In Vitro and In Vivo Abuse Deterrence (AD) Evaluation of Generic Opioid Products

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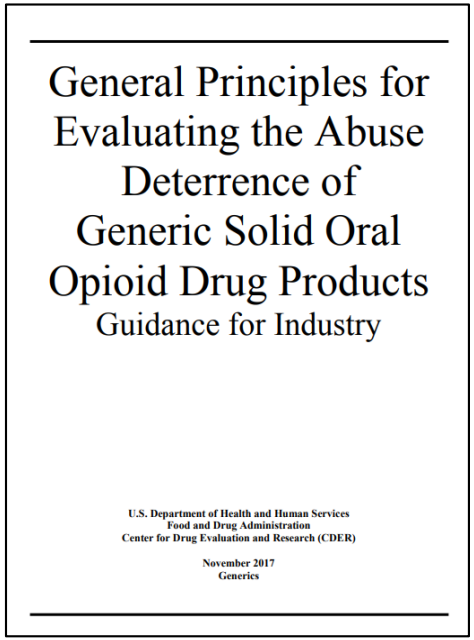
Overview of General Guidance for Generic AD Opioids

When reference listed drug (RLD) product has abuse deterrent properties described in its labeling:

- Test product is expected be no less abuse deterrent than RLD
- With respect to all potential routes of abuse
- Using comparative in vitro approaches

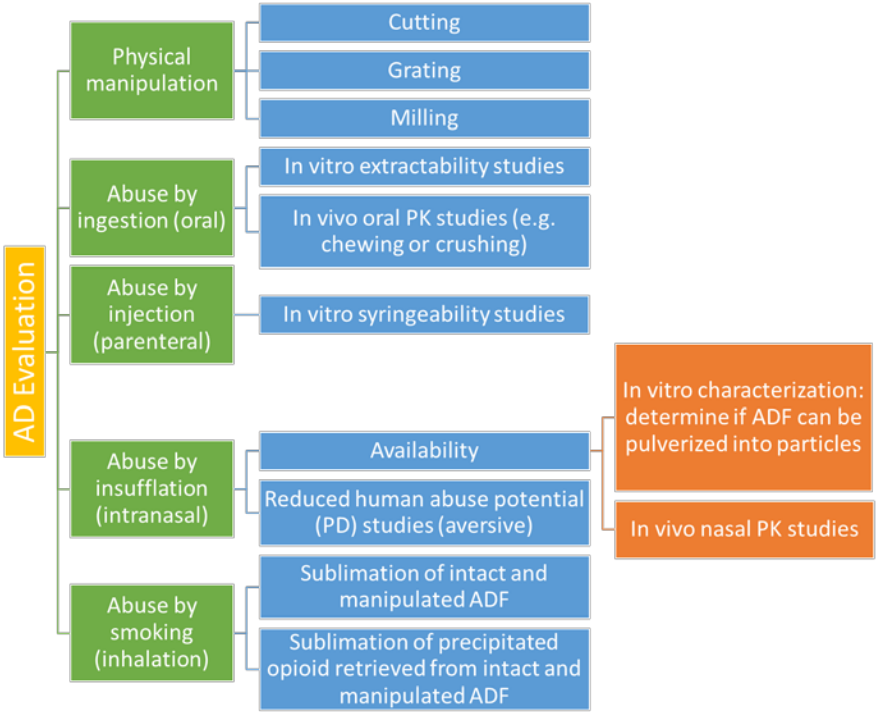


General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2017
Generics



https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf

*Consistent with general guidance, in vivo oral PK (chewing or crushing), nasal PK (availability), and nasal PD (human abuse potential) studies may not always be needed

General Considerations for In Vitro Studies

The challenge: complexity of the design

A possible scenario:

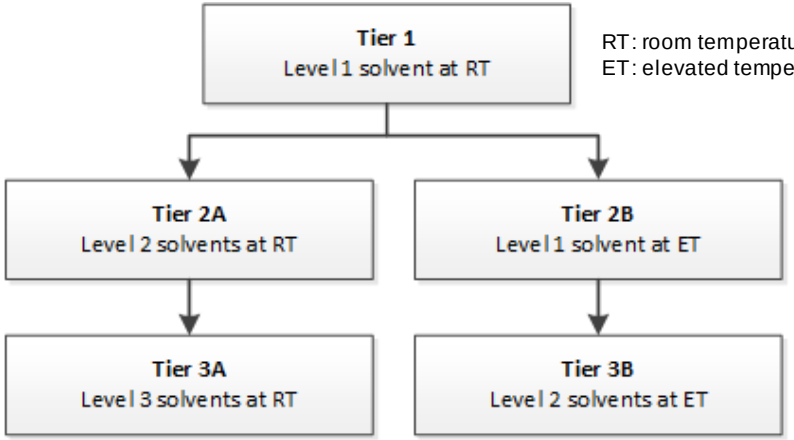
- Minimal of two comparators (reference, test)
- Minimal of two forms of sample (intact, compromised)
- With more than a dozen possible methods to achieve a desired manipulation outcome (e.g. compromise the integrity of the dosage form)
- Minimum of eight different solvents
- Various temperature conditions
- Different volumes
- Different time points

