The Role of Abuse Potential Assessment in Biologics Development

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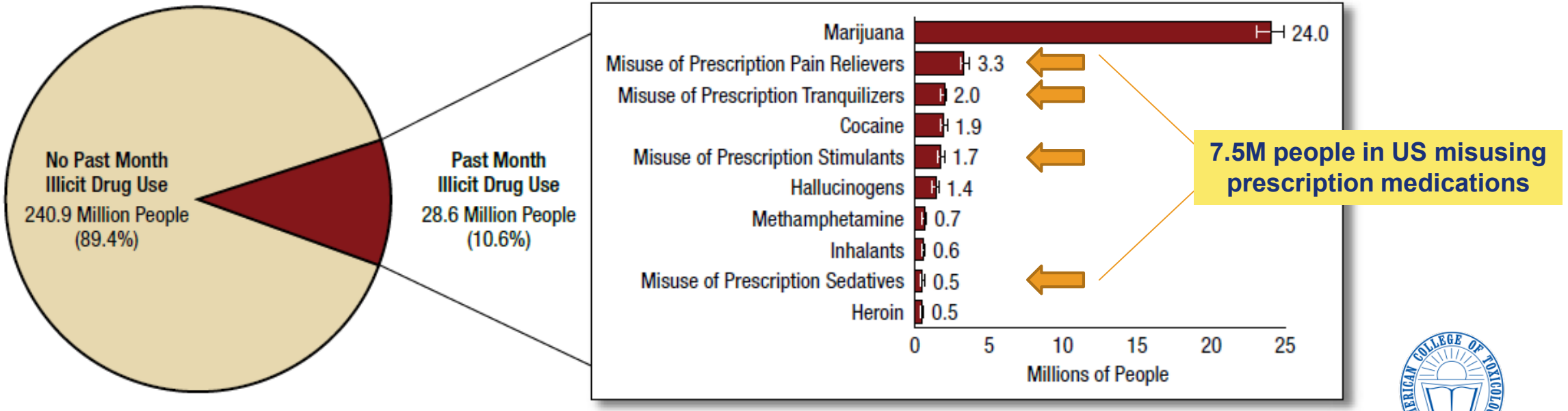
Overview

- Background
  - Why Health Authorities are concerned about abuse liability
- Regulatory obligations
- How is abuse potential assessed during drug development?
- Distinctions between large and small molecules and their impact on abuse liability
- What do we know about the CNS effects of large molecules?
- Summary and conclusions, references/resources

