Summary and Discussion Points for Pharmacokinetic (Category2) & Clinical Abuse Potential Studies (Category3)

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FDA Guidance: Conceptual Framework for Evaluation

FDA considers the development of these products **a high public health** priority.

…the extent to which an abuse-deterrent product is able to reduce abuse will **never be absolute**.

…FDA will take a **flexible, adaptive** approach to the evaluation and labeling of potentially abuse-deterrent products

Pharmacokinetics: Category 2

- Silvia's Questions:
  - What is the impact of the rate of rise, which may contribute to differential abuse potential among drugs, formulations, and routes of administration?
  - Is it possible to predict clinical abuse potential study results based on different pharmacokinetic profiles between formulations?

Panel Recommendations

Pharmacokinetic parameters such as Cmax, Tmax and AUC will nearly always need to be evaluated in the context of pharmacodynamic outcomes

- Particularly for intranasal studies
- Possible exception of oral study where PK of tampered is identical to PK of intact (for simple physical barrier formulation)

Pharmacokinetic data alone can answer questions about BE/BA, food effects , alcohol interactions

Subject Selection and Qualification

- Do the following influence subject selection?
  - Dose or doses of the test drug
  - Range of doses of the test drug
  - Setting or establishment of an appropriate placebo response

Use of <u>same</u> (or intermediate dose) in Qualification appears to have advantages over use of a lower dose

- Lower dose may result in plateau effects, increased dropouts and select for a less relevant population
- Subject eligibility criteria should attempt to strike balance between Type I and Type II errors (e.g., 2 doses vs. 1 dose in qualification)

Blinding and Manipulation

- How can we improve blinding?
- Is it acceptable to encapsulate crushed product that can not be taken into a solution?

- Lack of public data on appropriate manipulation techniques
- Blinding should be undertaken, but not to extent that it obliterates the features of the formulation you are trying to assess in the study
- (Encapsulation may be acceptable but should generally be last resort:
  - use of alternative vehicles (tomato juice? Apple sauce?) or placebo solution manipulations (flour in placebo solution?) preferable)

Measures and Interpretation

- Measures
  - Does it make a difference if measures are taken in a unipolar or a bipolar scale(s)?

- Primary measures of Drug Liking should be bipolar for most cases
  - Unipolar measures such as Good and Bad Effects important for interpretation

- Over reliance on Emax may increase risk of false negative
- Consider whole profile of effects and **in particular** end-of-day/next-day measures of Overall Liking and Take Drug Again
- Derived endpoints evaluating time course profile important for interpretation
- Value of open-ended feedback or development standardized follow-up questions?

Interpretation and CID

- Interpretation of results
  - What constitutes a clinically significant difference in drug liking between the test drug and positive controls?

Insufficient data <u>currently</u> available to support <u>pre-specifying</u> $\boldsymbol{\delta_1}$ super superiority margin

- $\boldsymbol{\delta_1}$ must be based on scientific/regulatory consensus
- Sufficient data to pre-specify $\boldsymbol{\delta_2}$ (PBO-Control) but probably not needed

- Interpretation of clinical relevance should consider whole profile of effects → Convergence of data
- Make use of anchors on bipolar scales – Strong liking/disliking vs. Neutral
- Make better use of other arms within the study (e.g., PBO vs. Test; intact arm in oral study, oral arm in IN study) or add additional comparisons → preferable to adding multiple doses
- (Start to consider how we may develop non-inferiority/equivalence margins in comparison to existing ADFs?)

Statistics

- Statistical analysis
  - What is the best approach?

