Working Group 1 Introduction

Bob Bianchi
Torben Elhauge

Working Group 1

How to streamline the Cat 1 testing

- Split the testing into a two parts
  - "Must have testing"
    - Simple QC like testing for comparision purposes
    - All 3 categories (PSD, Large vol and inectability)
    -
- Individual testing
  - Pre-testing (Development work) to inform the formal Cat 1 study
  - The approach how to do this could be standardized
- Standardize for sampling times and the number of samples
- Tool screening
  - Cutting, grinding and chrushing should be included
  - Explore the most promising way using different tools

Working Group 1

- Method verification
  - Verification of the assay method
  - Verification of the manipulations
  - Different level of verification at different stages of testing
    - Screening
    - Physical manipulation
      - The different tools
      - The optimized method
    - Extraction and simulated smoking
    - Methods used for Cat 2 and 3

Working Group 1

- Substances to test for?
  - API
  - Antagonist
  - **Aversive agent**
  - Excipients having an AD effect

Working Group 1

- Test parameters?
  - Assay(Substance concentrations)
  - **Particle Size distribution**
  - Viscosity
  - Hardness
  - Level of effort
  - “Cutability”
  - Others?

Working Group 2 Introduction

Chris Altomare,
Sebastian Schwier

Working Group Topics

1. Analytical Considerations
   Bob Bianchi and Torben Elhauge
2. Manipulation Methods
   Chris Altomare and Sebastian Schwier
3. New Generic ADF Guideline
   Dajun Sun and Karsten Lindhardt
4. Tampering in the Laboratory vs Clinic
   Beatrice Setnik

Working Group 2

Choosing physical and chemical manipulation methods

- Real world, advanced “test-to-failure” techniques
- Failure points
- Innovator vs. Generic manipulation methods
- New & relevant methods to include in Cat 1 testing

Cat 1 ADF performance testing *vs.* ADF Stability testing

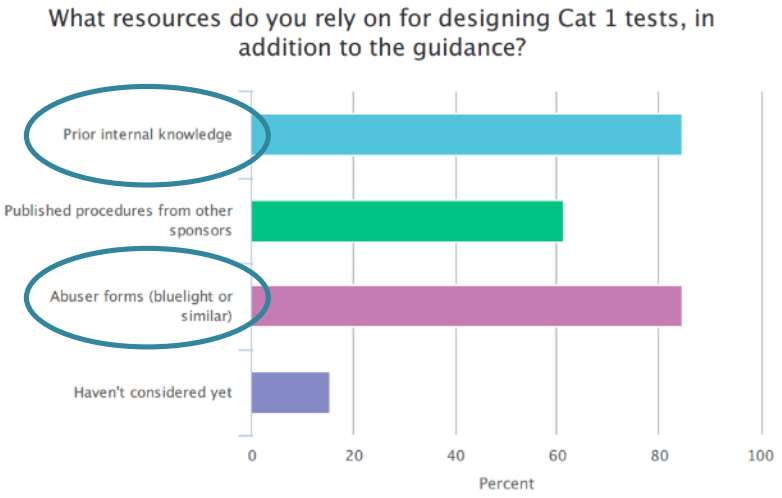
- Designing stability tests
- Based on Cat 1 outcomes
- What is important, what is irrelevant?