Why regulators are concerned about abuse liability

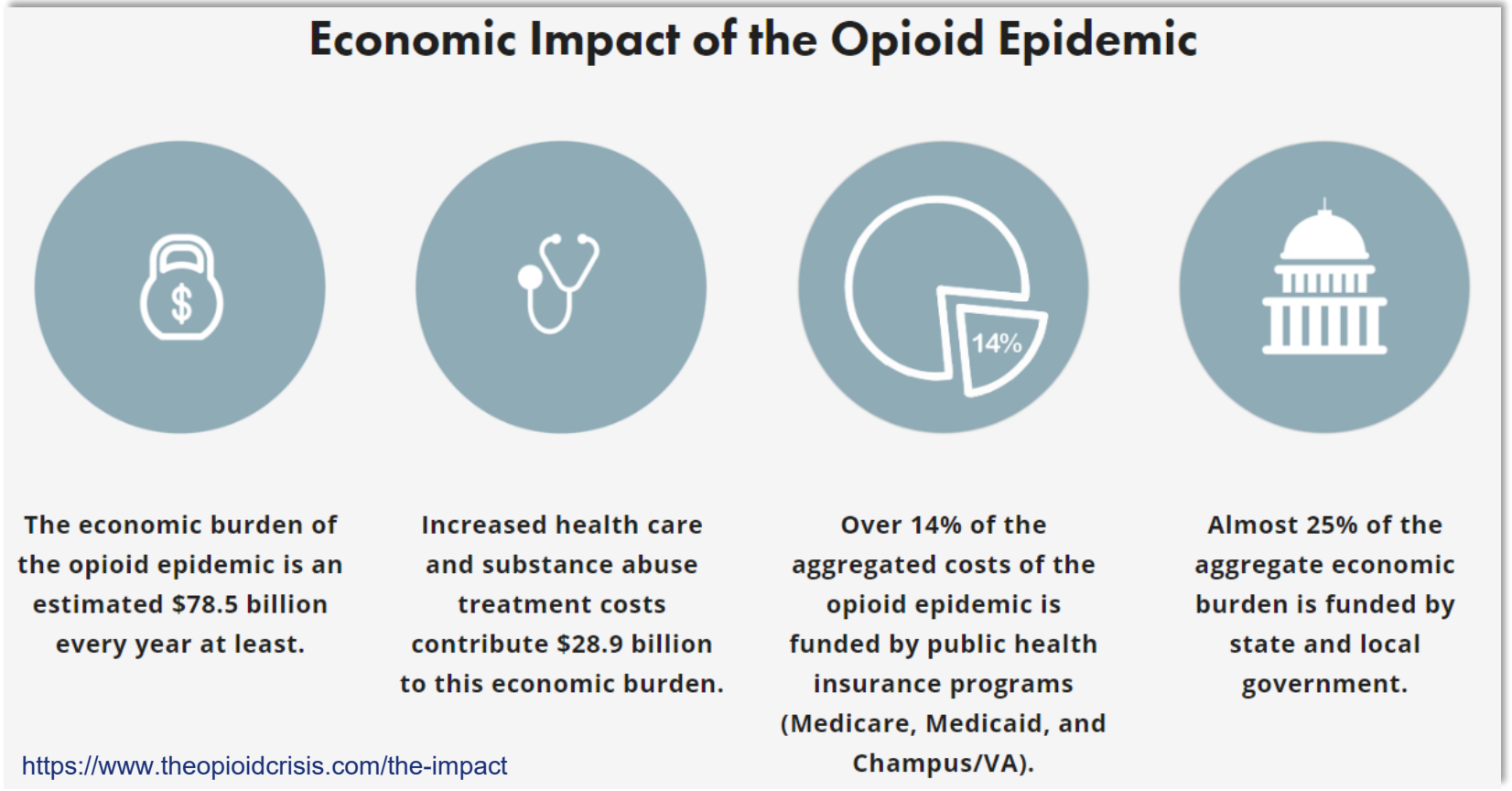
- Prescription drug abuse is a significant public health crisis
  - In 2017, >70,000 overdose deaths, majority from opioids; most opioid abusers started with prescription opioids
  - Prescription and illicit stimulant abuse on the rise
  - Abuse liability of some drugs increasing due to increased availability (e.g., gabapentin)



Substance Abuse and Mental Health Services Administration (2017)

Beyond the individual, tremendous societal impacts of abuse

https://www.northpointrecovery.com/blog/10-surprising-statistics-addiction/



https://www.theopioidcrisis.com/the-impact

Definitions (1)

- Abuse potential
  - A property of a drug, due to its activation of central reward circuitry, leading to its likelihood to be abused
- Abuse
  - Intentional non-therapeutic use of a drug to achieve a desired psychological or physiological effect
    - Euphoria, hallucinations, sedation, etc.
- Abuse liability
  - The probability that a drug will be abused in light of its abuse potential as well as additional factors, including availability, amenability of formulation to abuse, etc.
- Drug misuse
  - Non-medical use of a drug substance for a purpose or in a population other than that for which is was approved. Includes abuse, but broader.
    - e.g., erythropoietin (EPO)

Definitions (2)

- Drug
  - The Federal Food Drug and Cosmetic Act (FD&C Act) and FDA regulations define the term drug, in part, by reference to its intended use, as “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” and “articles (other than food) intended to affect the structure or any function of the body of man or other animals.”
  - Commonly understood to be chemical substances used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being
- Biotechnology-derived pharmaceutical (‘biologics’ per ICH S6(R1)
  - Products derived from characterized cells through the use of a variety of expression systems including bacteria, yeast, insect, plant, and mammalian cells
  - The active substances include proteins and peptides, their derivatives and products of which they are components; they could be derived from cell cultures or produced using recombinant DNA technology including production by transgenic plants and animals

