Common Deficiencies-OPQ Considerations

How to Resolve Current Challenges in ANDAs in Transdermal Delivery Systems (TDS)
Complex Generic Drug Product Development Workshop

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Issues Associated with TDS

Clinical Concern	Quality Aspects
Adhesion to skin	• **Selection and quality control of raw materials** *(particularly adhesives)*
Irritation/Sensitization of skin	
Effectiveness/Bioequivalence	• Uniformity *(robust manufacturing process)* • In vitro release testing • **Stability** *(comparative clinical endpoint studies typically are performed on fresh batches, not on aged batches)* – Adhesive property change and cold flow – Drug crystallization – Delivery profile change – Drug-substance/excipient migration
Safety	• **Impurities of toxicological relevance** – **Adhesive impurities** (monomers, catalysts, crosslinkers, etc.) – **Extractables and leachables** • **Residual drug** *(accidental or environmental exposure, abuse)* • Heat influence *(e.g., application of a heat pack)* • Proper labeling of each system
Patient use	• Release liner peel • **Product design**

Quality Issues Associated with TDS

Presentation Overview

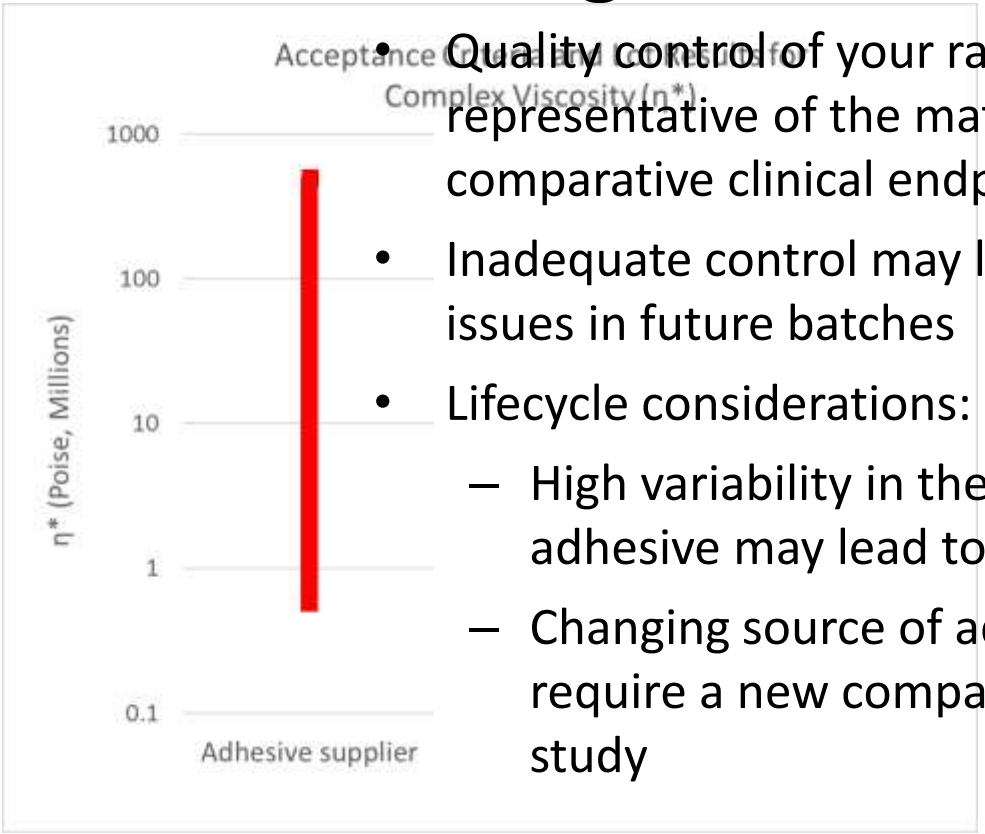
Selection and Quality Control of Raw Materials

- Transdermal and topical delivery systems (TDS)
- Not required to be Q1/Q2
  - Qualitatively different
  - Quantitatively different