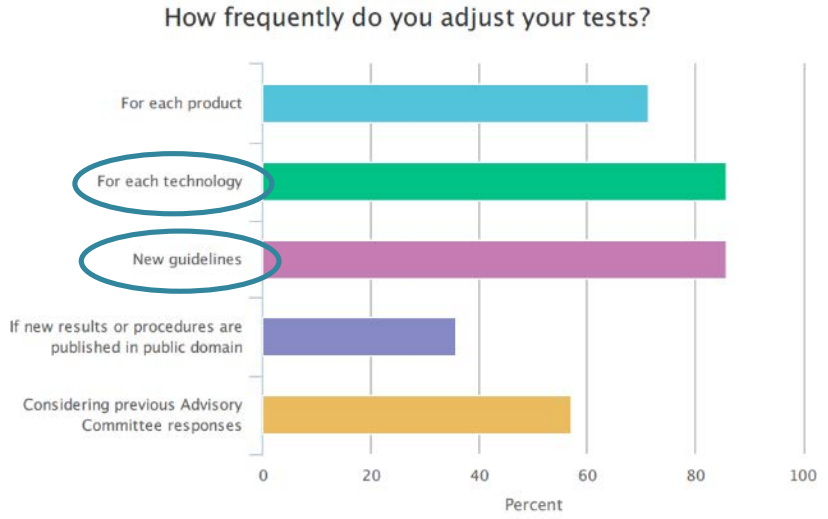
Working Group 2

CATEGORY 1 - FOCUS GROUP

In Vitro Abuse-Deterrent Studies

Webinar results





Working Group 2

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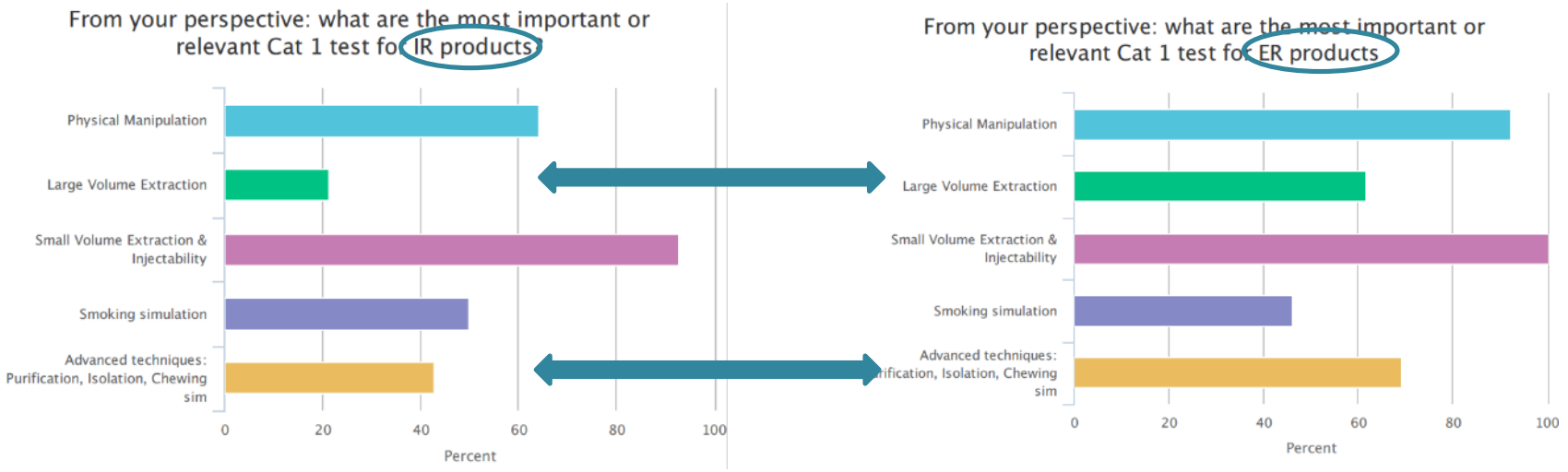

Working Group 2 - Topics

Tests & Tools

- Compare street and lab methods
- Physical manipulation:
  - Which tools to be assessed?
  - Proposal to ”determine” Energy?
- Syringe-ability:
  - Are all aspects included?
  - If not, what is missing and should be added (and how?)
- Designing ADF Stability test from Category 1?

Goals

- What is the goal of pre-treatments per category (e.g. thermal impact on brittleness vs viscosity)?
- What is the goal of the methods (test to failure in Category 1 vs Stability)?
  - Dissolution not good enough
- New methods in the real world, how much is too much?

Formulations / Technologies

- For which release profiles which tests?
- Which tests for which ADF technology?
- New technologies on the horizon, new methods
  - Does Generic guidance allow thorough enough characterization of product