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Regulatory guidance related to abuse liability

- FDA – Assessment of Abuse Potential of Drugs (2017)
  - Provides key definitions, info on nonclinical and clinical AL studies
  - "*Drug products with abuse potential generally contain drug substances that have CNS activity and produce euphoria (or other changes in mood), hallucinations, and effects consistent with CNS depressants or stimulants*"
- EMA – EMA/CHMP/SWP/94227/2004 (2006)
  - More emphasis on dependence
- Health Canada – Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity (2007)
- Japan – Yakuma Notification # 113 and 383 (1975, 1978)
- ICH – M3(R2)
  - *"There are regional guidance documents on the conduct of nonclinical abuse liability assessment that can be helpful in designing specific abuse liability packages"*

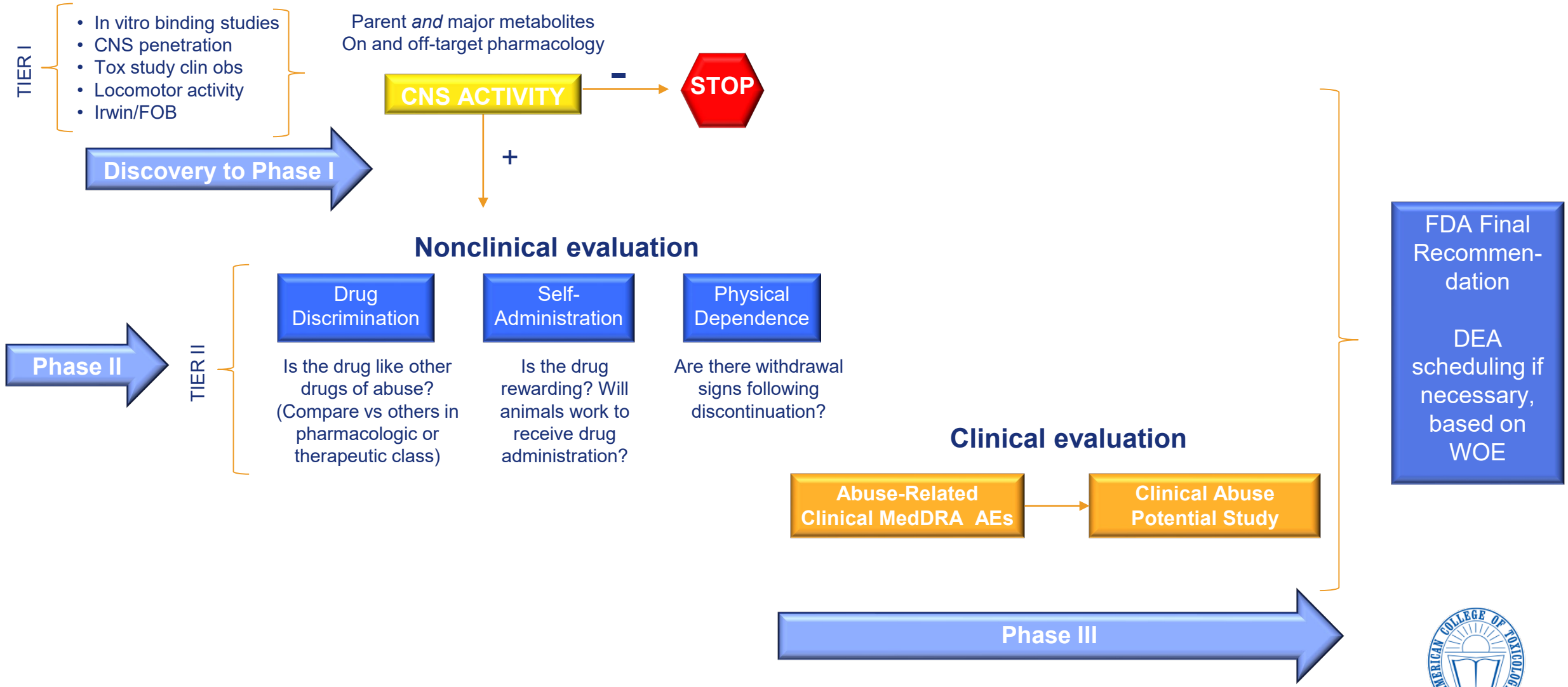
How is abuse liability assessed?