Number of experiments goes into thousands (2x2x12x8x2x3x4=9216)

- Battery of tests should not result in data-dumping which burdens both industry and the Agency
- The experimental design should be guided by the understanding of the ADF design mechanism and failure mode of the RLD product

Tier-based Approach to Testing

- Hierarchical testing (limit the number of tests)
- A tier refers to manipulations of ***similar*** complexity, difficulty and effort
- Subsequent tiers with ***increasing*** complexity, difficult, and effort



Solvent Level					
1	Deionized Water				
2	Vinegar	0.2% baking soda	40% Ethanol	Carbonated drink	
3	100% ethanol	100% isopropyl alcohol	Acetone	0.1N HCl	0.1N NaOH

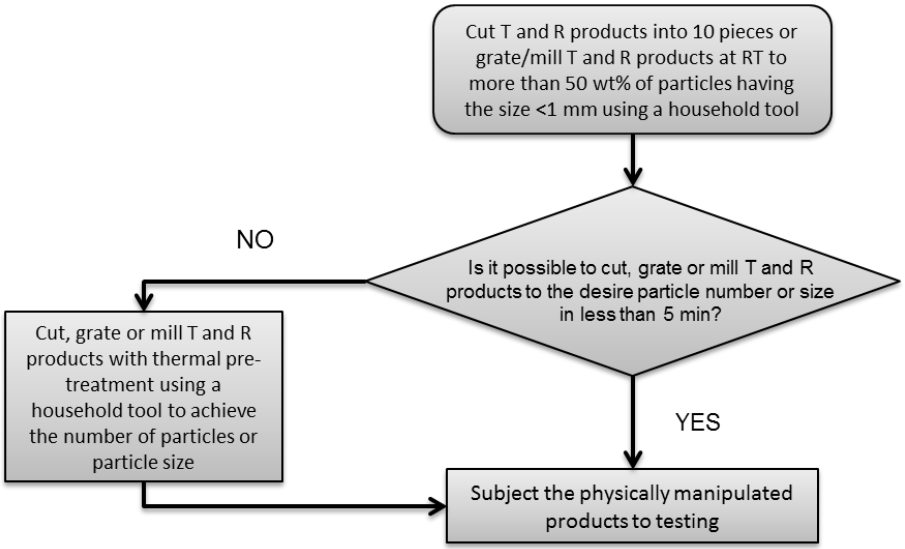
Where it applies?

Appendix 1	Extractability
Appendix 3	Injectability/syringeability (related to Appendix 1)
Appendix 4	Nasal insufflation
Appendix 5	Smoking

ET: boiling temperature of the solvents

Physical Manipulation Evaluation (Appendix 1)

- Manipulation is a critical step for several routes of abuse (nasal, injection, smoking)
- Both the process (effort) and endpoint (success) are important
- Highly dependent on the formulation design (e.g. matrix tablets, beads with coatings)
- Should be used to gain an understanding of the robustness of the AD properties



- What is the degree of difficulty of the manipulation?
- How successful is each manipulation method in achieving its goal (e.g., compromising a tablet's integrity)?
- If the structure of the dosage form is compromised, what are the size and size distribution of the resulting particles?

