# Recommendations from the Generic Industry Working Group for Comments on the Draft Guidance on General Principles for Development of Generic of Abuse-Deterrent Opioid Formulations

November 1, 2016

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On behalf of the
Generics Industry Working Group

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The remarks in this presentation do not necessarily represent the views of that individual, or that individual's company, or individual working group participant companies, but represent only the best available consensus views of the working group as a whole

# Day 2

- Standardizing In Vitro Testing to Evaluate Abuse Deterrence

# Overview

- Background
- FDA Questions to be Addressed
  - FDA Q1: What should FDA consider with respect o mechanical manipulations (e.g., equipment, amount of effort, time), chemical manipulations (e.g., solvent choice and availability), particle size distribution, and volume of solvent used for extraction? Slides 16-17
  - FDA Q2: How can FDA standardize in vitro testing to help substantiate appropriate and consistent product manufacture that assures abuse deterrence at release and through a drug product's shelf-life? Slide 18
  - FDA Q3: How can performance attributes measured by in vitro testing be quantified and linked to their impact on abuse deterrence? For example, discuss what amount of time delay in defeating an abuse-deterrent property should be considered significant and the basis for recommendation Slide 19
  - FDA Q4: How can FDA build flexibility into standardized testing so that it may be suitable for application to emerging technologies? Are there any specific technologies that might require new types of testing? Slide 20
- Other Considerations
- Summary

# Benefits of Standardizing Testing Methodology

- **Reduce test results variability and therefore increase relevance of the test results**
  - Allows consistent evaluation of product manufacture of ADF generic product with respect to abuse deterrence attributes
  - Allows establishment of meaningful performance target for critical quality attributes (CQA)
  - Facilitates assessment of formulation platforms to other drug products
  - Allows meaningful comparison between other generic ADF products

**Translates to increased confidence for regulators, prescribers, pharmacists, payers, and patients**

## Approaches to abuse-deterrence

- Physical/chemical barriers
- Combination of agonist/antagonist
- Prodrug

## Route of abuse

- Performance objective can be achieved for multiple technologies

## Testing requirements

- Platform/technology driven
- Needs more flexibility
- Opportunity to develop technology specific guidance

## Test Methodology

- Needs standardization
  - Reduce test results variability
  - Allow establishment of meaningful performance target for CQA
  - Allow meaningful comparison between products
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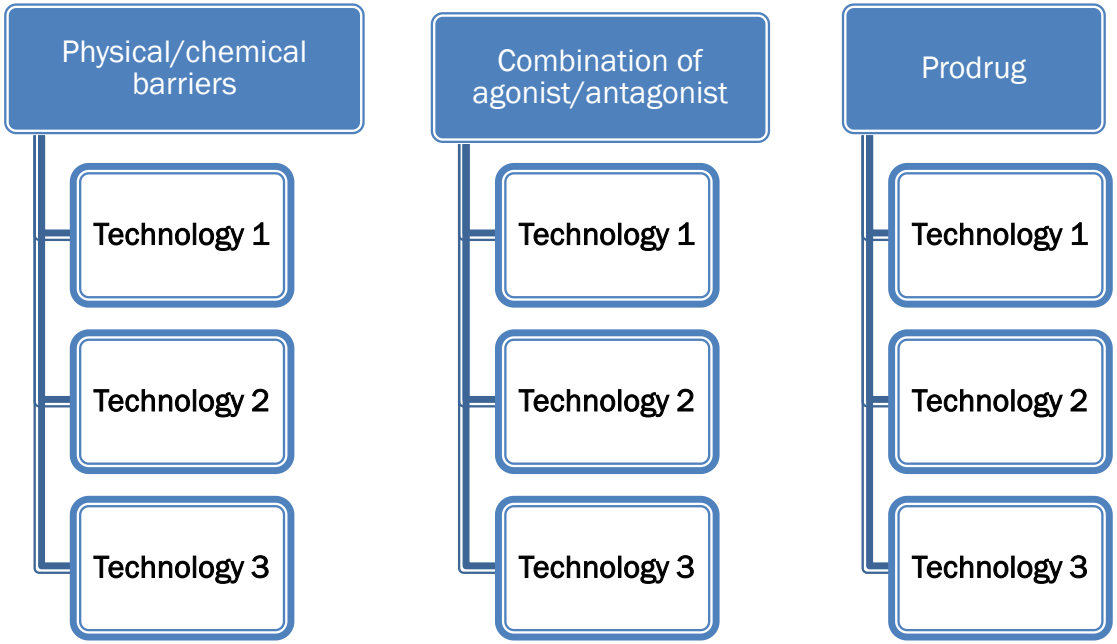
# Approaches to Abuse-Deterrence




