Working Group Topics and Rules

Dr. Sebastian Schwier
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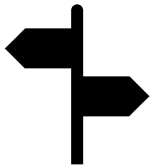
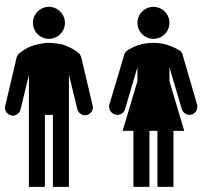
Working Group Topics

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

How will it work?



- Participants
  - Select topic of interest
  - 4 groups with 5-10 participants



- Moderator
  - One or two Moderators per group
  - Some key questions / topics to trigger discussion and brainstormig
  - Group / sort the items brought up

- Timing
  - 15min introduction (Day 1, moderators to present)
  - 90min working session (Day 1 after introduction)
  - Day 2: 15min presentation per group plus 15min panel discussion → all participants will know what was discussed in the groups

In Detail…

- Group – Brainstorming – Discussion

  - There is no predefined outcome
  - Collect ideas, topics on flip charts
  - Align on key outcomes that shall be discussed during the panel discussion
- Presentation
  - Create a short presentation (just one or two slides) for Day 2 (either during 90min session or after Day 1) – Moderator's responsibility
  - Presentation and topics from panel discussion will potentially be used for an editorial or for submission to the docket

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Working Group 1 Introduction

Bob Bianchi
Torben Elhauge

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Working Group 1

- Main Topics
  - Streamlining the Cat 1 testing?
  - Requirements for method verification?
  - Substances to test for?
  - Test parameters?

Working Group 1

- How to streamline the Cat 1 testing
  - Reduced experimental design?
  - Pre screening to focus testing on relevant parameters?
  - Determine the correct intervals and number of replicates?

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?

CATEGORY 1 - FOCUS GROUP

In Vitro Abuse-Deterrent Studies

Working Group 2 Introduction

Chris Altomare,
Sebastian Schwier

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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

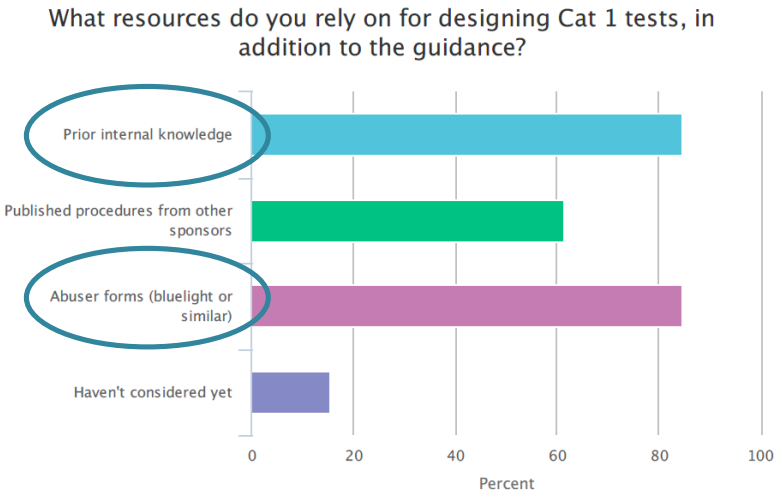
- Designing stability tests
- Based on Cat 1 outcomes
- What is important, what is irrelevant?

