

Quality by Design
for
Topical Dosage Forms

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Therapeutic Equivalence

- Therapeutic Equivalents
 - “have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling”
- Pharmaceutical Equivalents
 - “(a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity”
- Bioequivalence
 - “the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses “
- Current Practice
 - Pharmaceutical Equivalence + Bioequivalence
= Therapeutic Equivalence

Why Does Pharmaceutical Equivalence Matter?

- User experience and expectation
- Supports the conclusion of Therapeutic Equivalence based on a bioequivalence study
 - Pharmacokinetic or pharmacodynamic bioequivalence studies in healthy subjects
 - Extrapolation from a small group of healthy subjects to a broad patient population
 - Clinical endpoint equivalence studies in patients
 - Not sensitive to formulation differences
 - Creams and ointments could be the same
 - Extrapolating equivalence evaluated for one clinical indication to another

The Future of Pharmaceutical Equivalence

- Current definition of Pharmaceutical Equivalence is the first step toward quality by design
 - same drug, same strength, same dosage form
- 21st Century Paradigm
 - Designed to be equivalent (Quality by Design)
+ Demonstrate bioequivalence (Verify by in vivo testing)
= TE

Ensure ANDA Quality

Current Paradigm	Enhanced Paradigm
Pharmaceutical Equivalence	Quality by Design
+ Bioequivalence	+ Verified by Testing
= Therapeutic Equivalence	= Therapeutic Equivalence

Current Issues

- For topical products there are complex issues related to Pharmaceutical Equivalence
- A set of examples
 - What differences in formulation are appropriate?
 - Change of solvent
 - hydrophilic or lipophilic base
 - Water content
 - Are two products the same dosage form?
 - What indications should be used for clinical equivalence studies?

Implications for ANDA Sponsors

- Long Approval Times
 - Internal discussion and meetings
 - Challenges by RLD sponsors
 - Correspondence
 - Citizen Petitions
 - Ask ANDA sponsors for more information to resolve issues (multiple review cycles)
- More Product Development information in ANDA may help OGD be more efficient

Product Development Reports

- Harmonization Efforts (ICH CTD, ICH Q8) describe a product development report
- Not obvious or clear how this should apply to ANDA sponsors
- It is an opportunity and the only existing mechanism to
 - justify rational specifications
 - emphasize quality by design

Share with FDA

- Common Technical Document
 - 2001 Guidance for Industry
 - <http://www.fda.gov/cder/guidance/4539Q.htm>
 - section 3.2.P.2 Pharmaceutical Development
 - “The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application.”

Share With FDA

- ICH Q8 Pharmaceutical Development
 - “The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches, and risk management, to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle of a product. The guideline also indicates areas where the provision of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The Pharmaceutical Development section is intended to provide a more comprehensive understanding of the product and manufacturing process for reviewers and inspectors.”

Design for Equivalence

- Mechanism of Release may be different
 - must produce equivalent rate and extent of absorption
 - release rate may not control absorption rate
- Excipients may be different
 - differences must be understood
 - IIG limits are starting point
 - No new interactions

Design for Equivalence

- Quality by design for generic is to design a product to be equivalent
- What does design for equivalence mean for generic topical products?
 - Q1 and Q2 equivalent products
 - Products that have Q1 and Q2 differences
 - Dosage form classification

Q1 and Q2 Definition

- Classify product similarity
 - Q1: Same components
 - Q2: Same components in same concentration
 - Q3: Same components in same concentration with the same arrangement of matter (microstructure)

Q1 Q2 Q3 Identical

- Q3 identical products are bioequivalent
 - Example: Topical solutions
- For formulations more complex than solutions direct demonstration of Q3 equivalence is a challenge

Q1 and Q2 Identical

- Only potential differences are in Q3
- Require evaluation of
 - Rheology
 - In vitro release (diffusion cell)
- Are in vitro tests sufficient to ensure BE?
 - Concerns are potential Q3 differences due to the manufacturing process
 - In vitro tests are the best evaluation method for manufacturing quality