Recommendations for statistical analysis relatively clear

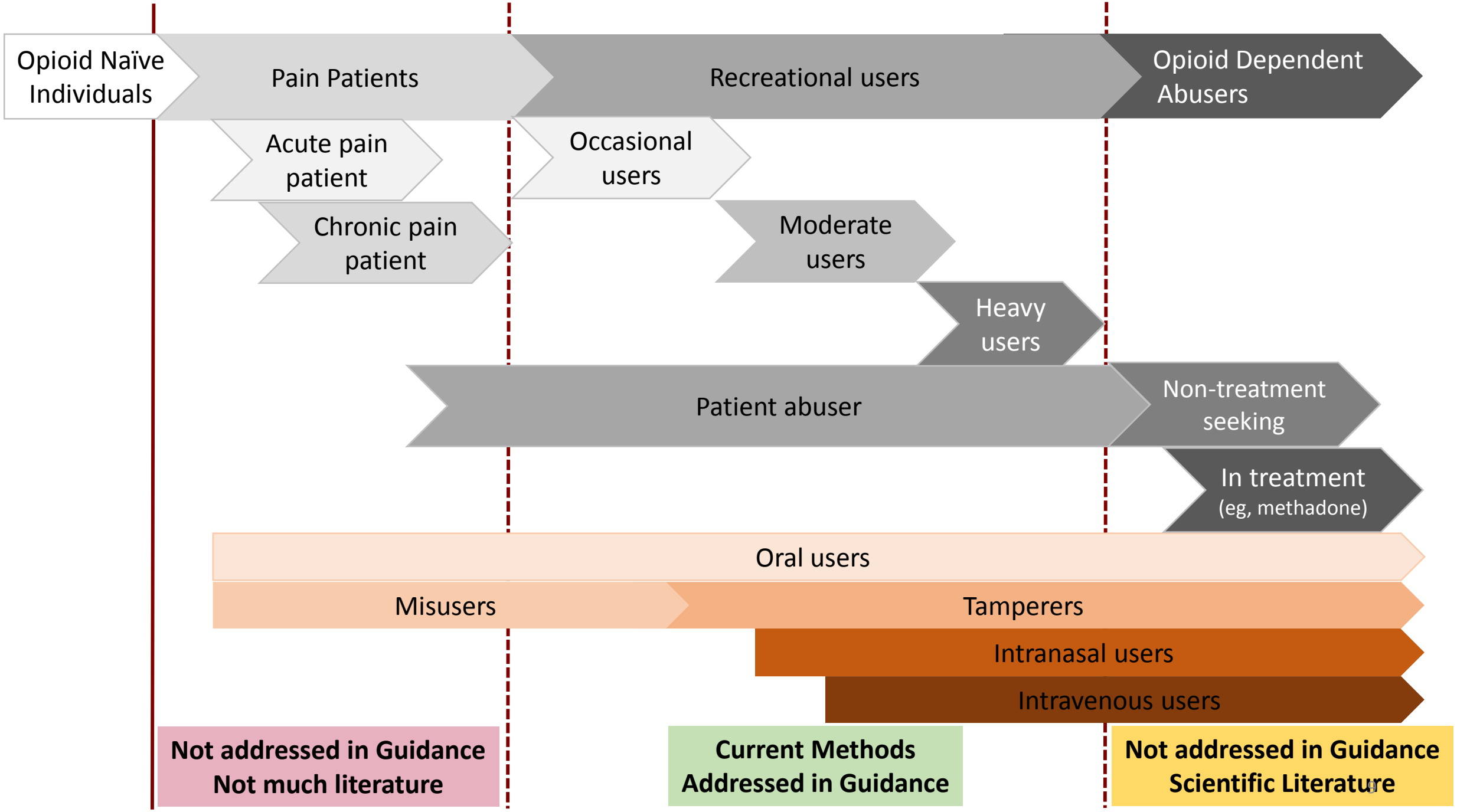
- Data may require non-parametric methods not mentioned in guidance

Use of responder analysis to arbitrarily convert continuous Drug Liking variable into categorical variable

- Potential loss of power
- Interpretability, i.e., assumptions of clinically relevant margins X 2 (% of subjects and % decrease in Liking)

Data presentations must consider the end-users of the labels (prescribers)

- Data presentation should be familiar and easy to understand


Opioid Naïve Individuals
Pain Patients
Recreational users
Opioid Dependent Abusers
Acute pain patient
Occasional users
Chronic pain patient
Moderate users
Heavy users
Patient abuser
Non-treatment seeking
In treatment (eg, methadone)
Oral users
Misusers
Tamperers
Intranasal users
Intravenous users
Not addressed in Guidance Not much literature
Current Methods Addressed in Guidance
Not addressed in Guidance Scientific Literature