Selection and Quality Control of Raw Materials

UNDERSTAND YOUR RAW MATERIALS	
Clinical Concern	**Quality Aspects**
• Performance: – Adhesion – Drug delivery (Effectiveness) • Safety: – Toxicity – Irritation and sensitization	• Adhesives – "Pharmaceutical grade" typically not offered – Concerns: • Rheological properties • Impurity profile • Lot-to-lot variability • Pouch stock, membranes/films, ink – Concerns: • Extractables/Leachables

Case Study: Inadequate Adhesive Rheological Control



- Quality control of your raw material should be representative of the material used for the comparative clinical endpoint study
- Inadequate control may lead to performance issues in future batches
- Lifecycle considerations:
  - High variability in the quality of supplied adhesive may lead to supply issues
  - Changing source of adhesive likely would require a new comparative clinical endpoint study

Case Study: Control of Adhesive Impurities

Assessment of the Adhesive DMF

DMF ###
ADHESIVE246

S.3

Potential impurities:

- Monomer J
- Monomer B
- Monomer O
- Initiator HE
- Crosslinker
- …

Demonstrates lack of communication

≠

Assessment of P.4 in the ANDA

ANDA ####
TDS Product

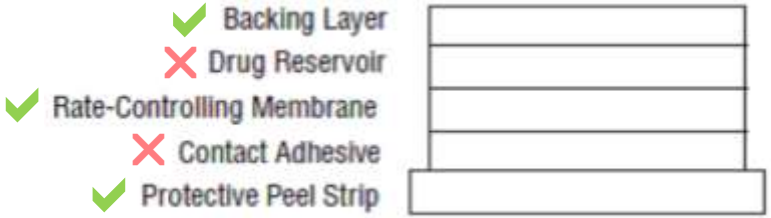
P.4

Control for adhesive impurities:

- Monomer B
  - NMT 10000 ppm

Extractables and Leachables (E/Ls)

- Potential sources of E/Ls:
  - Pouch stock ✔
  - Backing membrane (with ink)
  - Release liner
  - Internal membranes (e.g., release-controlling membrane or scrim)
  - *Note: Adhesive impurities are outside the scope of E/L studies*



- Ask suppliers about potential E/L impurities
- Follow USP<1663> and <1664>

  For AET calculation: Assume the patient is exposed to all impurity within a single day, not slowly throughout the intended wear period