Differences in Q1 and Q2

- When products differ in Q1 and Q2 dosage form classification can be a barrier to generic competition
- Q1 and Q2 differences may be required because of formulation patents
- Dosage form classification is uncertain

Possible Methods to Classify Topical Products

- Use whatever the sponsor claims as long as it is consistent with the traditional definitions
- Side by side physical examination
- Use an empirically derived quantitative decision tree
- Expect the sponsor to justify their formulation development

CDER Data Standards Definitions

- [CDER Data Standards manual](#)
 - Cream
 - A semisolid dosage form containing one or more drug substances dissolved or dispersed in a suitable base; more recently, the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.
 - Ointment
 - A semisolid preparation intended for external application to the skin or mucous membranes.

SUPAC-SS Definitions

- SUPAC-SS Guidance
 - Cream
 - Semisolid emulsions that contain fully dissolved or suspended drug substances for external application.
 - Ointment
 - An unctuous semisolid for topical application. Typical ointments are based on petrolatum. An ointment does not contain sufficient water to separate into a second phase at room temperature. Water soluble ointments may be formulated with polyethylene glycol.

USP Definitions

- Cream
 - Creams are semisolid dosage forms containing one or more drug substances dissolved or dispersed in a suitable base. This term has traditionally been applied to semisolids that possess a relatively fluid consistency formulated as either water-in-oil or oil-in-water (emulsions). However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.
- Ointment
 - Ointments are semisolid preparations intended for external application to the skin or mucous membranes..Ointment bases recognized for use as vehicles fall into four general classes: the hydrocarbon bases, the absorption bases, the water-removable bases, and the water-soluble bases. Each therapeutic ointment possesses as its base a representative of one of these four general classes

Problem with Traditional Dosage Form Classification

- Not consistent across FDA
 - none are “official”
- Not quantitative (opinion based)
- Can overlap (non exclusive)

FDA Research

- Presentation to prior ACPS meetings
- Surveyed existing products and devised a classification scheme
- Recent publication



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Topical drug classification[☆]