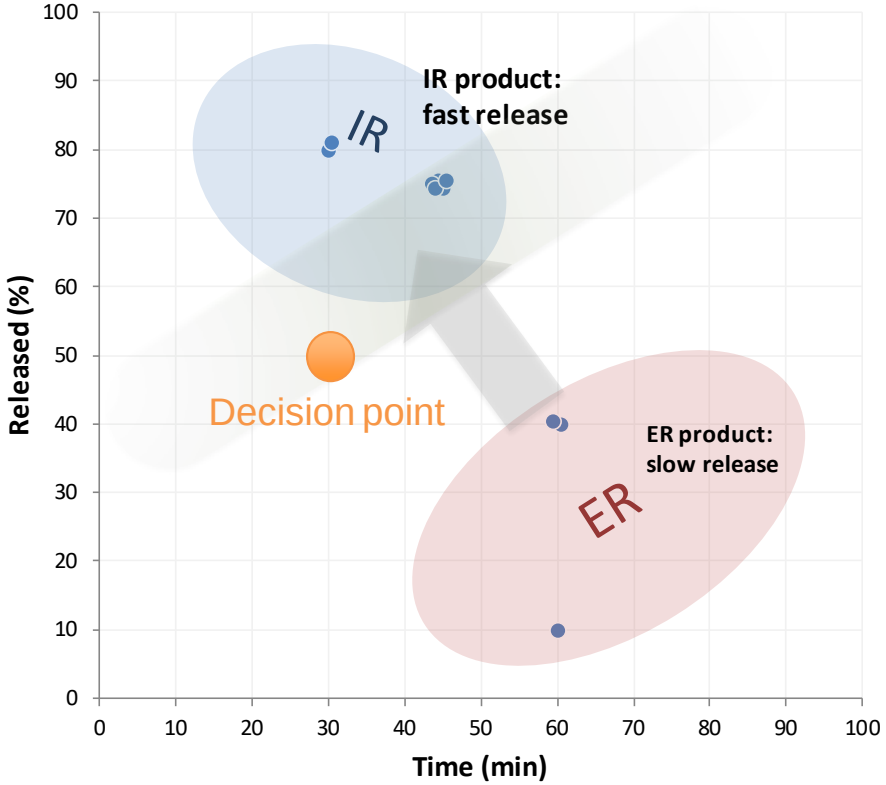
Physical Manipulation Evaluation (Most Effective Manipulation)

- **Most Effective Manipulation** may vary based on formulation design (e.g. ER matrix tablet)
- Generally the manipulation condition leads to the most successful compromise of the integrity of the product is the one potentially results in the most drug release (e.g. ER tablet losses its matrix, or ER coated granule losses its coating).

Cutting	Grating	Milling	Crushing	more…
w. Pretreatment w/o. Pretreatment Time/effort	w. Pretreatment w/o. Pretreatment Time/effort	w. Pretreatment w/o. Pretreatment Time/effort	w. Pretreatment w/o. Pretreatment Time/effort	

Appendix 1 Extractability (Oral Route) – Decision Point

Overlay of dissolution specifications of IR vs. ER opioid products



IR: immediate release, ER: extended release, AD: abuse-deterrence

When release of an ER product approaches release of an IR product, it will no longer be considered to have ER properties, regardless of whether it was intended to be an ADF product.

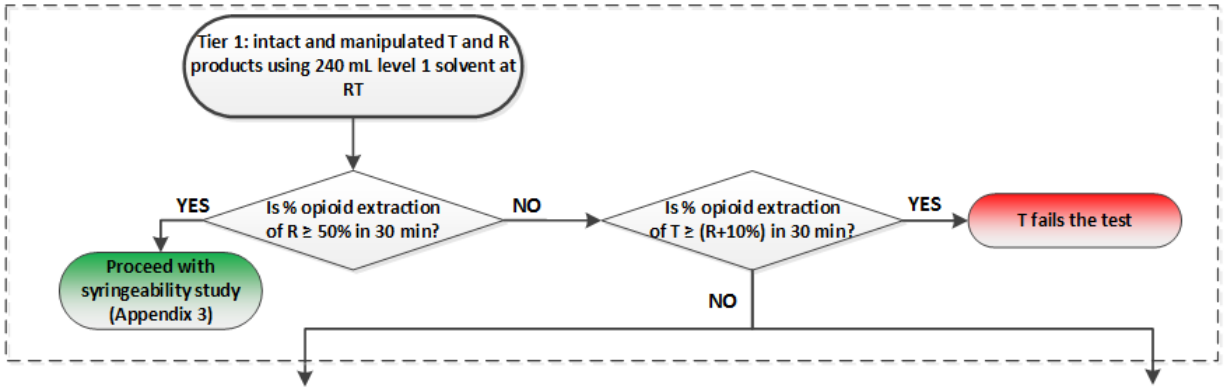
Recommended decision point:
50% release in 30 min based on IR/ER dissolution spec + extraction data in NDAs

Being worse than the decision point means the product is not AD

Being better than the decision point does *not* mean that the product is AD

Appendix 1 Extractability (Oral Route) – Tier Based Evaluation

An example of one tier evaluation



Step 1: Evaluate R for each solvent within the tier

Step 2: If % drug release from R in Step 1 is >50% @30 min for any solvent within the tier, proceed to the syringeability study

