



Material Variability – a Device Manufacturer's Perspective

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Material Variability – Intrinsic/Intentional



- Same formulation, same process, same site!
 - The drug/device development process quickly ties down the details associated with supply of any material in fine detail.
 - From the point that any stability work, or worse clinical work, has been conducted changes are very difficult – often impossible.
 - The stability of the manufacturing 'arrangements' needs to persist over many years (and ultimately decades)
 - Of course the world moves on, the commercial imperatives for certain grades change, and the manufacturing locations are under constant review and changes.
 - Off-takes into the Pharma business are often very small.
- So there is a need to minimise variability, by design, by selecting grades of materials which are 'commercially stabilised' by being 'mainstream' to the supplier.
- Often the esoteric needs of device or product design calls for specialist materials – need to check carefully that this is a good long term option.



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Material Variability – Intrinsic/Intentional



- Simplicity of formulation
 - Maintaining the status quo (formulation, process, site etc) across a wide variation of ingredients is a challenge.
 - The simpler the formulation the easier.
- Align materials to international standards (particularly applicable to aluminium grades used for foils, MDI cans etc) – as the standard itself will inhibit change.
- Change control
 - Changes are inevitable
 - A robust change control agreement with the supplier is essential
 - More important a good dialogue and understanding of what constitutes a relevant change.



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Material Variability – Intrinsic/Intentional



- Material Stability
 - Long shelf lives are essential.
 - Shelf life as a material, as a component, and as a constituent part of the product are all additive.
 - Hence 2 years as material, 2 years as a device/component and 3 years in the final product means 7 years.
- Pharmaceutical polymers/rubbers are rarely dual sourced
 - Extractables/leachables, stability, tox and performance issues in the final product means that most 'complex' materials are single sourced.
 - If the supply of a single sourced polymeric material is threatened, the typical response is to perform a 'one time buy' to cover the development time for an alternative.
 - A long shelf life is essential for 'one time buy' approaches to work.
- Hence highly stable products with minimal variation over time are an important business continuity consideration.



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Material Variability – Medical grades



- Many polymer suppliers offer 'Medical Grades'
 - Medical grades are often aligned with agreements on stability/change control.
 - Suppliers have a good understanding of pharmaceutical requirements
 - DMF support may be provided
 - Improved control over input ingredients (antioxidants/lubricants etc)
 - Some suppliers offer a 'mid cut' of the large synthetic runs making the base resin
- However, a 'Medical Grade' branding does not in itself provide product continuity over and above the commercial viability of the grade/manufacturing line/ manufacturing site.



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Material Variability - Control



- Most assessment techniques (and Pharmaceutical control processes) are based on looking for known components, ingredients, break down products, synthetic/manufactured impurities.
- Analytical techniques are comparative, and therefore you need reference standards – and hence need to know what's in the material.
- So....confidentiality is always a problem
 - Metal components – cleaning, anodising processes are highly confidential
 - Springs : the lubricant (soaps) used on wire is where the competitive edge resides for the wire suppliers – again highly confidential
 - Polymer suppliers ingredients and formulations are rarely released.
- Consequently developing the control strategy is difficult.
- Control strategies developed from extractable work.



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Material Variability - Control



- PQRI approach and guidance on extractables and leachables a huge step forward
 - Particular establishment of thresholds where compounds are deemed 'safe' without explicit identification.
- Much better to be able to control at input material level. FDA are generally asking for E&L control on moulded components.



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Material Variability – Unintended.



- Pharmaceutical companies are well versed in line clear downs
- Clear downs/cleaning typically involve wet cleaning process (water/ethanol etc)
- Cleaning processes are validated – and experimentally proven to work.
- Polymer material suppliers will typically use 'dry' cleaning systems (blowing, brushing). Some of the ingredients will be 'active' entities eg antioxidants, surfactants etc
 - There needs to be an understanding that pharmaceutical levels of product segregation are not achieved.
 - 'Visually clean' is a typical clean down standard.
- Transportation of polymers is a risk area. Often standard shipping containers are used. Need to check lining materials or offload arrangements.
- If 'tankers' are used it is often difficult to inspect for cleanliness.
- Physical parameters (granule size and dust levels) very important



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Material Variability – Control strategies



- Supplier Understanding of End product Use – as you move up the supply chain staff get more removed from the final product
 - Bepak has performed Town Hall style presentations to the work force of our key suppliers
 - Invite shop floor staff from suppliers to Bepak
 - Supplier days
- Understanding of Change control – an employee of a metal component manufacturer is unlikely to know that a change in detergent brand used for a degreasing operation could have a catastrophic effect.
 - ‘Understanding’ cannot be created through SOPs
 - SOPs can never be comprehensive when it comes to change control
 - Ideally establish a collective understanding, some guidelines....and some thresholds



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Material Variability – Control strategies



- Understand and discuss the ‘tension’ that exists between Continuous improvement activity and change control
 - Establish cross company and functional Continuous Improvement Teams.
- Work with suppliers to create ‘cells’ or ‘areas’ dedicated to Pharma/Med device supply
 - Often the supplier is pleased to develop their offering in this area, as it opens up access to other business in this sector
 - Medical Grade branding
 - External certification
- Consider transportation issues for bulk materials
 - Supplier packaged safest, however may not be commercially acceptable for very large volume materials (where silos and tankers/containers are used)



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Material Variability – Control strategies



- Plus all the usual activities:
 - Audits
 - Metrics
 - CAPA/Complaints management
 - Incoming QC (dimensional, visual, FTIR, Melt Flow etc)
 - Specifications
 - On line measurements???



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Summary



- Variability needs to be managed at a number of levels
 - On a macro scale over the years
 - On a batch by batch basis
 - Variability happens on an intended basis – and change management is the key
 - Variability happens for commercial reasons – and product viability is the key
 - Variability is accidental, and standard quality management techniques are required
- Pharmaceutical Products are very intolerant of changes, changes which are almost inevitable
- All parts of the supply chain need to stay constantly engaged, and hopefully one step ahead!



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End