Regulatory perspective

- A comprehensive, science-based evaluation of
  - Chemistry of the clinical candidate
  - Pharmacology studies (in vitro and in vivo)
  - Clinical studies
    - Pharmacokinetics and pharmacodynamics
    - Safety and efficacy
    - Human abuse potential
  - Abuse-related AEs reported in all clinical trials
  - Epidemiological studies
- The 2017 FDA guidance outlines expectations of Sponsors
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm198650.pdf
- This evaluation yields an Abuse Liability Assessment that can be discussed with Health Authorities

Abuse liability assessment – overview

Industry perspective



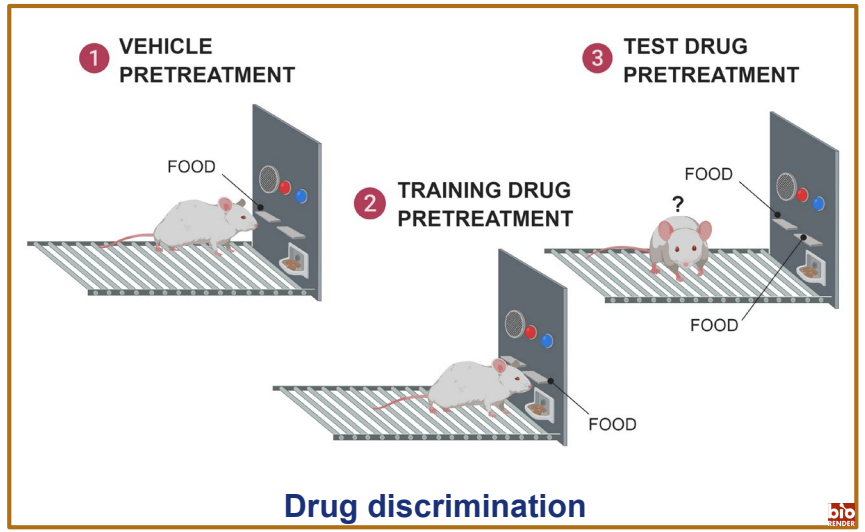
Zooming in: Preclinical abuse liability assessment (Tier 1)

- CNS penetration (regardless of therapeutic indication)
  - Direct measurement of CNS concentration
  - Observation of behavioral effects (stimulation, depression, performance changes), which can be obtained from pharmacology and/or general toxicology studies
  - Effects on CNS circuitry
    - EEG
    - Cerebral Microdialysis
- Novel modes of action
  - FDA are becoming more conservative in approaching
    - Prove that your clinical candidate is unlike standard/recognized drugs of abuse
- Active metabolites > 10% of parent must have its own assessment
- Biologics ***are not excluded*** at this time

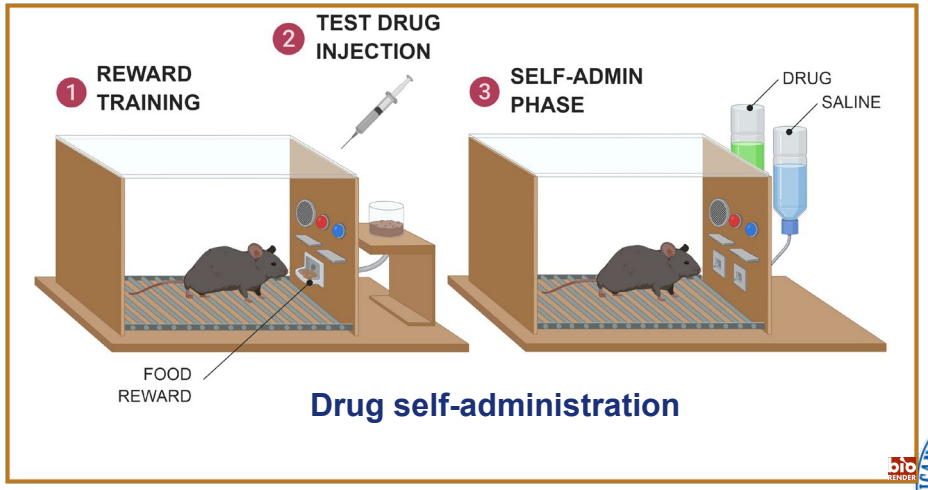
A summary of these findings in conjunction with a description of clinical AEs constitutes the typical abuse liability assessment, provided there are no signals of concern