Working Group 2 Results

Chris Altomare,
Sebastian Schwier

Working Group 2 - Topics

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  - **Proposal to ”determine” Energy?**
- Syringe-ability:
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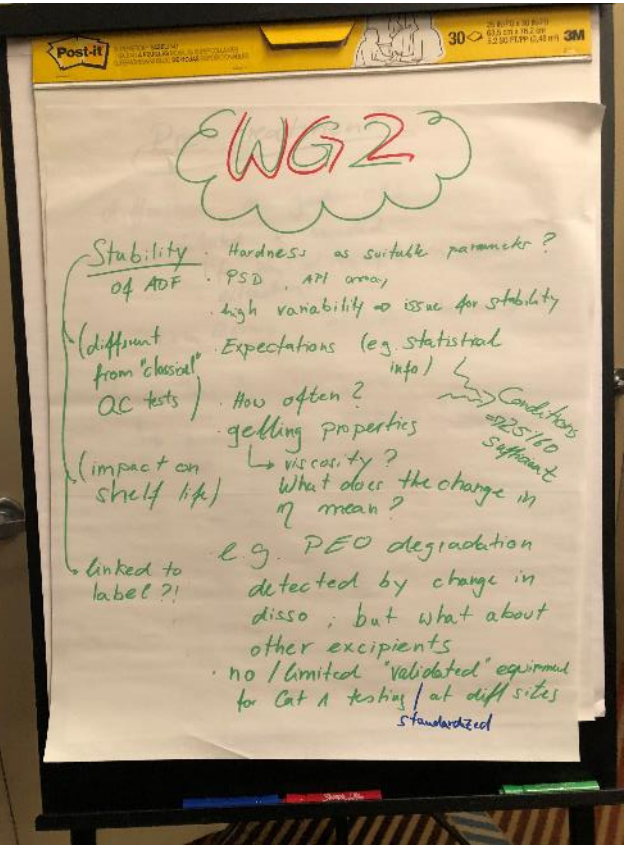
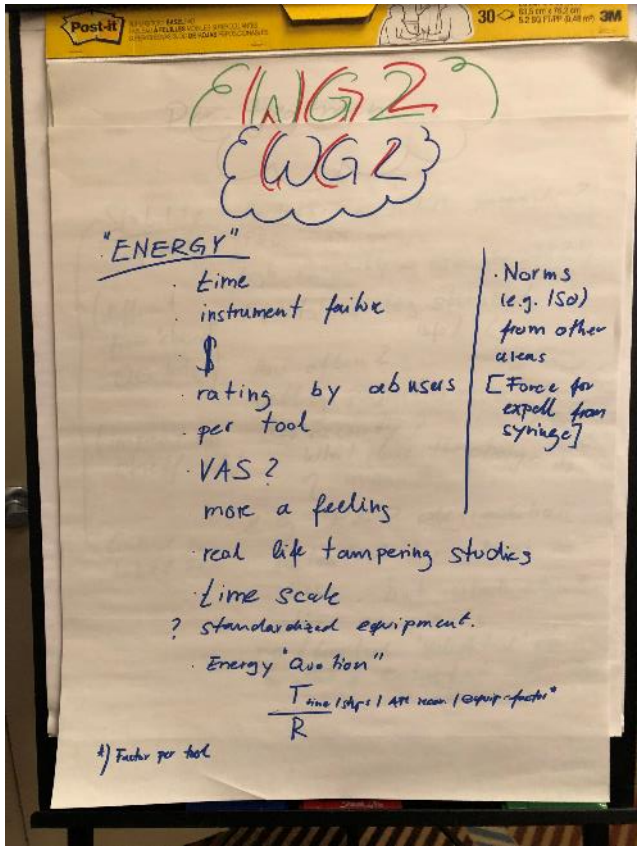
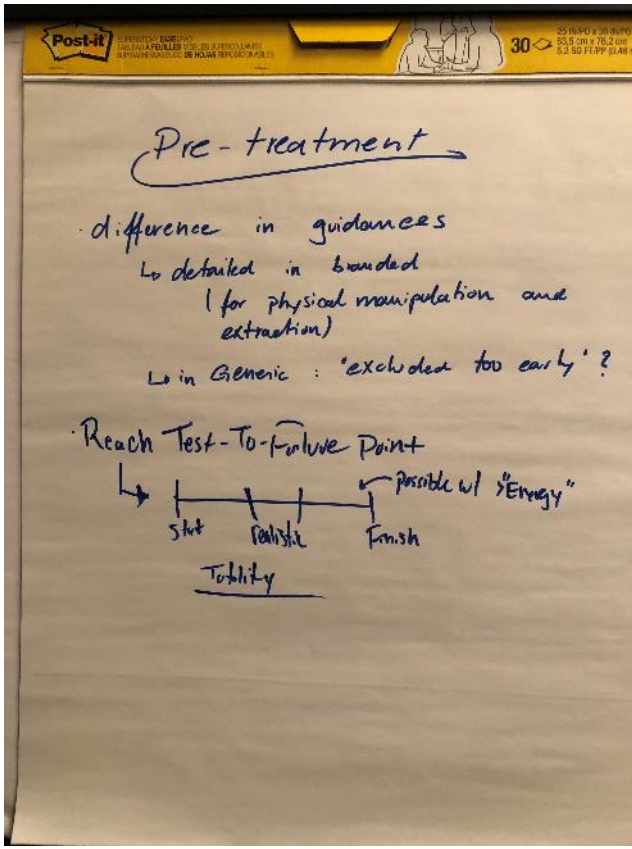
WG 2 - Session