Step 3: Otherwise,

- Identify the condition at which release from R is maximum
- Identify the condition at which release from T is maximum
- Compare maximum release from T with maximum release from R + 10%

Step 4: Advance to the next tier if T passes the test

Appendix 3 Syringeability (Injection Route)

Conduct syringeability test (Appendix 3) if

- the maximum extraction of drug substance from R product in large volume (240 mL) solvent is equal or more than 50% in 30 min in a tier, *or*
- T product successfully passes all tiers in the large volume extraction study (test the last tier)

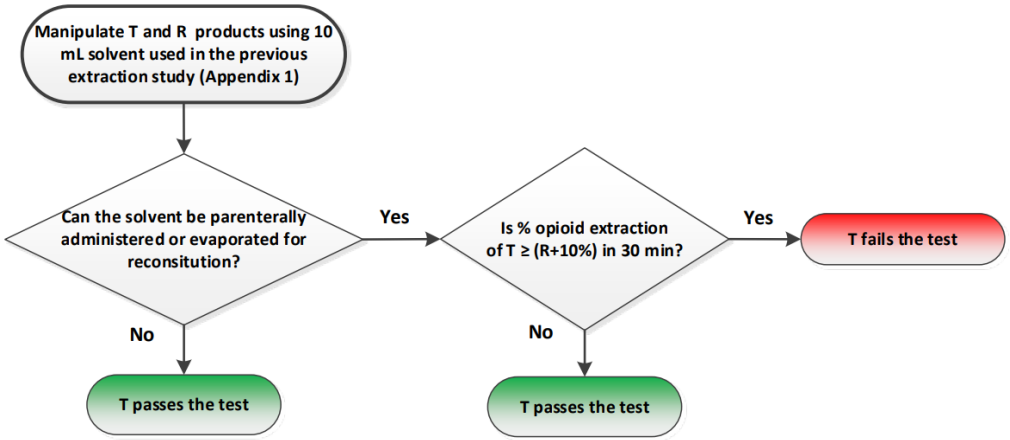
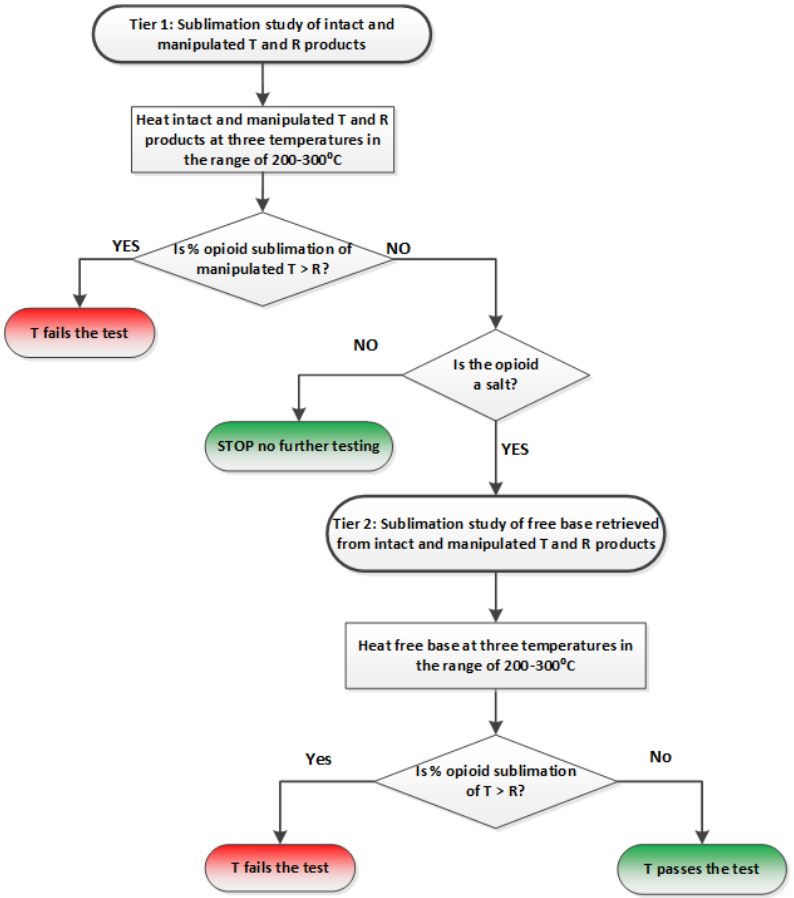


Figure 6: Decision Tree for Determining the Syringeability of Opioid to Evaluate Abuse-Deterrence Potential (abuse by injection)