Zooming In: Preclinical abuse liability assessment – Tier 2

- Drug discrimination – can an animal distinguish between drug and vehicle, and does the drug seem similar to a known drug of abuse?
- Drug self-administration – will animals actively work to receive doses of drug?
- Dependence potential – does administration of the drug produce tolerance, and/or does discontinuation of the drug cause symptoms of withdrawal?
- Underlying all these assays is the assumption that the PK of your drug, and relevant comparators, is well described
  - It's important to ensure coverage over the drug discrimination session and ensure exposure following IV self-administration, and may require frequent dosing in the dependence study



Drug discrimination



Drug self-administration

Clinical abuse liability assessment

- Phase I, II, and III events of:
  - Euphoria (euphoria, euphoric mood, elevated mood, mood alteration, feeling drunk, feeling abnormal)
  - Drug abuse
  - Hallucinations (visual and auditory)
  - Thinking abnormal
  - Sedation/somnolence
  - Cognitive impairment, confusion, ataxia
  - Insomnia
  - Dizziness, psychosis, aggression (captures NMDA-like effects)
- Adherence – excessive use or diversion during clinical development
- Physical dependence/tolerance
- Dedicated Clinical AP Study.

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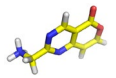
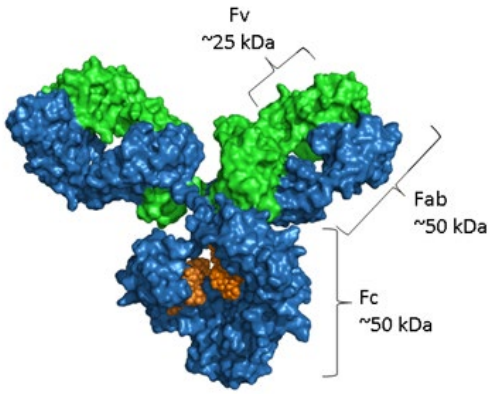
Characteristics of large vs. small molecule drugs

Characteristic	Small Molecule Drugs	Biologics
Production mechanism	Chemically synthesized	Produced by a host cell
Size	Low molecular weight	High molecular weight
Physicochemical properties	Well defined, stable High tissue/cell permeability	Complex • May be sensitive to light, heat, other stressors • May possess additional functionality (i.e., effector function) Low tissue/cell permeability
PK properties	• Oral bioavailability, may be administered by different routes • May be metabolized to active intermediate(s) • Short $T_{1/2}$	• Typically administered parenterally (IV/SC) • Catabolized to amino acids • Long $T_{1/2}$



