FDA Perspective on Long Acting Antiretrovirals for HIV Prevention

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Outline

- Development Scenarios
- Drug Development Considerations
  - Preclinical
  - Dose selection
  - PK/PD
  - Trial design
- Nanoformulations
- Summary

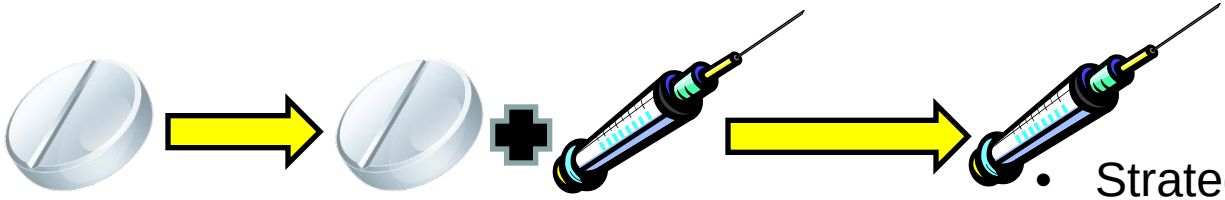
Scenarios For Prevention

- Approved Oral ARV → Long Acting Injectable or other delivery system
- New Investigational Long Acting ARV

New Long Acting Formulation (Injectable) Scenarios

Dose oral to steady state

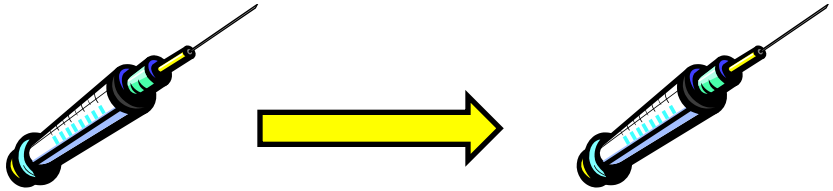
- Rule out safety concerns (eg hypersensitivity)
- Ensure “target” exposures are met



Dose oral

Overlap oral and injection dosing

- Strategy depends on ability to achieve “target” exposures



Loading injection dose

Maintenance injection dose

- May be ideal if no immediate safety issue, adequate exposures with loading dose

Approved ARV for Treatment ⇨ Prevention

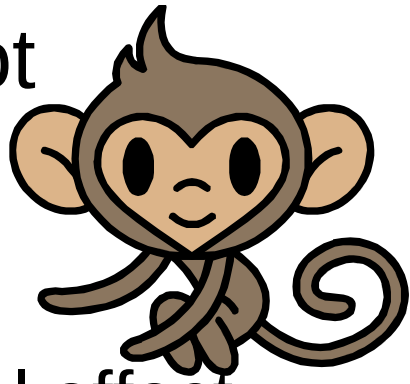
- Clinical trial needed regardless if using same formulation as treatment or different formulation [oral to injection]
- Exposure-response not known to bridge treatment and prevention response
- What's important: systemic exposures, genital secretion/tissue exposure, etc?
- No validated biomarkers