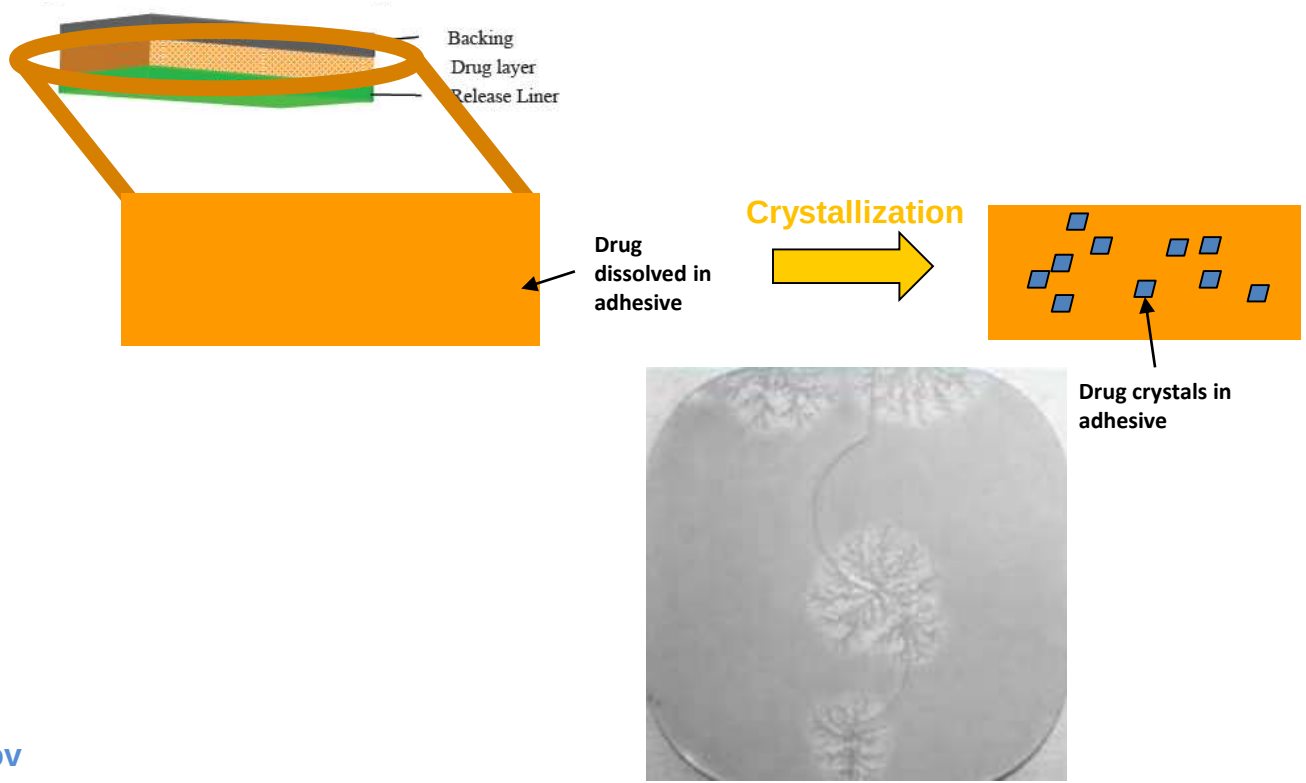
Quality Considerations: Selection and Control of Raw Materials

- A poorly chosen supplier may:
  - Not communicate all impurities to the applicant
  - Produce material with high levels of impurities
  - Not adequately control critical material attributes (CMAs)
- An applicant should understand:
  - Raw material CMAs
  - How CMAs affect finished product critical quality attributes (CQAs)

Stability Issues

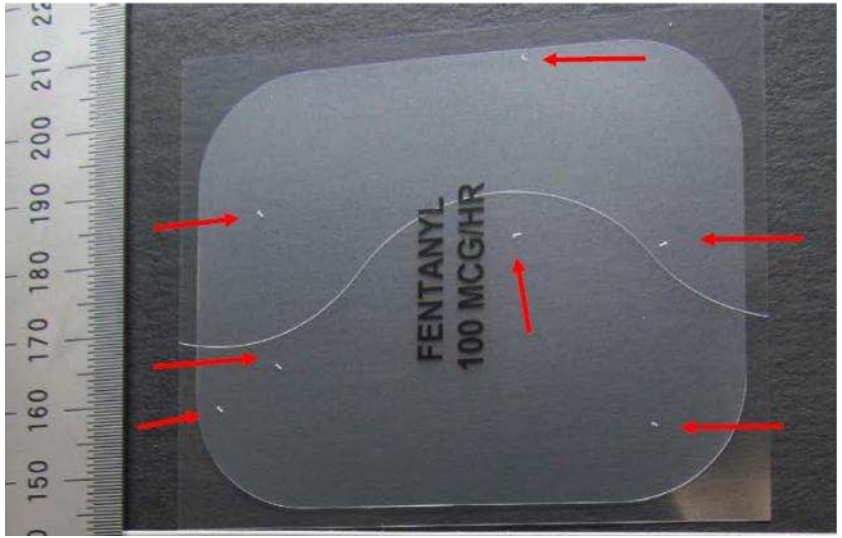
ANTICIPATE POTENTIAL STABILITY ISSUES	
Clinical Concern	**Quality Aspects**
• Performance: – Adhesion – Drug delivery (Effectiveness)	• Changes in test results (in vitro adhesion, drug release, appearance, phase changes, etc.) upon product "aging" • Need thorough characterization of: – "Fresh" product – Aged/stressed product • Concerns: – State of the product during comparative clinical endpoint testing? – Are the changes clinically meaningful?