<1000 Da

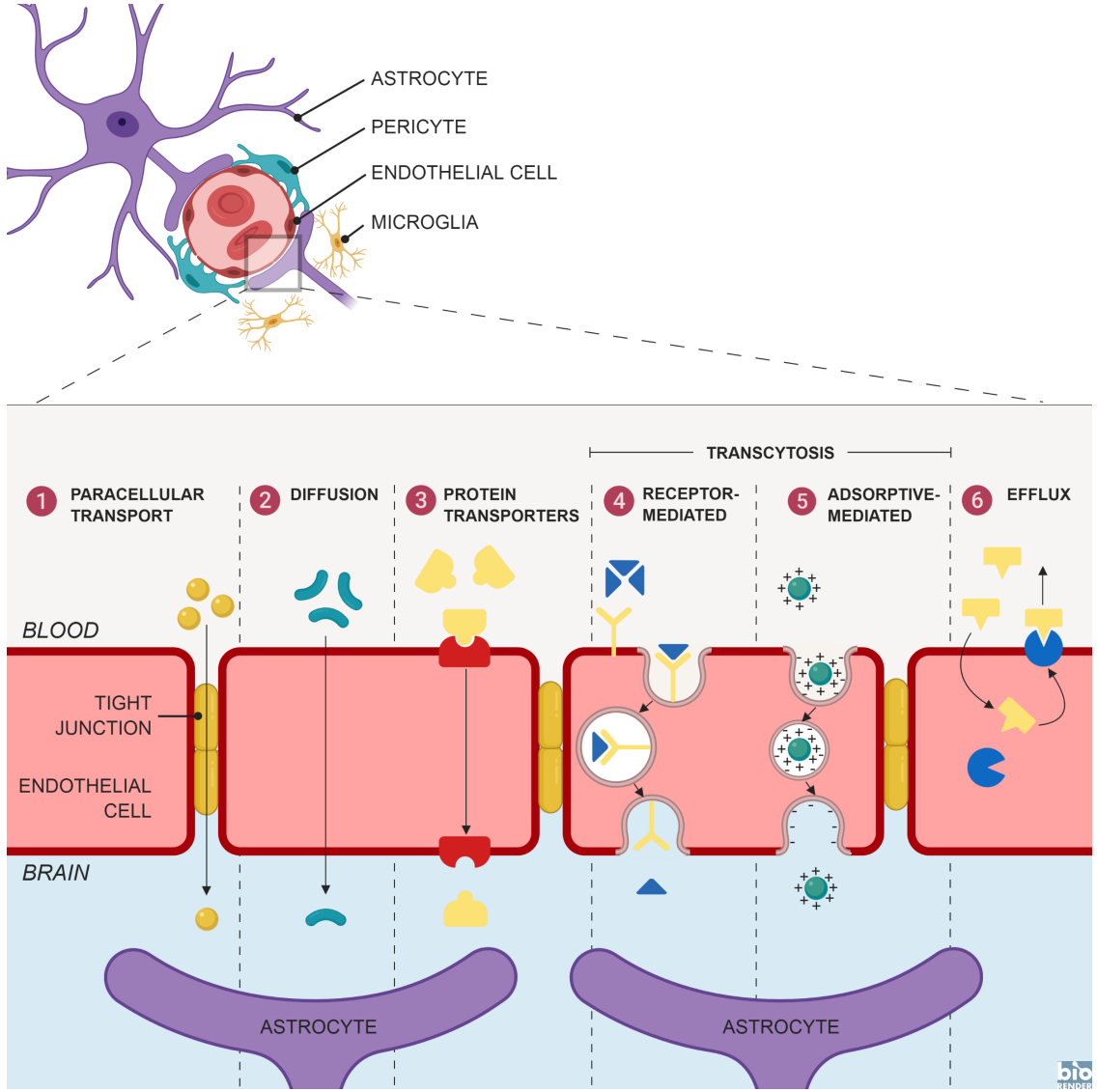


~150 kDa

How do these characteristics influence abuse liability?

- Brain penetration
- Binding to CNS receptors/transporters
- PK characteristics and physicochemical properties

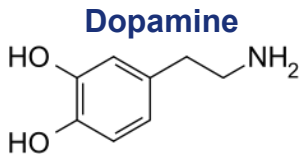
Brain penetration – is the candidate molecule CNS active?

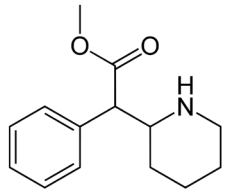


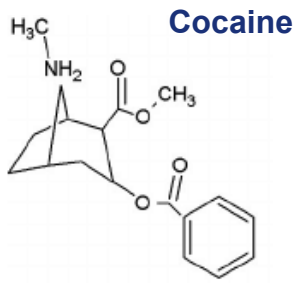
- The BBB is a serious challenge to drug delivery
  - Brain endothelial cells form tight junctions, have fewer fenestrations than endothelial cells in other organs, and possess high levels of efflux pumps (e.g., P-glycoprotein)
  - Large molecule drugs are effectively blocked from accessing the brain
    - Concentrations of therapeutic antibodies reaching the brain are 0.01-0.35% of plasma concentration
    - Exceptions: disease states which compromise BBB integrity; receptor-mediated delivery (Trojan horse technology)

Does the candidate molecule act on receptors of concern?