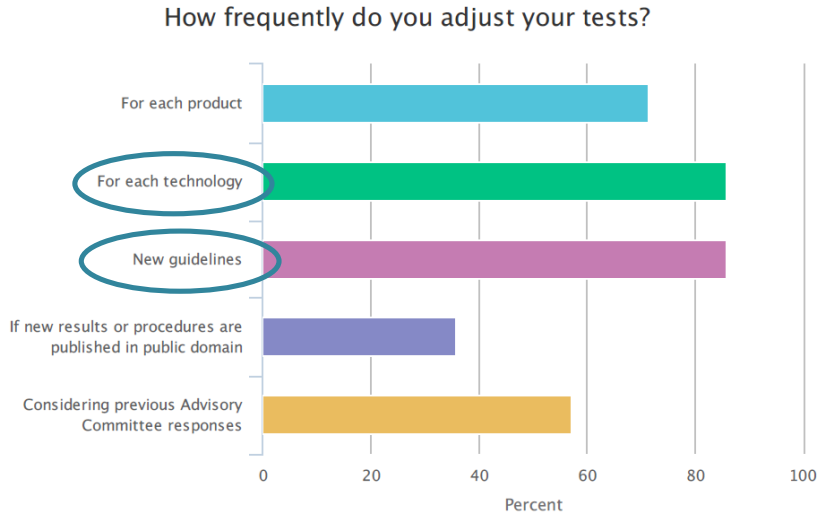
Working Group 2

CATEGORY 1 – FOCUS GROUP

In Vitro Abuse-Deterrent Studies

Webinar results



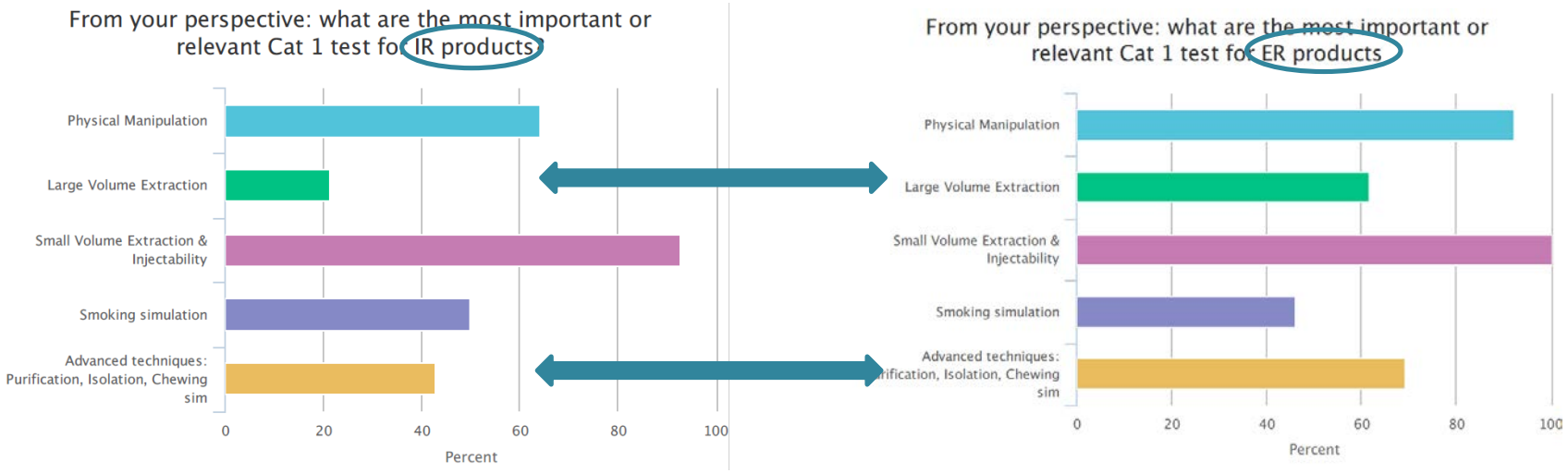


Working Group 2

CATEGORY 1 – FOCUS GROUP

In Vitro Abuse-Deterrent Studies

Webinar results



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

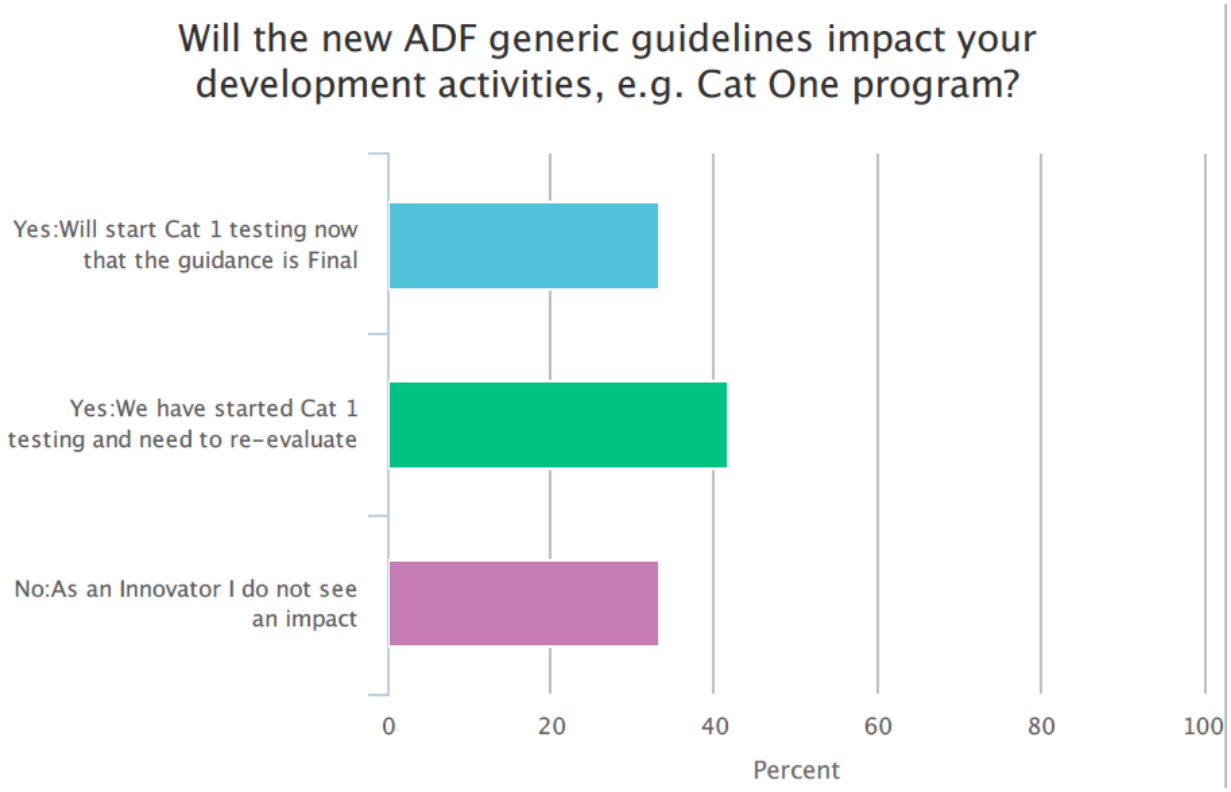
Working Group 3: Generic Guideline 3rd - Cat 1 Focus Group Meeting

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

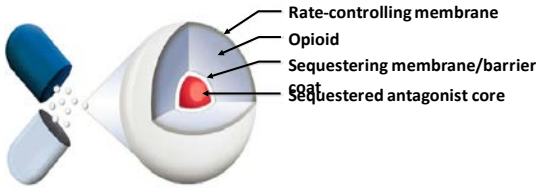
Feedback from Webinar



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?