- Same condition as R
- Low volume (10 mL)
- Both intact and most-effective-manipulated
- Expelled volume (through 21 gauge or finer) should be determined
- Report extraction time, syringe time, and filtering (if applicable)
- Statistical evaluation of T vs R+10%

Appendix 5 Smoking (Inhalation Route)



- Recommends conducting smoking test using at least three temperatures within the range of 200°C to 300°C to identify optimal conditions for drug recovery
- Draft Guidance recommended conduction smoking test at one temperature at 233°C (ignition temperature of paper)
  - Temperature at 233°C may be below sublimation temperature of opioids
  - In NDAs, volatilization was evaluated at several temperatures between 200°C and 300°C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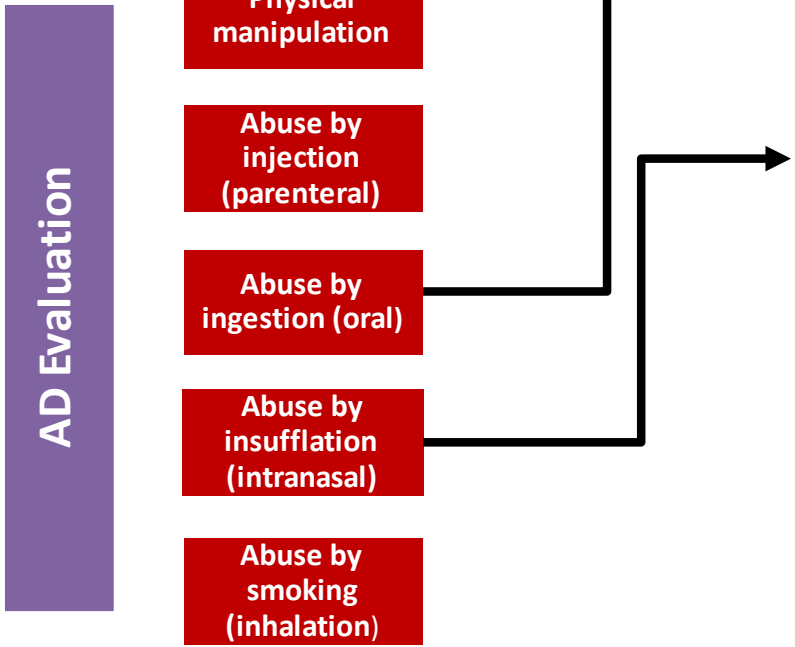
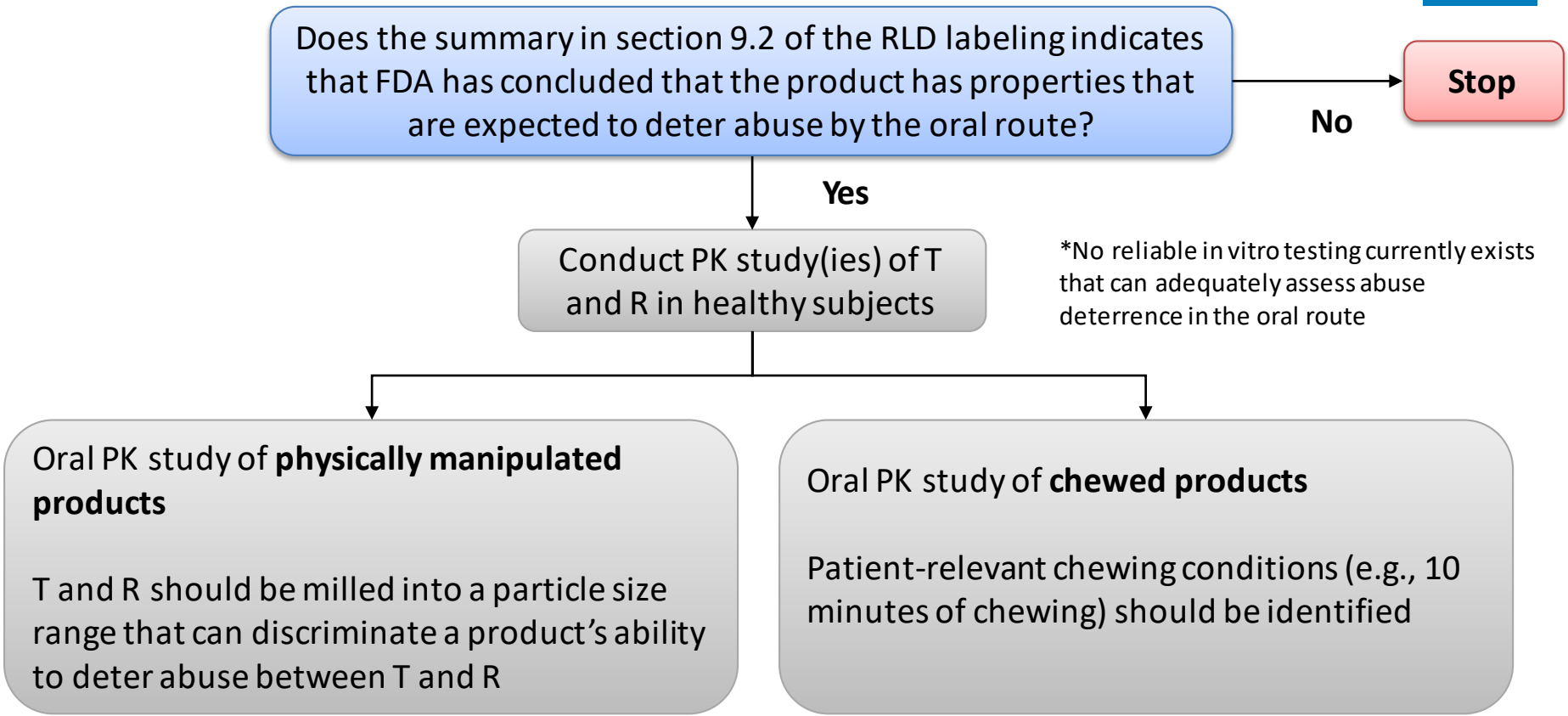
In Vivo Studies for Evaluating Abuse Deterrence