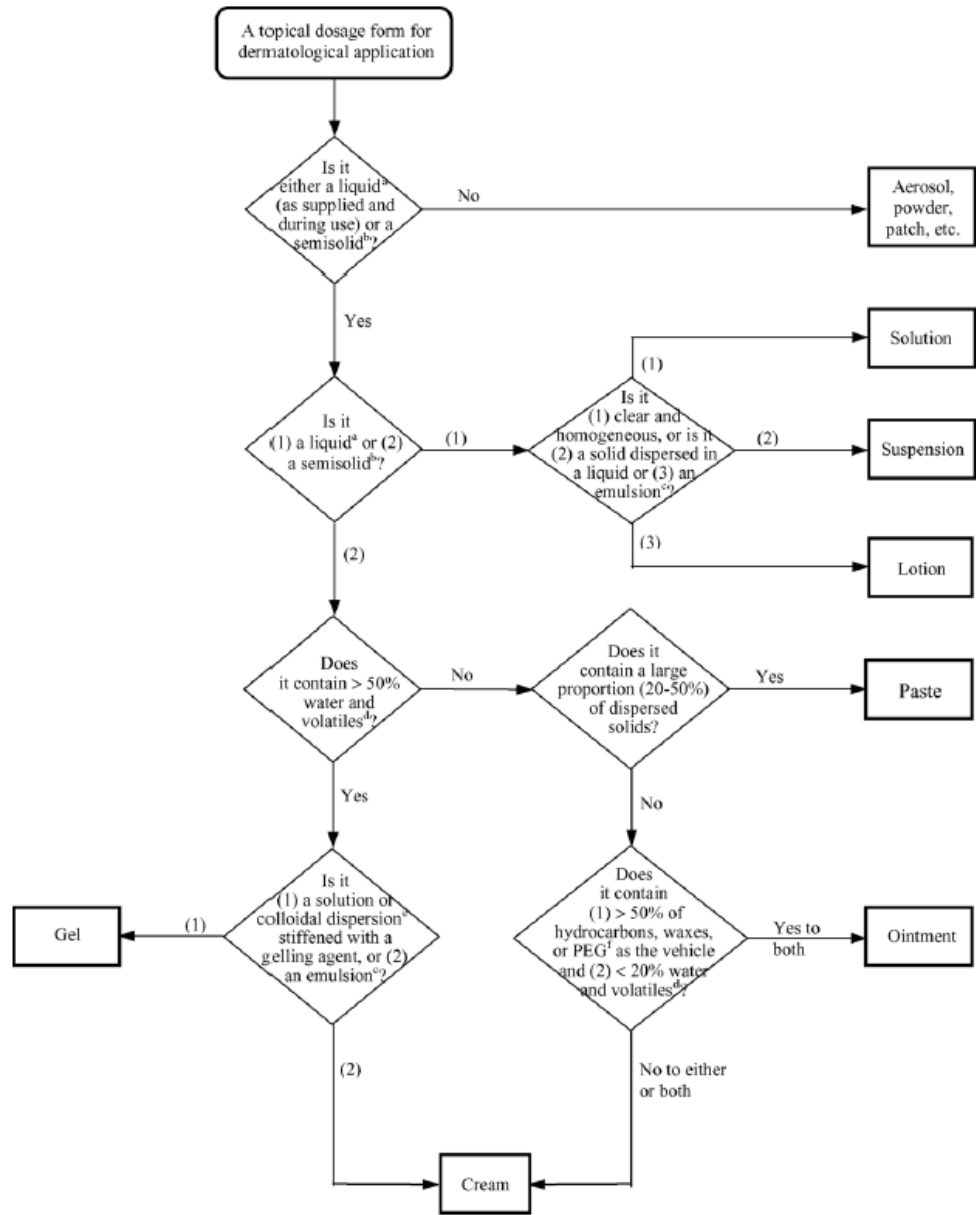
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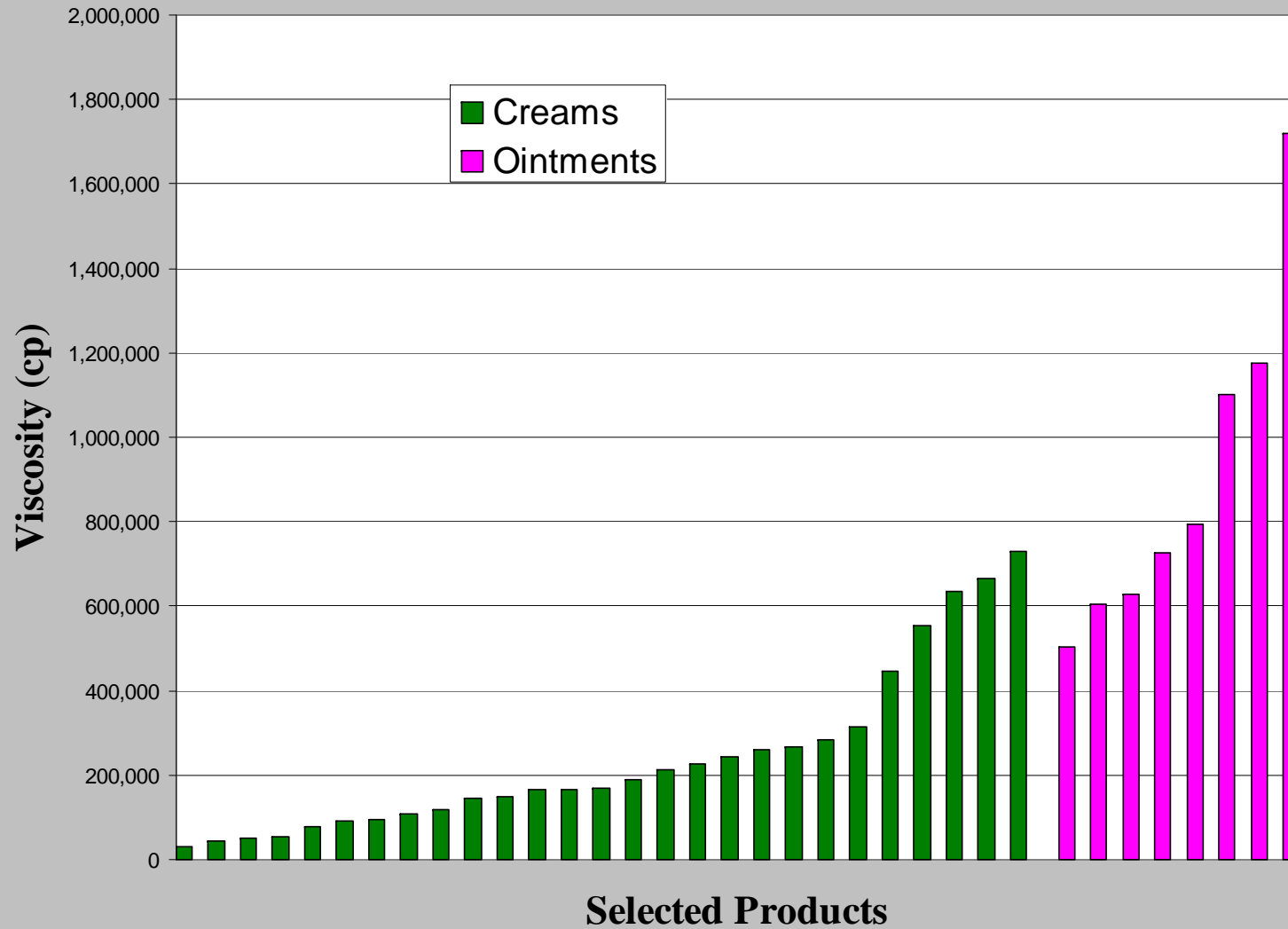