- Brain penetration
- Binding to CNS receptors/transporters
  - Neurotransmitter systems known to play a role in the biology of addiction include dopamine (DA), norepinephrine (NE), serotonin (5-HT), gamma-aminobutyric acid (GABA), acetylcholine (ACh), opioid, N-methyl-D-aspartate (NMDA), and cannabinoid
  - The ability of a candidate molecule to bind to these neurotransmitter receptors and/or transporters increases the level of concern for abuse liability
  - Small molecules, or metabolites, may target receptors/transporters directly or indirectly
    - They may even be structurally similar to endogenous ligands
  - Large molecules – in particular, monoclonal antibodies – have exquisite target specificity and little off-target binding
    - With few exceptions, large molecules are **not** expected to bind to CNS receptors/transporters
    - By virtue of their size, large molecules are **unlikely** to interact meaningfully with neurotransmitter receptors/transporters to impact their function







What are the duration of action and stability characteristics?

- Brain penetration
- Binding to CNS receptors/transporters
- PK characteristics and physicochemical properties

Characteristic	Small Molecules	Large Molecules
Route of administration	Typically oral, can be dosed by other routes	Typically parenteral due to stability concerns (catabolized in GI)
Half-life (T1/2)	Short half-life (hours)	Long half-life (days to weeks)
Metabolism	Can be transformed to active metabolite which may have CNS activity	Metabolized to inactive component amino acids
Formulation stability	Stable at room temperature, typically no special storage requirement; tampering may not alter pharmacologic activity	Sensitive to changes in storage conditions and stress, not easily stored and distributed; tampering may diminish pharmacologic activity

Overall assessment of molecule characteristics

- The cause for concern that large molecules have abuse potential is **low**
  - Brain penetration is limited
  - Target specificity is high
    - Low risk of binding to CNS receptors/transporters
  - Pharmacokinetics do not favor abuse potential
    - Long half-life is inconsistent with risk of physical dependence
  - Physicochemical characteristics impact stability and influence route of administration
    - Poor stability outside recommended storage conditions (i.e., -70°C to 4°C)
    - Tampering is expected to diminish activity
    - Non-parenteral administration expected to diminish activity
- A weight-of-evidence assessment of abuse liability potential should be undertaken for every candidate therapeutic, regardless of molecule class
- A case-by-case approach should be employed and feedback sought from Health Authorities

Considerations for nonclinical AL studies of large molecules

- Choice of species
  - Large molecule cross-reactivity is typically limited to non-human primates
    - While it is possible to do AL studies in primates, rodents are the preferred species
    - The bar is higher for selection of primates for in vivo studies – 3Rs of ethical animal use
- Route of administration
  - Guidance documents specify that more than one ROA should be evaluated in AL studies because drugs are commonly abused by >1 route, including those which are not the intended ROA
    - Large molecules are administered parenterally due to stability limitations associated with oral delivery
- Assay limitations
  - Drug discrimination assay requires a training drug for which candidate molecule can substitute
    - No mAbs with direct CNS activity available to fulfill this role
  - Drug self-administration assay needs a positive control from same pharmacological class as candidate therapeutic
    - >50 mAbs have been approved, none with demonstrated AL risk, so no positive control exists
  - Demonstration of physical dependence relies on rapid exposure decrease upon discontinuation
    - Long half-life of large molecules precludes abrupt withdrawal

Alternate viewpoints

- Recent publications suggest that despite the considerations discussed today, nonclinical AL studies should nonetheless be done (Gauvin et al., 2015, 2019)
  1. Risk assessment is not a choice
     - Weight of evidence evaluation is a risk assessment
  2. The drug industry is developing therapeutics in conjunction with their delivery systems
     - Majority of biologics don't require delivery systems; if delivery to CNS is intended, then higher level of scrutiny is appropriate
  3. The BBB is not immutable
     - Greater scrutiny when BBB is compromised is warranted
  4. The disease of addiction should be a major focus of the biologics approval process
     - This is an opinion of the authors which is counter to prevailing guidance/regulation
  5. Developing a biologic for treatment of RA without investigating the effects of the biologic on opiate analgesics used to address chronic disease-associated pain is not good science
     - Depends upon the mechanism; a case-by-case, science-based approach is appropriate

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What is known about approved biologics and abuse potential?