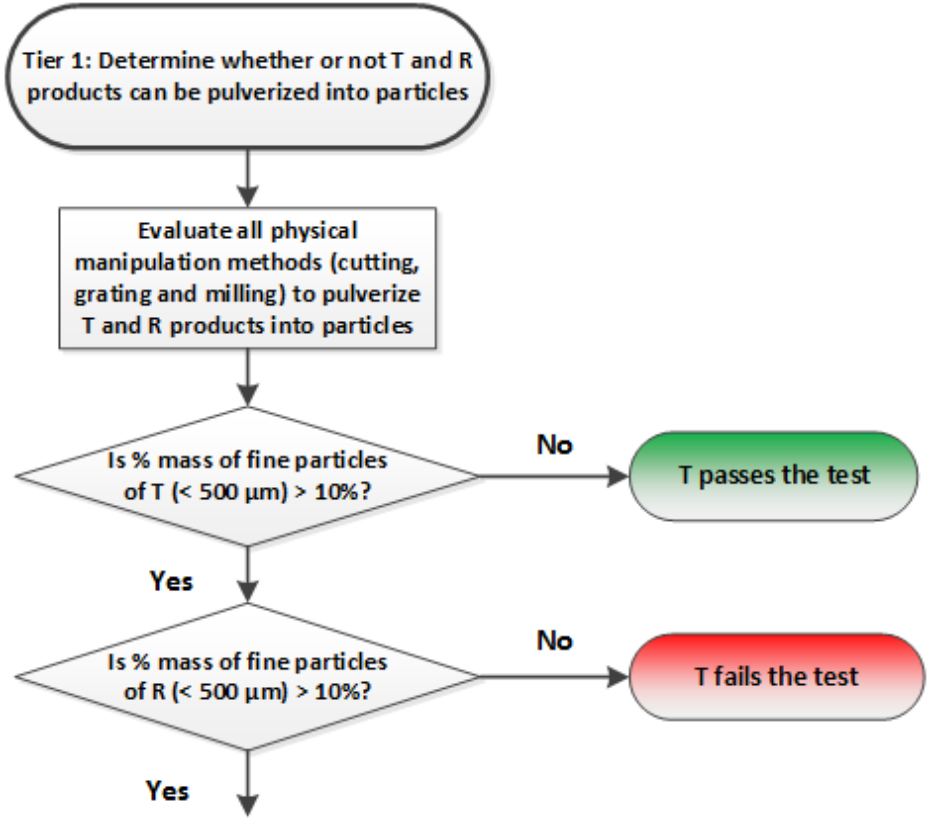


- AD evaluation in the oral route
  - Oral chewing PK studies
  - Oral crushing PK studies
- AD evaluation in the nasal route
  - Nasal PK studies
  - Nasal PD studies
- Multiple strengths
- Study subjects
- Agonist/antagonist combination products
- Statistical analysis (non-inferiority testing)