- Different abuse deterrence approaches will require different testing approaches
- The approach will dictate the performance target that a generic product has to meet
- The performance target (s) can be accomplished using more than one technology
- A generic product has to use the same approach to abuse deterrence as the RLD, however for a given approach, the performance of the RLD can be accomplished by using different technologies

| | |
|---|---|
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| **Testing requirements** | • Platform/technology driven<br>• Needs more flexibility<br>• Opportunity to develop technology specific guidance |
| **Test Methodology** | • Needs standardization<br>  • Reduce test results variability<br>  • Allows establishment of meaningful performance target for CQA<br>  • Allows meaningful comparison between products<br>  • Allows consistent evaluation of product manufacture of ADF generic product with respect to abuse deterrence attributes |

# Routes of Abuse

- For a given approach to abuse deterrence, multiple technologies may be used to meet performance objectives
  - As part of evaluation of the RLD, all potential routes of abuse should be evaluated to establish a development target for the generic product.
  - From a generic drug perspective the abuse deterrent ability can be demonstrated by focusing on the critical performance attributes relevant to the technology used
  - A generic product has to be no less abuse deterrent than the RLD with respect to the routes of abuse listed on the RLD label.

# Testing Protocol vs Technology: Example

Key Performance Measures: Drug Extraction and Ability to Syringe

Dictates

Route of Abuse: Injection

Solvation rate (extractability) and low volume viscosity (i.e. <10 mL) of crushed dosage form in biocompatible solvents would be the key drivers for assessing AD capability

**RLD:** crush resistant matrix + viscosity building agent in biocompatible solvents
**Generic:** different crush resistant matrix + viscosity building agent in biocompatible solvents

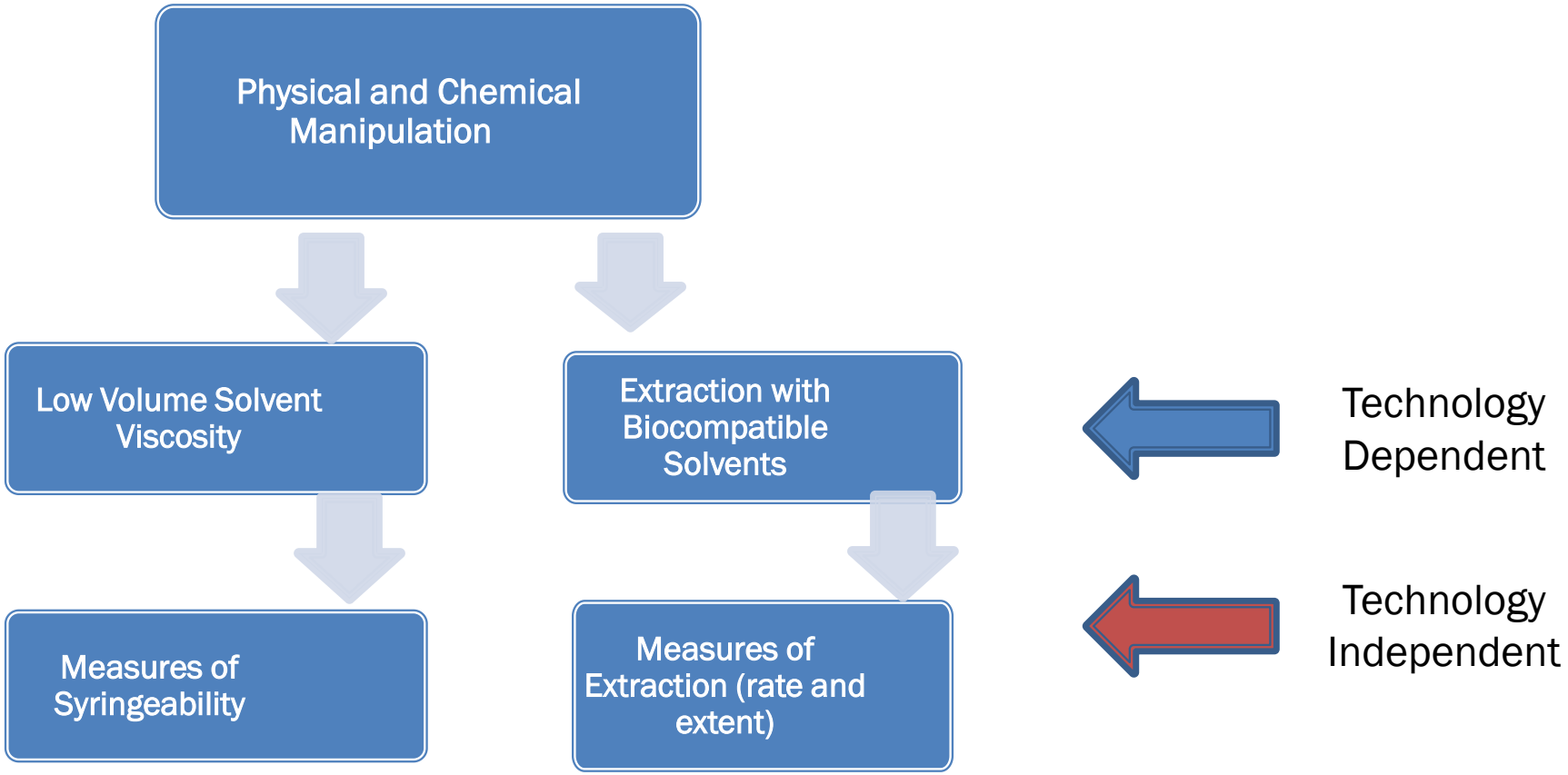
Tablet hardness and resulting PSD would not be critical for this example dosage form.