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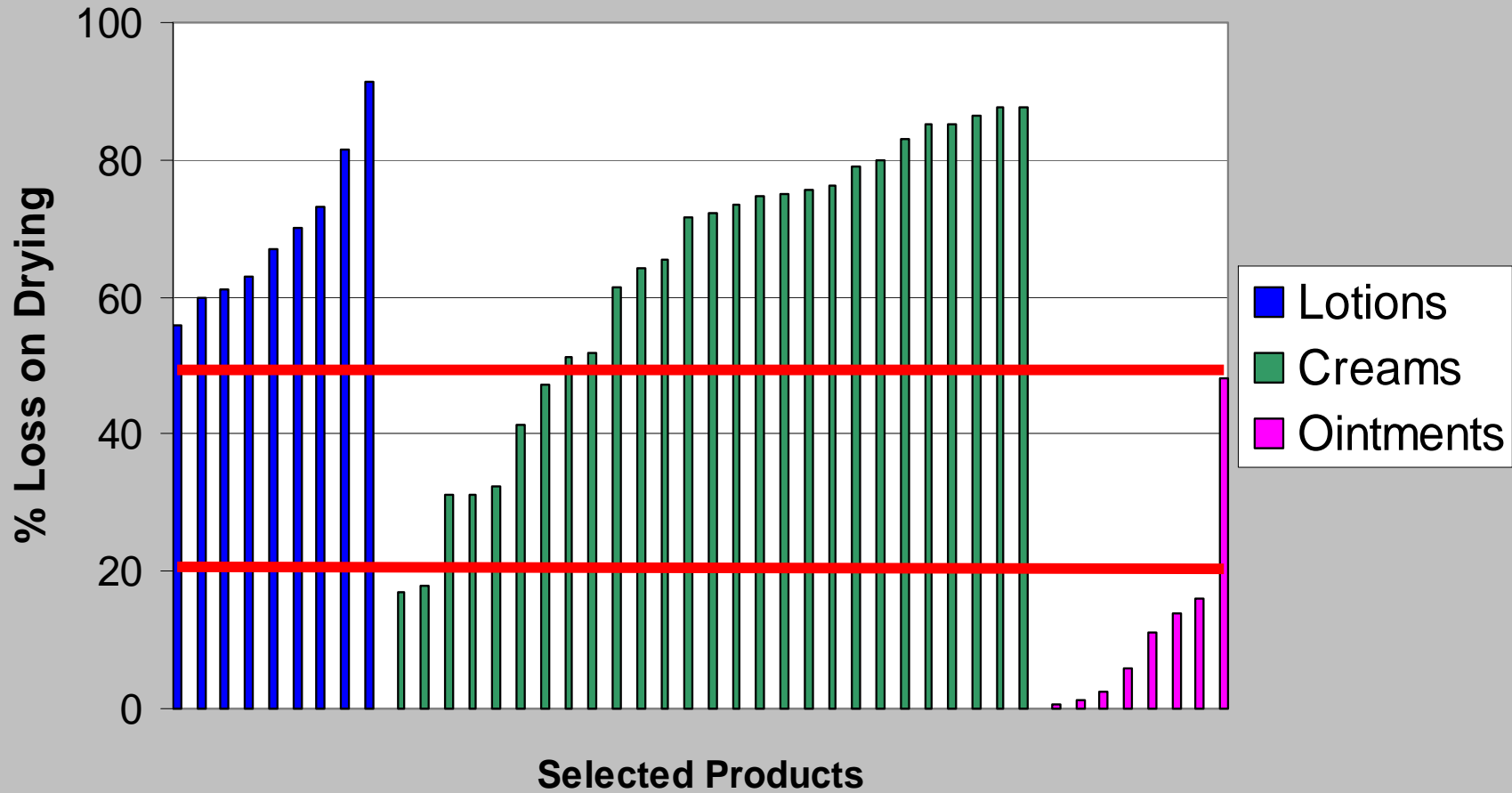