Appendix 2 Oral Route – In Vivo PK Studies

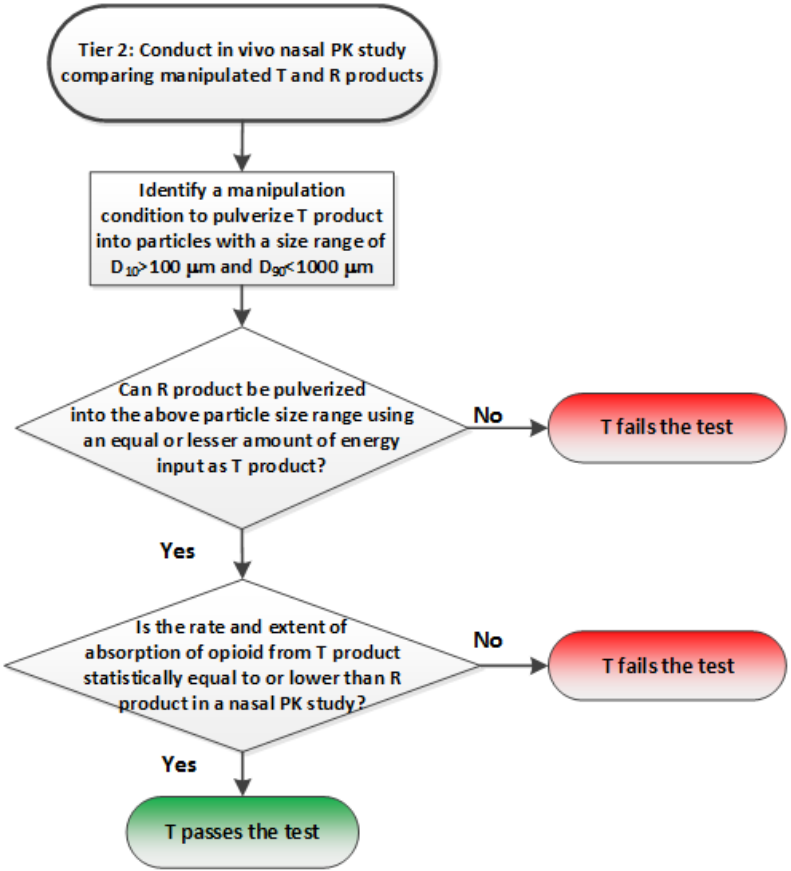


Appendix 4 Nasal Route – Tier 1 In Vitro Characterization



- If T (<500 µm) <10%, T **passes** the test (unsuitable for insufflation)
- If T (<500 µm) >10%, then mill R product under the same manipulation condition
- If R (<500 µm) <10%, T **fails** the test because T is deemed less resistant to physical manipulation than R
- When both T (<500 µm) and R (<500 µm) >10%, then **proceed** to Tier 2 in vivo studies