A standardized test related to the difficulty of crushing the dosage form would not be appropriate.

Technology Driven Performance Evaluation

If brand and generic product are based on different technology the guidance testing hierarchy can be misleading

# AD Performance



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# Testing Requirements

- Test requirements should be standardized around technology/platforms

- Current Draft Guidance does not meet this need, it is tiered, rigid in sequence of execution: one size fits all approach

- This may lead to unnecessary tests for some technologies or may not provide adequate depth for others.

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# Testing Methodology

**FDA Q1. What should FDA consider with respect to mechanical manipulations (e.g., equipment, amount of effort, time), chemical manipulations (e.g., solvent choice and availability), particle size distribution, and volume of solvent used for extraction?**

## Mechanical Manipulation:

- Performance characteristic:
  - particle size distribution (PSD) when subjected to the same level of effort (including time)
- Parameters to Consider for Standardization:
  - tools/equipment (ex. Dr. Hoag recommendation), use of performance indicators, number of units (tablets), and/or tablet mass (different strengths, proportional formulation), time

## Chemical Manipulation; Extractability (parenteral and oral):

- Performance characteristic:
  - how much drug is extracted in a solution
- Consider the solubility of the API; that impacts the volume of the solvent
- Parameters to Consider for Standardization:
  - tools/equipment, sample/solvent volume ratio, Particle size, Choice of solvent (pH, polarity, accessibility), Time of exposure, Temperature, Agitation

