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# Adapting Traditional Human Abuse Liability Testing to Tobacco Products

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# What is Abuse Potential?

# Abuse Potential as per FDA

**Assessment of Abuse Potential of Drugs – Guidance for Industry (January 2017)**

- Abuse Potential (AP) – the likelihood that a drug product or substance will be intentionally used in a non-therapeutic manner to achieve a desired psychological or physiological effect
- Dependence
  1. Physical:
     - withdrawal symptoms after abrupt discontinuation of the drug
     - mitigated drug response after repeated dosing resulting in a higher dose requirement to elicit the same response once achieved with a lower dose (tolerance)
  2. Psychological:
     - Mental desire to seek rewarding properties of the drug
- What is the link?

Reward → Abuse → Dependence → **Addiction**

# FDA Requirements for Drugs

# FDA Requirements for Abuse Potential Characterization

**Assessment of Abuse Potential of Drugs – Guidance for Industry (January 2017)**

- Section III-C: All primary data related to the abuse potential characterization of the drug from:
  - a. Chemistry
  - b. Receptor-ligand binding and functional studies
  - c. Pharmacokinetics
  - d. Abuse-related animal studies
  - e. Human abuse potential laboratory & physical dependence studies
  - f. Abuse-related adverse events from clinical studies
  - g. Any overdose related information from clinical studies
  - h. Incidence of abuse during clinical studies

# Human Pharmacokinetics & AP Studies

- Pharmacokinetic studies
  - The PK profile is very important in determining the abuse potential of a substance
    - Faster Tmax and higher Cmax → rapid onset of effect
    - Shorter half-life → greater drug seeking behaviour
- Drug discrimination
- Behavioural economics
- Acute dose-effect studies
  - Within subject comparison of varying doses, positive/negative controls
  - Pre-qualification phase – baseline discrimination testing adds statistical power
  - Most common approach, high predictive validity

# Drug AP - What Do We Want to Know?

- What are the endpoints?
  - Subjective measures (VAS):
    - Drug liking (at the moment, overall), would take drug again
    - Positive and negative effects
    - Drug similarity
  - Questionnaires:
    - Addiction Research Center Inventory (ARCI)
    - Profile of Mood States (POM)
  - Physiological:
    - Pharmacokinetics
    - Pupillometry (opiates), tachycardia (stimulants)

# FDA Requirements for New Tobacco Products

# FDA Requirements for AP of New Tobacco Products

## Pre-Market Tobacco Product Applications for ENDS – Draft Guidance (May 2016)

- Section VI – H(2)
  - Abuse liability evaluations should consider the addictiveness and abuse and misuse potential of the e-liquid and aerosolizing apparatus independently as well as when the products are used together
  - Exposure to nicotine during use (pharmacokinetic data)
  - Other considerations:
    - Likelihood of tobacco users switching from other tobacco products to the new tobacco product
    - Likelihood of nonusers, never users, and former users, who may initiate or relapse tobacco use with the new tobacco product

# FDA Requirements for AP of New Tobacco Products (cont'd)

**Modified Risk Tobacco Application – Draft Guidance (March 2012)**

- Section VI – A(2-3)
  - Effect on tobacco use behaviour among current tobacco users
    - Human studies to assess the abuse liability and the potential for misuse of the product as compared to other tobacco products on the market
    - Likelihood that current tobacco users will start using the product (switching)
  - Effect on tobacco use initiation among nonusers
    - Likelihood that consumers who have never used tobacco products will initiate use of the tobacco product
- Section VI – B(3)
    - Impact of pharmacologically active constituents and other ingredients on the speed and efficiency of nicotine delivery and the formation of unprotonated nicotine

# Abuse Potential of Tobacco – What is the focus?

# Human AP of Tobacco – What Is the Focus?

- Abuse potential for drugs
  - Multiple pharmacological classes
  - Almost limitless number of different molecules to consider
- Abuse potential for tobacco products
  - One molecule to consider - nicotine
  - Does this make things less complicated ? Not at all!

# Complications of Nicotine Pharmacokinetics and AP

- Abuse potential influenced by rate and extent of nicotine exposure (Tmax, Cmax)
  - Inhalation (i.e.: smoking) leads to rapid delivery of nicotine into lungs and brain = high abuse potential
  - Buccal/oral or dermal absorption is slower and has lower bioavailability = lower abuse potential
- PK influenced by user behavior and experience
  - Inexperienced users
  - Experienced users - adaptable
- Physical properties
  - Particle size

# Complications from Reinforcing Effect of Sensory Stimuli

- Smoking produces a distinct sensory stimulus that can be attractive, pleasurable and reinforcing
- Denicotinized cigarettes when used by dependent subjects
  - Show significant subjective 'liking' VAS scores
  - Can alleviate some of the craving and withdrawal
- Other additives and by-products
  - Humectants, flavours, acetaldehyde
- Therefore, it cannot be assumed that the 'liking' scores from smoking come just from nicotine delivery

# Use of Different User Populations To Predict HAP

- Current users
  - Most likely population to switch to new tobacco product
  - Should discrimination testing be implemented?
  - Level of experience can influence subjective ratings
    - Can include training period of ad libitum use
    - Include subjects with familiarity of new product (i.e.: E-cigs)
  - Positive control is their ‘own brand’ cigarettes
- Nonusers or former users
  - At risk population of starting/re-starting tobacco use
  - Cigarettes not necessarily an appropriate positive control
  - Non-pharmacological factors more influential?

# Tobacco AP - What Do We Want To Know?

- What are the endpoints?
  - Subjective measures (VAS):
    - Product liking, use of product again
    - Direct effects of nicotine or product
    - Abstinence/withdrawal symptoms
  - Questionnaires:
    - Questionnaire of Smoking Urges (QSU Brief)
    - Modified Cigarette Evaluation Questionnaire (mCEQ)
  - Physiological:
    - Pharmacokinetics
    - Cardiovascular

# HAP of New Tobacco Products – A Balancing Act

- Goal with drugs is to eliminate the human abuse potential
- Goal with most modified risk tobacco products is to switch over smokers BUT not convert naïve or former users to users of the new product
  - If HAP is eliminated, then smokers are not likely to switch
  - If HAP is too high, then risk of naïve subjects initiating use and becoming dependent increases

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# Q&A

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# Thank you!

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