Scientific Considerations for Abuse Deterrent Generic Opioid Drug Products

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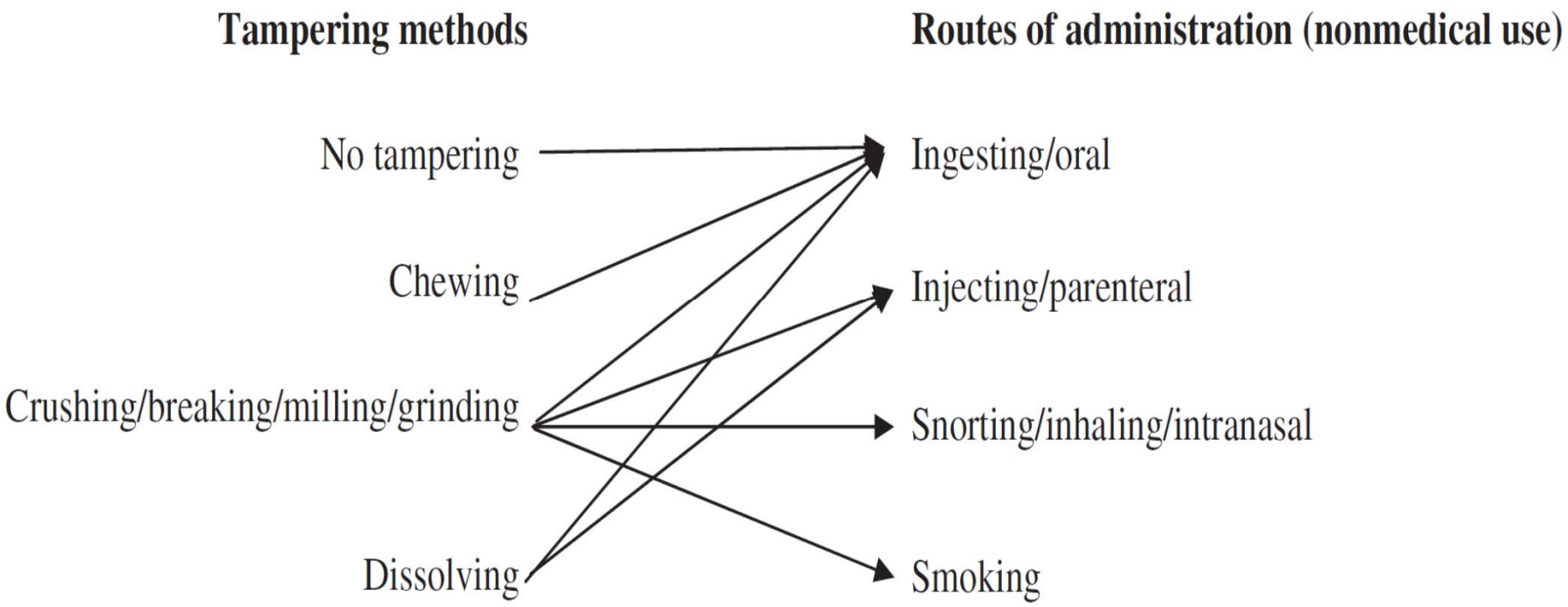
Abuse of Prescription Opioid Drug Products

- In the United States, opioid overdose is one of the leading causes of accidental death
- The Agency has taken several measures to mitigate this problem:
  - Appropriate labeling
    - Boxed warnings
  - Risk evaluation and mitigation strategy (REMS)
  - Make available abuse-deterrent opioid drug products

Common Tampering Methods and Abuse Routes



Katz N et al. Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. Am J Drug Alcohol Abuse. 2011; 37:205-217

Abuse-Deterrent Formulations

- Physical/ Chemical Barrier

  Physical barrier – Prevent chewing, crushing, cutting, grating, or grinding

  Chemical barrier – Resist extraction of opioids using common solvents
- Agonist/Antagonist combinations

  Interfere, reduce, or defeat euphoria associated with abuse
- Aversion

  Produce unpleasant effect if the dosage form is manipulated or higher dosage
- Delivery system

  Designs or methods of drug delivery offering resistance to abuse
- Prodrug

  Prodrug lacks opioid activity until transformed in the GI tract
- Combination

  Two or more of the above methods can be combined

- **Other Technologies Under Development**

U.S. Food and Drug Administration
Protecting and Promoting Public Health

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NEWS

FDA Leaning Toward Requiring Generic Opioids to Contain Abuse-Deterrent Qualities, Hamburg Says

Latest News | Posted: 11 January 2013

By Alexander Gaffney, RF News Editor

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Join the discussion on Regulatory Exchange

US Food and Drug Administration (FDA) Commissioner Margaret Hamburg, writing in a letter to congressional legislators, has determined that the agency has the regulatory authority to require generic medications containing opioids to have abuse-deterrent qualities, providing a potentially significant boost to branded opioid manufacturers who for months have argued that their potential generic competitors should not be allowed to market first-generation non-abuse-deterrent opioid products.