Case Study: Crystallization



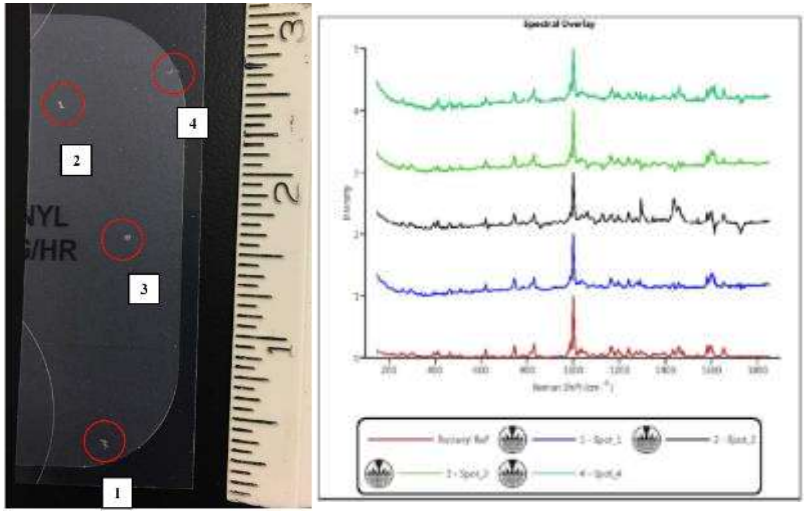
Case Study:
Fentanyl TDS Crystallization

- Drug product samples sent to FDA lab
- Lab findings: 12 batches had crystals visible with the naked eye



Crystallization of Drug Substance

- Crystal identification
  - Raman microscopy
  - Crystals are drug substance (fentanyl)
- Concern: Do the crystals affect…
  - Drug delivery?
  - Adhesion?



Quality Considerations: Potential Stability Issues

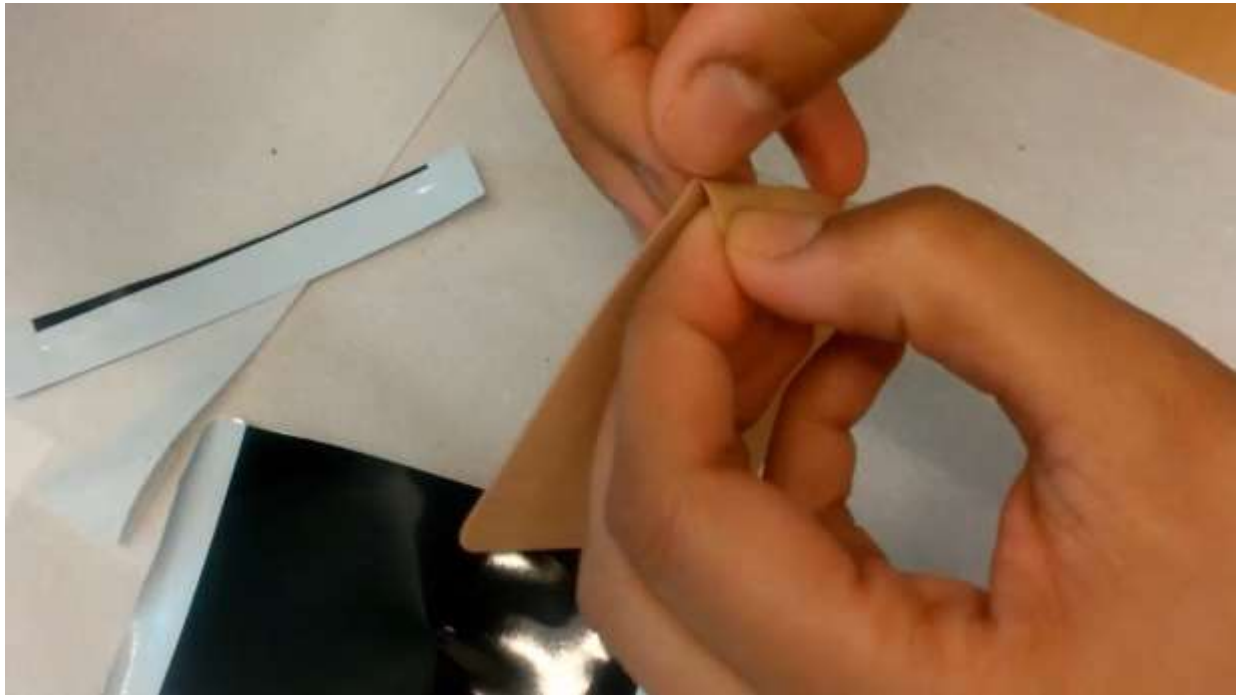
Understand:

- Potential stability issues
- Effects on shelf life
- How quality changes may affect clinical performance

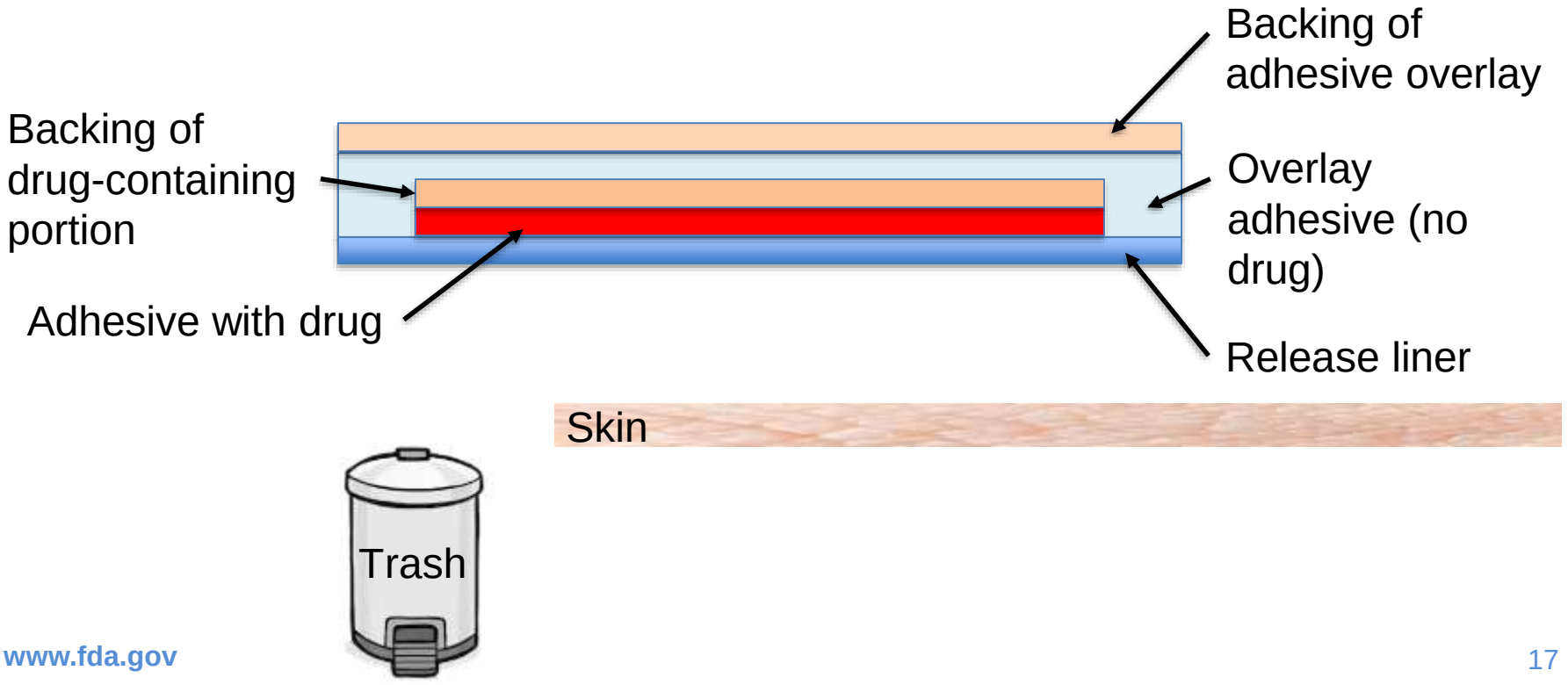
Design Issues

DESIGN/FORMULATE PRODUCT WITH END USER IN MIND	
Clinical Concern	**Quality Aspects**
• Patient Use • Safety	• Design should consider patient use and safety • Concerns: – Potential issues for the patient to apply the product? – Disposal concerns? – Residual drug level minimized?

Inadequate Interlaminar Adhesion



Intended Patient Administration



Potential Clinical Issue: Efficacy and Safety Concerns

Overlay adhesive (no drug)

Potential unintentional exposure!

Skin

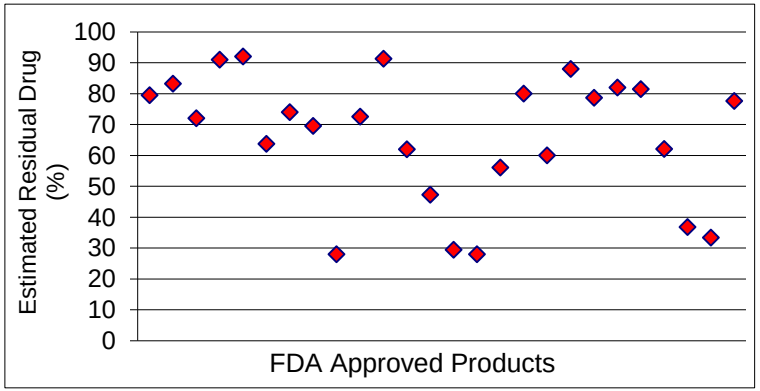
No drug delivery to patient!

Residual Drug

FDA Residual Drug Guidance:

The amount of residual drug substance:

- Has a significant potential to impact quality, efficacy, and safety (including abuse potential)
- Should not exceed that of similar FDA-approved products
- Should be "minimized consistent with the current state of technology"



FDA Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems, August 2011

Quality Considerations: Product Designed/Formulated with End User In Mind

The design and formulation of the product should:

- Facilitate correct product use by the patient/caregiver, and
- Mitigate safety issues associated with the product

Concluding TDS
Quality Considerations

- Quality issues associated with clinically relevant concerns may require:
  - Changes to product formulation, design, or manufacturing process
  - Manufacture of new batches
  - New stability studies
  - New comparative clinical endpoint studies
- Thoroughly characterize and understand the quality of batches used in your comparative clinical endpoint studies (including raw materials, manufacturing process, and stability)
- Future commercial product should perform:
  - as represented in your submitted comparative clinical endpoint studies, and
  - as indicated in the labeling

Acknowledgements

OLDP

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Jason Rodriguez *(OTR/DPA)*

David Keire *(OTR)*

Common Deficiencies: Rheological Control

- We recommend that you tighten your acceptance criteria for viscosity of ADHESIVE246 to be consistent with the quality of the adhesive lot used to manufacture your clinical batch 987654X.
- Tighten your in-vitro adhesion testing acceptance criteria to be consistent with the results from your clinical batch 987654X.
- We are concerned that the rheological and other raw-material properties of the adhesive used in the pivotal clinical trial may not be consistent with historical or future adhesive lots. We recommend you request historical rheology values from the adhesive manufacturer to better understand the adhesive manufacturer's process capabilities and the potential influence on the finished product, and assess the need to establish or tighten internal controls for the raw material.