CATEGORY 1 - FOCUS GROUP

In Vitro Abuse-Deterrent Studies







Working Group 2 - Stability

Parameters

- Hardness, PSD, assay, gelling properties (viscosity as surrogate, what does a change mean?) Degradation of PEO may be detected via change in dissolution rate.
- Storage conditions: 25°C/60%rh only, after 12 and 24 months only

Challenges

- High variability → issue for stability statements and statistical assessment
- No / limited standardized / validated test equipment for Cat 1 tests (e.g. at different sites)

Points to consider

- Different from classical QC tests
- Stability ≠ Cat 1
- Impact on shelf life?
- Linked to label? (e.g. for product with i.n. claim only PSD as stability parameter?)
  - Single measures from each study:
    - Physical Manipulation = PSD
    - Extractability = Single time point API recovery
    - Injectabiliyt = Single condition API recovery

Working Group 2 - Energy

How do we convey effort (time, energy, resources) required to defeat ADFs?

Parameters

- Time & Effort & money invested
- Instrument failure
- Pictures/Videos?

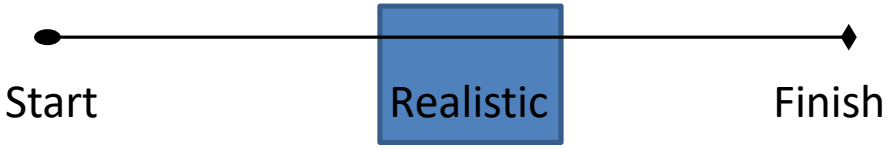
Proposals / Points to consider

- Real life tampering studies → VAS / rating by abusers OR more a feeling than a value?
- Time scale
- ⊖ Energy quotient: $\frac{\text{Test (time, steps, API recovered, equipment factor)}}{\text{Reference}}$
- Can ISO or other norms from other areas be used? (e.g. medical devices: force required to expel from syringe)

Working Group 2 – Pre-treatments

Challenges

- Difference in guidelines:
  Detailed in innovator guideline (for physical manipulation and extraction)
  VS
  Reduced in generic guideline
- Is it necessary at all if comparator is easily syringed?
- Pre-treatment excluded too early? Risk of "blind spots"?
- How to convey "Reaching test-to-failure Point" / Totality?



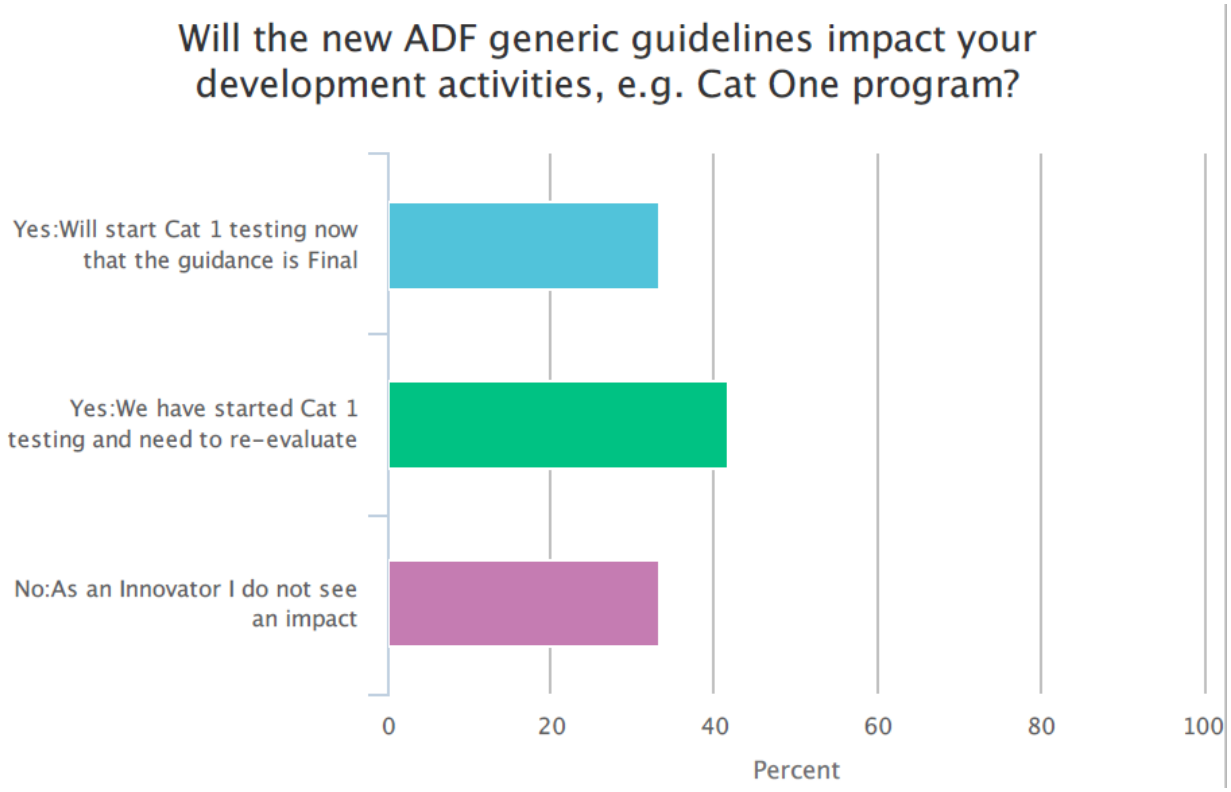
Working Group 3: Generic Guideline 3rd - Cat 1 Focus Group Meeting