"As part of the agency's review, Hamburg said regulators were now reviewing the evidence to determine if the newer formulations "actually deter abuse."

If the newer formulations are found to deter abuse, the agency will have the legal authority to require generic versions of the products to have those qualities as well, though Hamburg stopped short of saying that FDA definitely would exercise that authority."

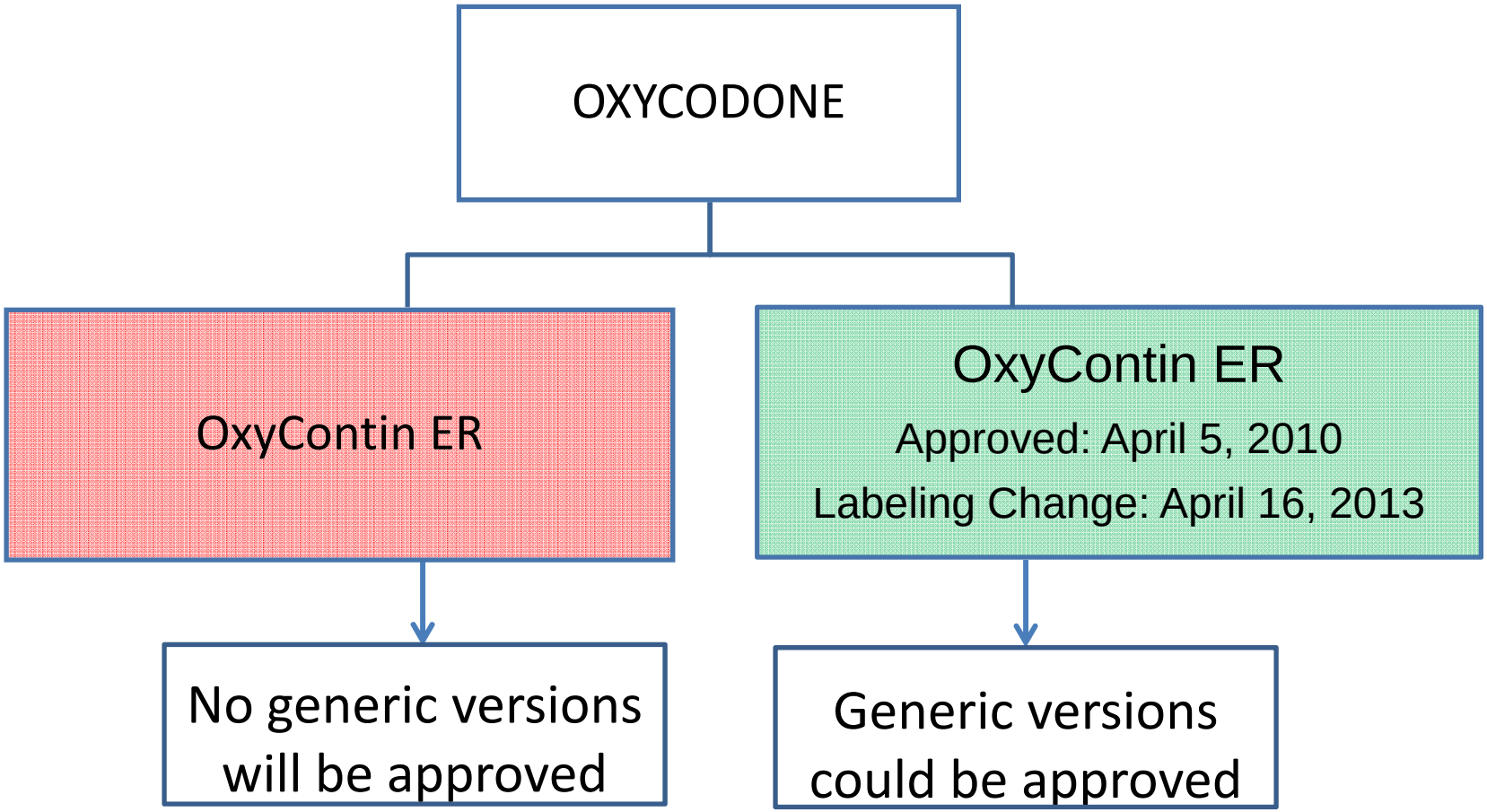
What is a Generic Drug?

- A Generic drug is therapeutically equivalent to the brand name drug.

- FDA Practice
  - Pharmaceutical Equivalence + Bioequivalence = Therapeutic Equivalence

- Therapeutic Equivalence
  - "Drug products are considered to be therapeutic equivalents if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."