Common Deficiencies: Control of Adhesive Impurities

- Please consult with your adhesive manufacturers about adhesive impurities (including catalysts, initiators, and side-products, such as tetramethyl succinonitrile (TMSN)). Test the final laminate for residual monomers and other adhesive impurities and provide acceptance criteria with justification for such impurities if of toxicological relevance.
- Frequent adhesive DMF deficiency:

  Provide a list with chemical structures of all known residuals (monomers, solvents, and catalysts), by-products, and other impurities (including carryover impurities from the starting materials) that could be present in the final polymer. Discuss the related risk and your control strategy to minimize the risk. In addition, demonstrate that you have communicated the potential presence of these impurities to each referencing ANDA applicant so that they can adequately control for these impurities in their final drug product. You may demonstrate communication of this information by providing an updated CoA that contains this information or providing a copy of a letter sent to each referencing ANDA applicant with this information.)

Common Deficiencies: Control of Impurities from Other Components

- Perform extractable and leachable studies to provide a thorough understanding of potential impurities originating from the non-adhesive and non-API components (such as backing, release liner, rate-controlling membranes, ink, and pouching). … We recommend that you contact the suppliers of your drug-product components to obtain information regarding any potential impurities. Your studies should be consistent with the approach described in USP <1663> and <1664>.
- We acknowledge that you provided information on extractables and leachables in your application. However, please note that your calculated Analytical Evaluation Threshold (AET) and Qualification Threshold (QT) in your extractables-and-leachables report should be calculated with the assumption that the product user is exposed to all leachable impurity within a single day and not gradually over the course of the multi-day wear period. Recalculate the AET and QT and submit revised study results per the new thresholds.

Common Deficiencies: Control of Impurities in General

- Please note that the MDD for TDS products should be the same as the total drug content in the maximum number of applied systems, regardless of the intended drug delivery rate or wear period. (I.e., if a TDS with a 7-day wear period has 7 mcg of unknown impurity, it is inadequate to assume exposure to that impurity at a rate of 1 mcg/day; instead, it should be assumed that the patient is exposed to all 7 mcg in a single day.)

Common Deficiencies: Product Understanding and Stability Risks

- Discuss the homogeneity of the components within the adhesive matrix, as well as the potential for phase separation or movement of a dispersion to occur throughout the shelf life of the drug product. A full understanding of all components in the drug product, including the physical state and location of the drug substance within the adhesive matrix (such as in a dispersed system versus completely dissolved in the matrix), and any potential changes to the homogeneity of the matrix over the proposed shelf life or between unique batches is recommended to support adequate product quality. Useful tools to support your discussion may include (but are not limited to) confocal microscopy, light microscopy, SEM imaging and Elemental Mapping (SEM-EDX) of the cross-section and surface of the drug product at manufacture and throughout stability as well as across multiple unique batches.

Common Deficiencies: Product Understanding and Stability Risks

- Establish a test and acceptance criteria for cold flow to be used at release and on stability. Include assessment of cold-flow by a combination of quantitative and qualitative methods. Appearance criteria can assess potential use issues caused by cold flow if systems are difficult to remove from pouches, if release liners detach from the adhesive matrix during attempted removal due to cold flow adhering the backing membrane to the pouch, as well as adhesive residue transferred to the pouch after removal of the system. A quantitative cold flow method captures the degree to which cold flow extends beyond the perimeter of the backing membrane. Evaluate all lots on stability for cold flow using the established cold flow method, justify the proposed acceptance criteria, and discuss the impact of the proposed criterion on product quality and cold-flow–use-related concerns (e.g. potential for clothing to remove TDS from body or TDS transfer due to a tacky ring, unintentional drug exposure due to adhesive transfer to packaging, etc.).

Common Deficiencies: Product Understanding and Stability Risks

- Establish a test and acceptance criteria for the absence of crystals in the drug product to be used at release and on stability. Microscopic and photometric methods are preferred rather than a simple visual count.
- As crystal formation or crystal growth of the drug substances in the drug product throughout stability is a concern, perform stability challenging studies such as temperature excursions, freeze/thaw, photostability, and/or crystal seeding


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