- Review of biologics BLAs for AL information
  - From 2010 (when draft FDA abuse liability guidance was published) through 2018, 65 biologic drugs were approved in the US
  - The Overdose, Drug Abuse Potential, Withdrawal and Rebound sections (Sections 7.3.8, 7.6.4, or 8.5.7) of these BLAs were reviewed for content
  - 0 of 65 BLAs contained nonclinical or clinical data in the Drug Abuse Potential sections
    - Some contained no information; others reported receiving confirmation from the CSS that no studies were needed; others provided various rationales for the lack of data
    - Rationale included: no distribution to the CNS; is administered in a hospital setting; is not chemically or pharmacologically similar to known drugs of abuse; has a long half-life; has a toxicity profile incompatible with recreational use

What is known about approved biologics and abuse potential?

- Conducted a search of biologics (mAbs, recombinant proteins, vaccines) in Pharmapendium, reviewing labels for AL signals using terminology acceptable to CSS/FDA
  - 1º Euphoria-related terms
  - 2º Dissociative/psychotic terms
  - 3º Terms indicative of impaired attention, cognition, or altered mood; added neurological signs as part of assessment of CNS activity

Neurological/Psychiatric AE reported in labels

Anticonvulsants (25% of all AEs) Affect and Cognition	mAbs (1.2% of all AEs) Neurological and Cognition	Proteins (2.5% of all AEs) Affect and Consciousness	Vaccines (5% of all AEs) Affect and Consciousness
Somnolence	**Confusional state**	Anxiety	Irritability
Disturbance in attention	Anxiety	Syncope	**Somnolence**
Memory impairment	Nervous system disorder	**Somnolence**	Seizure
Nystagmus	Seizure	Seizure	Agitation
Euphoric mood	Somnolence	Agitation	Nervousness
Hallucination			

- CNS signs are rare, and certainly more related to negative than positive affective states

Why are there *any* CNS-related AEs with biologics?

- Some spurious / not drug-related
- Peripheral immune response → central effect
  - e.g., CAR-Ts and encephalopathies
  - Cytokines → sickness behavior
- Interaction of disease process with medication, e.g., alterations in BBB permeability
  - Interferons – reduce 5-HT synthesis via endocrine pathways → depressive symptoms
- Vagal stimulation
- Active transport into CNS (e.g., insulins)
- Biology that we still don't fully understand

Summary and Conclusions

- Abuse liability assessment is an integral part of the development of drug and biologic candidates
  - A weight-of-evidence assessment should be undertaken for every candidate therapeutic, regardless of molecule class or therapeutic indication
    - Not necessarily to include dedicated Abuse Potential Studies
- Available guidance documents define expectations, but important considerations must be taken into account depending on molecule class
- The cause for concern that large molecules have abuse potential is **low**
  - Nonetheless, potential direct or indirect CNS activity should be carefully monitored in clinical trials
- A case-by-case approach should be employed and feedback sought from health authorities in the development of new biologics
  - The conduct of unnecessary and inappropriate in vivo AL studies is contrary to 3Rs principles of ethical animal use

Resources

- Nonclinical Assessment of Abuse Potential for New Pharmaceuticals (2015)
  - Editors: Markgraf, Hudzik, and Compton; Academic Press
- de Zafra, Markgraf, Compton, and Hudzik, Abuse liability assessment for biologic drugs – All molecules are not created equal. *Reg. Tox. Pharm.* 92: 165-172 (2018)
- Cross-Company Abuse Liability Council (CCALC)
  - Mission: to improve public health by advancing the science of assessing abuse liability and potential across the product life cycle to promulgate best practices by working with regulators, academic researchers, and public policy advocates
  - Work Groups include Preclinical, Clinical, Regulatory, Post-marketing, and Abuse-Deterrent Formulations
  - Has interacted directly with FDA from 2008-2018