Viscosity of Selected Topical Products



October 2003 ACPS Meeting

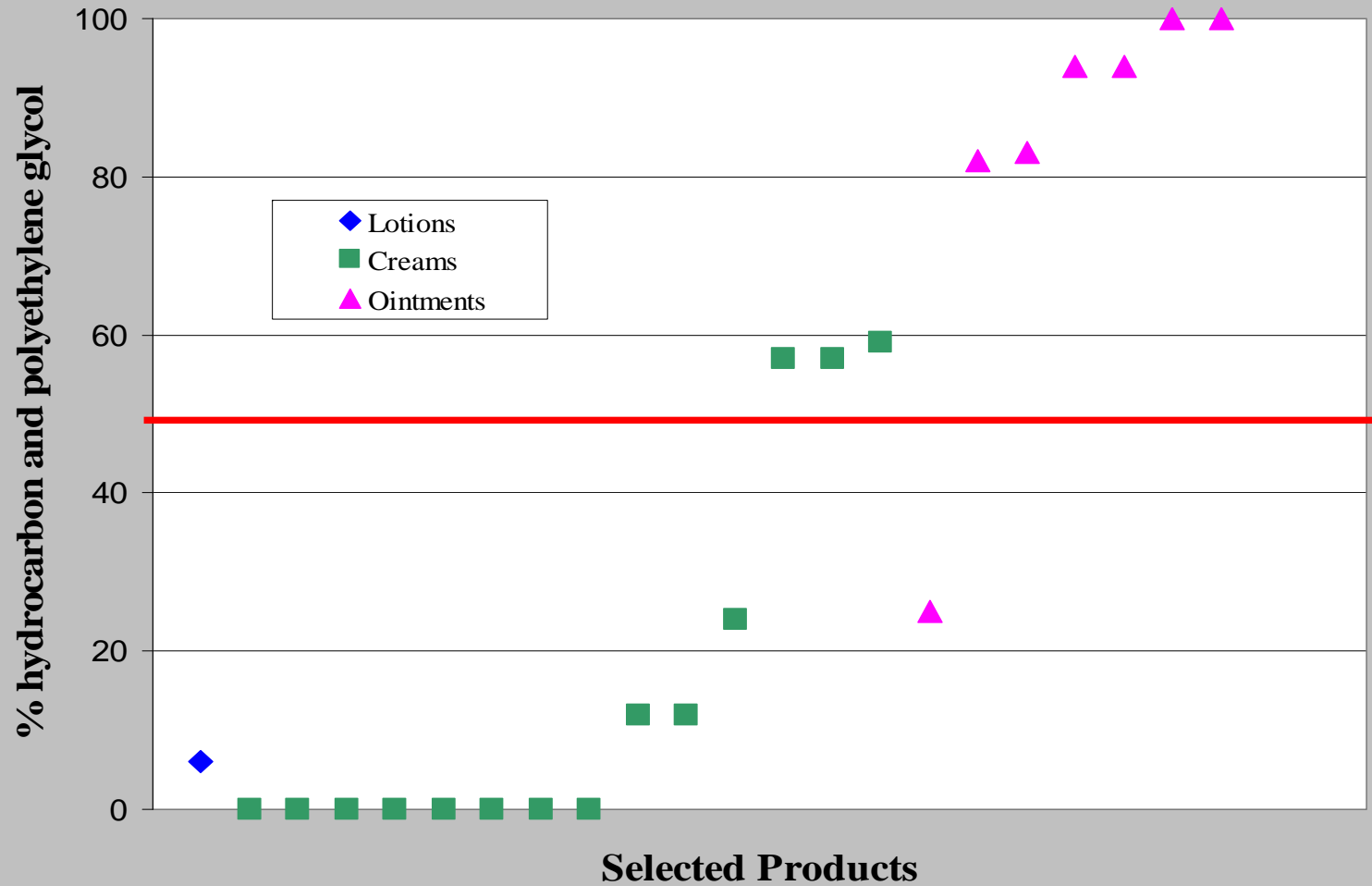
%Loss on Drying for Selected Topical Products