Appendix 4 Nasal Route – Tier 2 In Vivo PK Studies

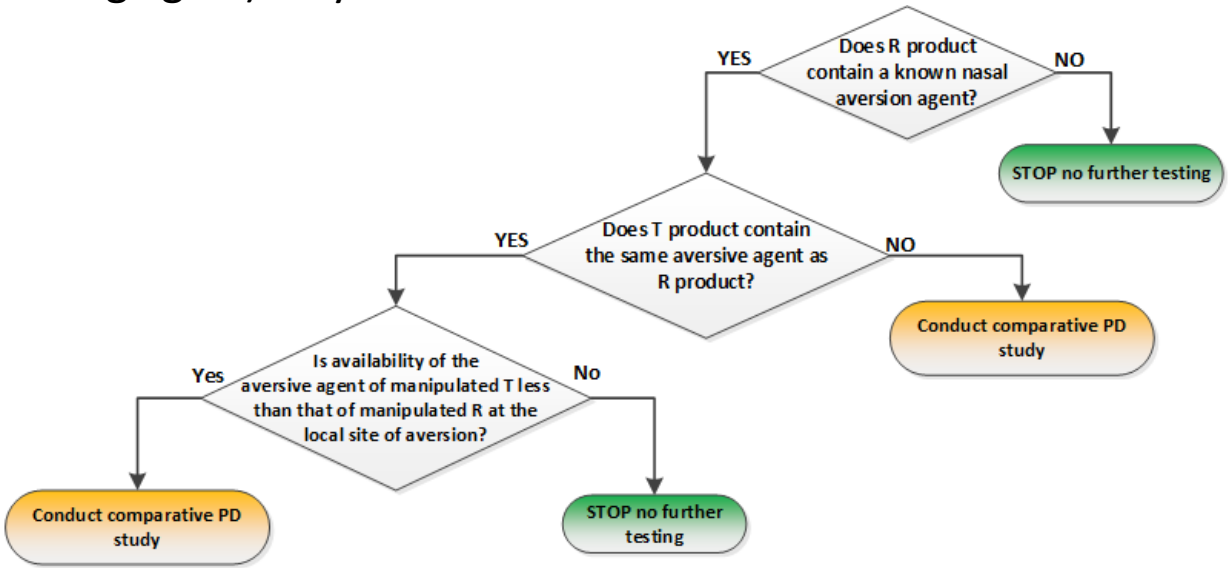


- Particle size range that is considered safe and tolerable for human insufflation PK – D_{10} >100 µm and D_{90} <1000 µm
- Particle size should be characterized in the submission
- R should be milled into the above particle size range using the same milling condition used for T or a lesser amount of energy input

Appendix 4 Nasal Route – In Vivo PD Studies

- **Nasal aversive agent(s)** – excipients that produce an unpleasant effect if the dosage form is manipulated and insufflated

- If the RLD formulation contains nasal aversive agent(s), in vivo nasal PK studies may not be sufficient; human abuse potential PD studies (e.g., willingness to take the drug again) may be needed



Multiple Strengths of Abuse Deterrence Opioid Products

- The strength(s) selected for the oral/nasal PK or PD AD studies, if needed, should be based on the strength(s) used to evaluate the R product's abuse deterrence as per the RLD labeling

- The strength(s) selected for the in vivo abuse deterrence studies are generally intermediate strength(s)

- If the RLD labeling does not identify the strength(s) for PK or PD abuse deterrence studies, FDA intends to provide recommendation in **product-specific guidance**

Study Subjects for Oral/Nasal In Vivo Abuse Deterrence Studies

- Oral/nasal PK AD studies should incorporate naltrexone or other opioid antagonist to block the PD effects of the opioids except for combination products

- Take scientifically appropriate and ethical steps to protect human subjects
  - Monitor opioid-related adverse events
  - Recreational opioid users – Ensure that subjects not dependent on opioids (e.g., naloxone challenge test)
  - Combination products – Confirm an adequate naltrexone release from the physically manipulated combination products prior to conducting in vivo PK AD studies

In Vivo AD Studies	Study Subjects
Oral chewing PK studies	Healthy volunteers
Oral crushing PK studies	Healthy volunteers
Nasal PK studies	Recreational opioid users*
Nasal PD studies	Recreational opioid users*

*Non-dependent opioid users from the general population who have experience in the use of opioids for non-therapeutic purposes

Combination Products Containing Opioid Agonists and Antagonists

- Appropriate bioanalytical methods to measure both agonists and antagonists
- Oral PK BE studies – minimum antagonist absorption when fully intact combination products are orally administered
- Oral/nasal PK AD studies – antagonist is sequestered within formulations and released upon chewing or physical manipulation; no naltrexone or other antagonist blockade should be used for combination products

To use opioid blockade in in vivo AD studies?	Opioid only	Combination (agonist/antagonist)
Oral chewing PK studies	Yes	No
Oral crushing PK studies	Yes	No
Nasal PK studies	Yes	No
Nasal PD studies	No	No

Statistical Analysis for In Vivo PK Abuse Deterrence Studies

- T product is no less abuse deterrent than R – Non-inferiority (one-sided) statistical analysis to evaluate PK metrics

- Opioids – 95% confidence interval (CI) for PK metrics (e.g., Cmax, AUC, pAUC) should be less than 125.00%

- For combination products, antagonist – 95% CI for PK metrics (e.g., Cmax, AUC) should be greater than 80.00%

Summary of Abuse Deterrence Evaluation of Generic Opioid Products

- If the RLD has labeling describing AD properties for at least one route of abuse, the generic oral opioid drug products should be no less AD than RLD with respect to all potential routes of abuse:
  - **Oral** route –
    - in vitro extractability studies
    - in some cases, in vivo oral PK studies (chewing or crushing) depending upon labeling for RLD
  - **Parenteral** route – in vitro syringeability studies
  - **Nasal** route –
    - in vitro characterization
    - in vivo nasal PK studies if ADFs can be pulverized in particles of a certain size
    - in vivo PD studies if there is an aversive agent
  - **Inhalation** route – in vitro sublimation studies

- **Product-specific guidance** – continue to monitor for the availability of new and revised guidances in the *Federal Register* and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm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