# Summary of (Physical) Manipulation Assessment on Select NDAs/INDs

| Method (Brief) | Temperature | Tools | Effort: Steps | Effort: Time | Particle size and PSD | Technique to determine the size |
|---|---|---|---|---|---|---|
| Grinding | RT | Spice grinder (Waring) | 1 | 1 min | 355 to 4000 um | sieve |
| Grinding | RT | Coffee grinder (Cuisinart) | 1 | 1 min | 355 to 2000 um | sieve |
| Grinding | RT | Coffee grinder (Krups) | 1 | 1 min | majority <1 mm | sieve |
| Grinding | RT | KRUPS F203, Rotating blade style coffee grinder | 1 | 20 sec | >1 mm | Sieve |
| Grinding | RT | Cofee grinder | 1 | 2 min | 2 mm | Sieve |
| Grinding | RT | Coffee grinder | 1 | N/A | N/A | N/A |
| Grinding/heating | 40 | | 2 | 2hrs | N/A | N/A |
| Grinding/cooling | 5 | | 2 | 2hrs | N/A | N/A |
| Grinding | RT | Manual spice grinder | 1 | 30sec | N/A | N/A |
| Milling | RT | Manual food mill- Electric peper mill (Trudeau)-Manual Crank paper mill | 1 | 30sec | N/A | N/A |
| Grinding | RT | Electric mini food processor | 1 | 30sec | N/A | N/A |
| Grinding | RT | Electric coffee bean grinder(Cusiinart) | 1 | 3min | N/A | N/A |
| Grinding | RT | Electric coffee bean grinder(Krups) | 1 | 45sec | N/A | N/A |
| Milling | RT | Waring laboratory blender(model HGB2WT83,WITH SS110-65CUP) | 2 | 30 sec to 90 sec | <600 um to > 2 mm | Sieve |

Key lessons:

- Standardization with PS can alleviate problems/variability of tools/methods/time

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# FDA Q2: How can FDA standardize in vitro testing to help substantiate appropriate and consistent product manufacture that assures abuse deterrence at release and through a drug product's shelf-life?

- **Evaluation of the drug product's AD performance would not be part of routine QC testing**
  - Sponsor demonstrates significant formulation/process understanding during product development related to the abuse deterrent functionality
  - Requires appropriate release testing of key AD excipients (critical material attributes) as well as critical process parameters

- **QC Test should be based on a primary function of the formulation critical quality attributes for the specific abuse deterrent mechanism**
  - Case 1: Antagonist- assay of antagonist
  - Case 2: Resistance to Crush Tablet- tablet hardness
  - Case 3: Mucoadhesive- if the quantitative composition is constant a test for a parameter such as viscosity may prove acceptable

## FDA Q3: How can performance attributes measured by in vitro testing be quantified and linked to their impact on abuse deterrence? For example, discuss what amount of time delay in defeating an abuse-deterrent property should be considered significant and the basis for recommendation

- From a generic manufacturer perspective, the generic drug has to be no less abuse deterrent than the RLD
  - This includes the effort and time in defeating the product

## FDA Q4: How can FDA build flexibility into standardized testing so that it may be suitable for application to emerging technologies? Are there any specific technologies that might require new types of testing?

- This has to be collaborative ongoing/iterative process of a joint committee of FDA review teams/generic industry & other potential stakeholders to look into this and make recommendations

- The gap between the technologies that are covered by the current guidance vs those of emerging technologies should be addressed in product specific (and/or technology/platform specific) guidance

# Other Considerations for the Guidance

## Dissolution Studies

- Standard dissolutions conditions provided in the guidance may not always be appropriate. Depending on product they may either not be sufficiently discriminating or may be over discriminating

- Opportunities for exploring different dissolution methods based on API solubility, using biorelevant dissolution media should be available options

- Physiologically based pharmacokinetic (PBPK) modeling options should be available to establish a biorelevant predictive dissolution method to be used for evaluating abuse deterrent capability

*This will not only provide an opportunity for science and risk based decision making but will also reduce the number of unnecessary clinical studies - this is an opportunity to bridge between Cat 1 and Cat 2 before going to Cat 2*

# Summary & GIWG Recommendations

- **For the same approach to abuse- deterrence, performance objectives can be achieved for multiple technologies**
  - A generic product has to be no less abuse deterrent for each route of abuse as indicated on the RLD label,
  - For a given approach the performance of the RLD can be achieved by the generic using different technologies
  - From a generic drug perspective, abuse deterrence can be demonstrated by focusing on the critical performance attributes relevant to the technology used

- **Test requirements should be standardized around technology/platforms**
  - Current Draft Guidance does not meet this need; one size fits all approach
  - Standard dissolution methods provided in the guidance should be augmented by exploring opportunities to develop biorelevant predictive dissolution methods to reduce the requirements for PK studies (physiologically based pharmacokinetic (PBPK) modeling)

- **Test methodology requires standardization to mitigate variability that could impact test results**