FDA's Policy

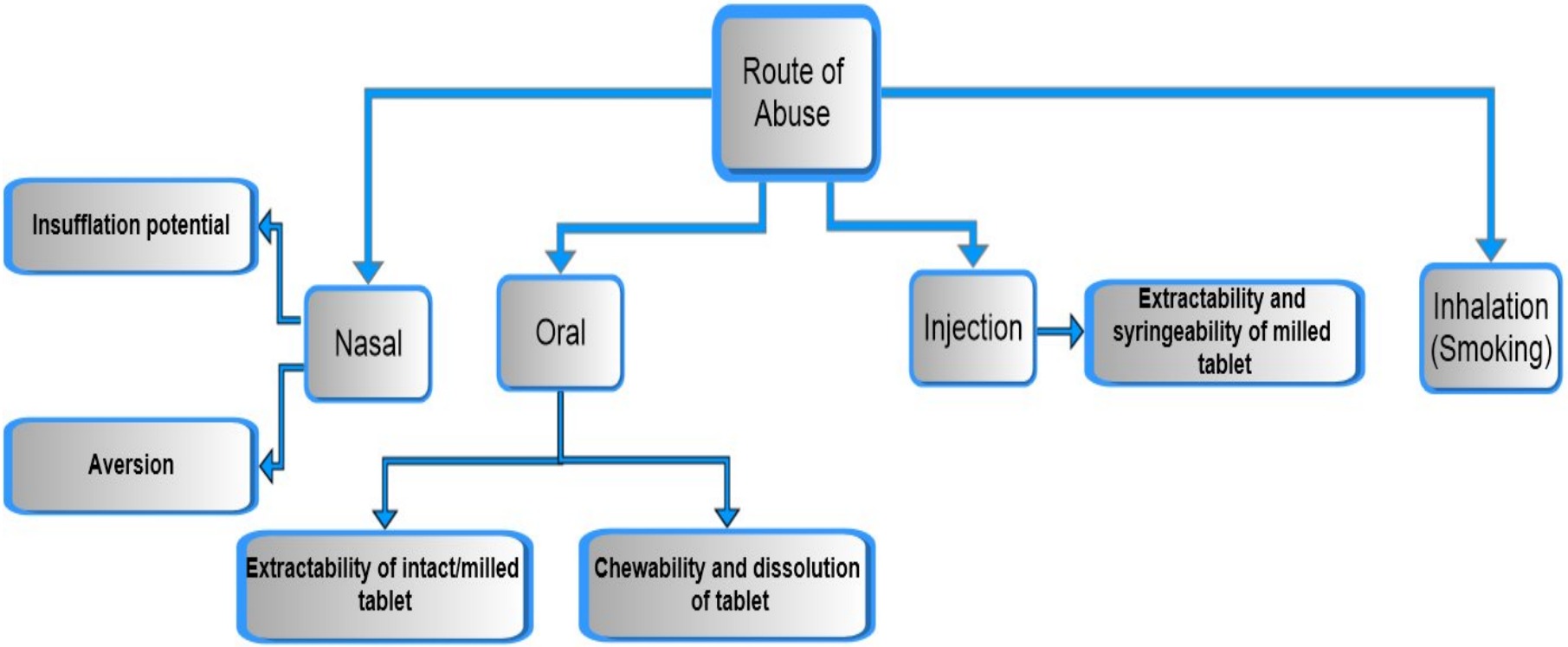


Withdrawn from sale for reasons of safety and effectiveness

Current Thinking

- The abuse-deterrent formulations developed to date do not totally eliminate misuse or abuse.
- The generic should not be less abuse deterrent than the RLD.
- OGD will have sponsors follow a step-wise approach to evaluate abuse-deterrent properties of the test product (T) and RLD, using an array of tests.

Current Thinking



Alcohol-Induced Dose Dumping

- Palladone® (hydromorphone modified-release product, NDA # 021044) was withdrawn from sale due to uncontrolled release of the drug with concomitant alcohol use.

- At present, all generic versions for modified-release opioid drug products are required to conduct in vitro alcohol-induced dose dumping study to ensure that the generic drug product is no worse than the RLD upon exposure to alcohol.

Guidance for Industry
Residual Drug in Transdermal and Related Drug Delivery Systems

The amount of residual drug substance in TDDS, TMDS, and topical patches has a significant potential to impact the products' quality, efficacy, and safety (including abuse potential).

It is expected that the amount of residual drug in a newly developed system (including new generic drug products) will not exceed that of similar FDA-approved products.

This discussion of the product and process development and justification for the final formulation and system design.

OGD's Research Initiatives

The science of abuse-deterrence is evolving and additional work is needed

Internal initiatives:

OGD is collaborating with the FDA laboratory to develop standards for evaluation of abuse-deterrent properties of generic opioid products

External initiatives:

Evaluation of Drug Product Formulation and in-vitro performance characteristics related to abuse-deterrence for solid oral dosage forms of opioids**:**

https://www.fbo.gov/?s=opportunity&mode=form&id=81097151079184467f03b5fcb431b4f2&tab=core&_cview=0

Next Steps..

- Develop decision trees that will aid in the evaluation of generic opioid drug products.

- Knowledge gained from internal and external research initiatives will be used to better inform the evaluation standards for generic opioid drug products

- Agency's recommendations for generic opioid drug products will be communicated through Draft Guidance

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