many will not cooperate because they say their products are not designed with sensitive applications in mind, mainly because of liability issues.
- Who pays for out of spec material???



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