Moderators:

Dajun Sun, PhD, Staff Fellow
U.S. Food & Drug Administration|Center for Drug Evaluation and Research
Office of Generic Drugs|Office of Research and Standards |

Karsten Lindhardt, PhD MS DBE, CSO Egalet Corp.
CCALC Cat 1 Focus Group Chair

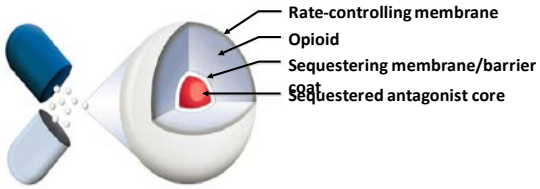
Feedback from Webinar



Approved Products Span a Diverse Range of Technologies

- Different approaches to AD (barrier versus antagonist)
- Physical forms – monolithic tablets and multiparticulates
- Inactive ingredients – gelling polymers, waxy materials, insoluble coatings
  - Range of solubility, melting points, physical properties

Hardened tablet



Pellets in a capsule
(sequestered antagonist core)

Waxy microspheres in a capsule

Branded v Generic Guidance

Branded Guidance
Evaluation: Totality of Evidence

- Chewing, crushing, cutting, grating, or grinding
- Spoons, cutters, and coffee grinders
- The effect of heat and cold
- Particle size distribution

Risk of evaluation based on <u>less data</u> is highly dependent on the experience of the reviewer and the similarity of technologies

Generic Guidance
Evaluation: Totality of pre-defined Evidence

- 3 different tools should be tested
- Cutting (Knife): 10 pieces
- Grating: < 1mm (50% W/W)
- Milling (Coffee grinder) : < 1 mm (50% W/W)
- Mechanical manipulation(s) most likely to be used by abusers
- Effect of freezing or heating
- PSD (Photograph with scale, Image analysis, Sieve analysis, Laser diffraction)
- 5 minutes only

Question 1:

- Input: Both the branded and generic guidelines mention the review will be based on totality of the evidence, but the evidence may be different.
- Question: *What do we mean with ”totality of the evidence” and does it mean the same for generic and branded products?*

Question 2:

- Input: A critical element of reducing data and still have predictive evaluation of similarity to comparator products would be the similarity of the formulation technology.
- Questions: *What is meant by similarity of technology and how can we generate data to secure that differences are sufficiently studied*

Question 3:

- Input: The generic guideline mention methods for PSD, but unclear if fractions should be analyzed
- Question: *Do we need to analyze the concentration in various fractions of particle sizes and if so how will potential differences be evaluated/interpreted*

Questions 4:

- Input: The generic guideline is more descriptive in the Cat 1 studies than the innovator guideline, but still has a level of uncertainty and not like a BE study.
- Question: *Would generic companies be able to use the guideline to generate new generic products with AD features or is the risk related to the uncertainty still too high?*

Question 5:

- Input: ”Level of effort” has been identified as a key element in the overall AD evaluation
- Question: *How can similarity in ”level of effort” be secured for generic products ?*

Question 6:

- Input: Standardization may be a challenge as we have limited understanding what we want to standardize against – suggestion made by the branded industri working group at FDA hearing?
- Question: *What is the Pro's and Con's of this approach of standardization and can we find a better approach and does this correspond to the final generic guideline?*

Question 7:

- Input: FDA may provide more detailed recommendations for conducting in vitro and in vivo testing to evaluate specific AD technologies.
- Question: *How can the industry provide feedback/comments in response to product-specific guidance or seek clarification of the recommended appraoches?*

BIWG Recommendation

- May be possible to establish a "core" set of tests that evaluate certain AD features
  - Within core, parameters for each test can be standardized
  - Consider tailoring core to AD mechanism (e.g., different core tests for barrier and antagonist products)
  - Core should be supplemented with product specific tests (core is only the starting point)
- Monitoring of select AD properties on shelf-life should be driven by risk assessment and justified in pharmaceutical development report

Core *in vitro* tests

- Parameters (or ranges) specified for tests in each of following areas:
  1. Mechanical manipulation
  2. Extractability
  3. Injectability/Syringeability
  4. Particle size for Nasal Administration
  5. Vaporization
- Applicable tests determined based on mechanism of AD

Product Specific *in vitro* testing*

- Driven by product design, product specific knowledge
- Supplement core tests with additional parameters
- Examples – additional tools/combinations, pre-treatments, secondary extraction steps, etc.

Category 2 and 3 Studies*

- *In vitro* studies inform manipulations used in PK and human abuse potential studies

**For generics, requirements outlined in product specific guidance. Consider public health implications of disclosures*

Presented by: Alison Fleming at the FDA Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products 1. Nov 2016

Opioid Guideline Paradox

Guideline (Cat 1)

- "*…sufficient to fully characterize the product's abuse deterrent properties, including the degree of effort required to bypass or defeat those properties*"

Guideline (Cat 3)

-"*….should be manipulated based on results from Cat 1 studies to cause the highest release of the opioid and the highest plasma levels"*

(Guideline: Abuse-Deterrent Opioids – Evaluation and Labeling, April 2015)

- Liking data are generated without the manipulation or effort parts with an FDA focus on Take Drug Again at 12 and 24 h as a critical element of the evaluation?

IN Abuse Cat 1 for Generic

- Guideline says that it should be the same as RLD
- Mainly relevant if ”same technology”
- Show ”similarity” in Cat1 first

Totality of Evidence

- Totality means an ”overall” evaluation effort, outcome, methodology (recipe)/AD response
- Finding the most effective method to manipulate the generic, specifically may mean you would need to do a larger exploratory package
- Large technology change would mean extensive studies to show ”similarity”

Technology?

- Can ”not worse than” be used to use different manipulation as long as overall ”totality of evidence” is as good as or better than the RLD
- Similarity may be an issue for generics from an IP perspective
- Can we make testing approach similar to a AD product B, but use another AD product A as RLD?

Take Drug Again

- Take Drug again - a complex evaluation combining a number of elements, but typically not the manipulation
- Can we do a more simple evaluation combining Cat 1, Cat 2 to show similarity which could link meaningfully to Cat 3 for an RLD?

Real-World

- Real world findings for branded products may not be relevant for ”different” technologies used in generics, but action needed for both if they are ”the same”
- In silico modelling can be useful for limiting studies, but needs to be validated with PK data
- PK/PD relation not yet established

Generic Guideline - General

- Final guideline improved a lot from the draft
- Regarded as useful from a generic perspective

Working Group 4

Category 1 Link to Category 2/3 Studies

General Considerations

- Bridging in vitro to in vivo methods:
  1. Feasibility
  2. Reproducibility (large samples)
  3. Safety (subject and pharmacy)
  4. Methods for test and reference

Testing Parameters

- Identify method that leads to most reduced particle size/greatest release of opioid
- Practical method that can be replicated consistently in a pharmacy
- Tools that can be safely used
- Efficient procedures (7 min)

Testing Parameters

- Stability of manipulated product (storage conditions; duration)
- Preparation of single vs multiple tablet
  - Batch uniformity
  - Method for recapturing dose
  - Recovery
- Safety

Testing Parameters

- Equipment
  - Maximum time for use/replacement
- Blinding
  - Matched placebos
  - Assessment of visual differences of T and R
- Preparation fatigue

Tampering – Focus Group Studies

1. Descriptive studies
   - Present product overview
   - Rate each product
   - Bias consideration
2. Hands-on tampering
   - With/without administration of drug
   - Variable exposure to drug

Chewing – in vitro to in vivo

- Need for definition of ‘rigorous’ chewing
  - Settings may be consistent with in vitro chewing parameters
- Hardness of tablet
  - Safety
  - Defining acceptable range for clinical trials
- Buccal administration (suck/chew)