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Ointments <20% and Lotions >50%.

Chemical Composition of Selected Topical Products



Ointments have %hydrocarbon or Polyethylene Glycols >50%.

Decision Tree

- Quantitative and provides unique reproducible classification consistent with previous actions
- Data driven
- Could be overly restrictive
- Some RLD's may not be labeled consistently with their classification

Legal Requirement to Review Formulation Design

- 21 CFR part 314.94(a) (9) (v)
 - (v) *Inactive ingredient changes permitted in drug products intended for topical use.* Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an abbreviated application may include different inactive ingredients provided that the applicant **identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy** of the proposed drug product.

Current Review

- Check new excipients against IIG
 - Safety of individual excipient
 - Not effect of excipient on product performance
- Passing bioequivalence test
 - Evidence that formulation change is acceptable
- Product Development report is an opportunity for sponsors to “characterize the differences”

More Legal Requirements

- 21 CFR 314.127 (8)(ii)(Reasons to reject ANDA)
 - (ii)(A) ... FDA may identify changes in inactive ingredients or composition that may adversely affect a drug product's safety or efficacy. The inactive ingredients or composition of a proposed drug product will be considered to raise serious questions of safety or efficacy if the product incorporates one or more of these changes. Examples of the changes that may raise serious questions of safety or efficacy include, but are not limited to, the following:
 - (5) The use of a delivery or a modified release mechanism never before approved for the drug.
 - (6) A change in composition to include a significantly greater content of one or more inactive ingredients than previously used in the drug product.
 - (7) If the drug product is intended for topical administration, a change in the properties of the vehicle or base that might increase absorption of certain potentially toxic active ingredients thereby affecting the safety of the drug product, or a change in the lipophilic properties of a vehicle or base, e.g., a change from an oleaginous to a water soluble vehicle or base.
- A product development report is an opportunity for sponsors to explain why these differences are acceptable

Conclusions

- Use Q1 Q2 Q3 classification to
 - Identify appropriate in vivo bioequivalence studies
- Evolution from Pharmaceutical Equivalence
 - traditional dosage form definitions
 - empirical decision trees
- To Quality by Design
 - Mechanistic understanding and review of formulation design could reduce the need for testing and expand the design space beyond past experience