Investigational Long Acting ARV For Prevention

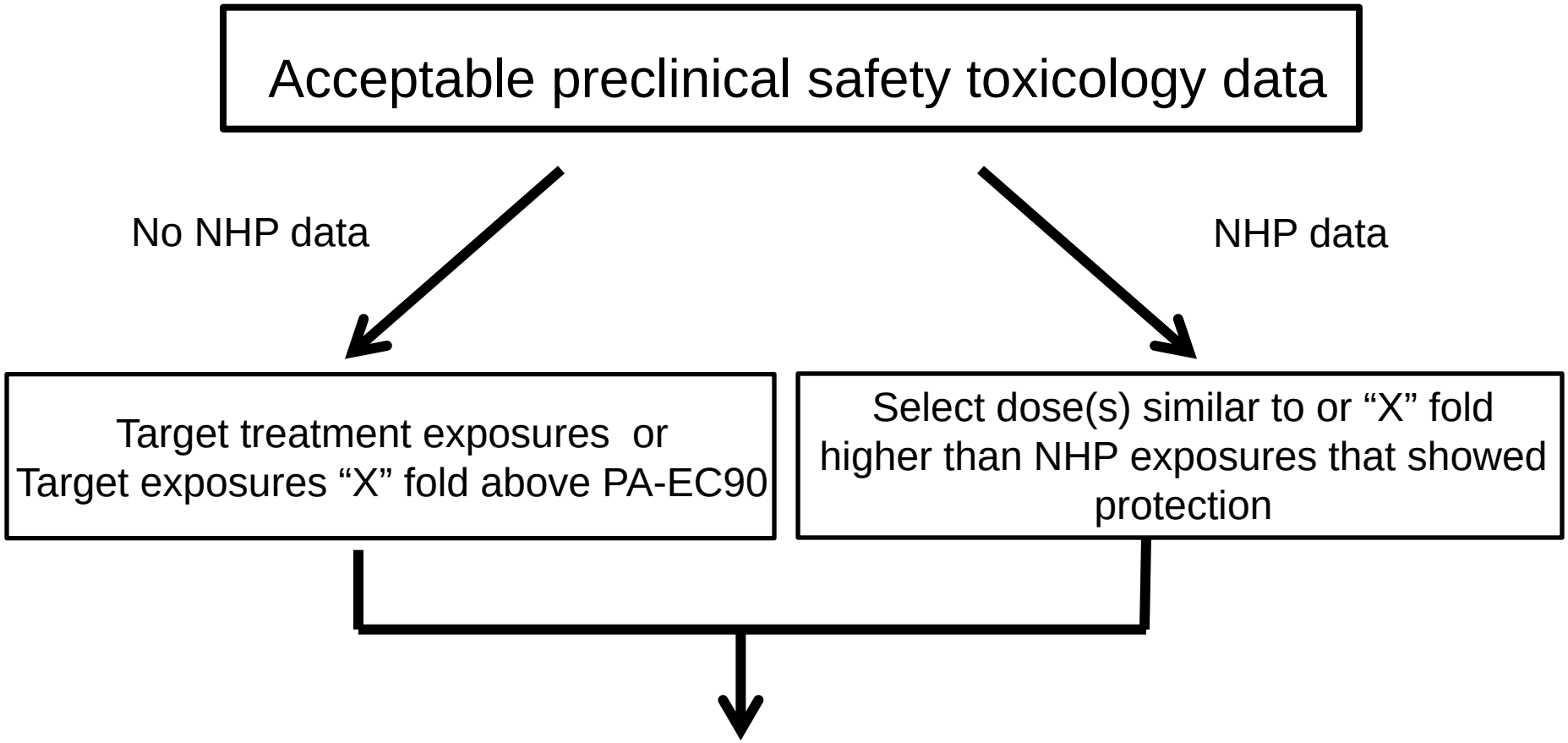
- Can be developed in absence of immediate release formulation
- In addition to routine toxicology development, long-term animal studies are needed to cover half-life of drug in humans
- Typical drug development pathway
  - Single and multiple ascending dose trials
    - May dose one subject at a time for safety reasons
  - Dose-finding trials
  - Phase 3 trials

Preclinical Consideration

- Non human primate (NHP) vaginal or rectal viral challenge studies are not required
- Role of NHP studies
  - Provide “target” exposures for antiviral effect
  - Determine threshold concentration at which infection occurs
- Totality of NHP data and EC50 data can aid in initial dose selection



Dose Selection



Is An Oral Lead-In Necessary?

It Depends

Risk Mitigation Strategies for No Oral Lead-In

- Safety concerns depends on product and population involved in trial
- Stringent enrollment criteria
- Start with small number of subjects
  - Dose 1-2 subjects
  - Stagger dosing between subjects for specified interval
- Stringent stopping rules for individual subjects, cohorts and the study
- Consideration for an independent unblinded medical monitor or data monitoring committee to oversee safety

PK/PD Considerations

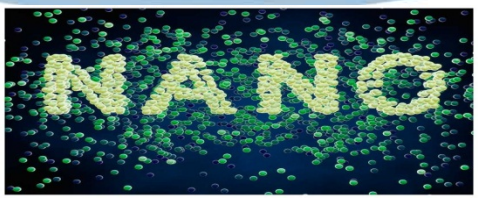
- Monitor window of protection in event of missed injection
  - PK simulations
  - Evaluation in phase 2/3
- Evaluate PK tail
  - Safety
  - Potential development of viral resistance
- Tissue collection
  - Relationship between plasma and tissue not well understood
  - Exploratory analyses to advance field

Trial Design Considerations

- Phase 2b/3 lead-in design
  - Enroll sexually active or high risk and not restrict to low-medium risk
  - Advantage
    - Enroll fewer subjects than separate phase 2 and 3 trials
    - Allow more safety evaluations before expand enrollment
    - Provide some preliminary data on efficacy and may facilitate faster development timeline
- Patient Population diversity
  - High-risk females, MSM, discordant couples, IVDU
- Control Arm
  - Placebo vs Active control
    - Non inferiority methodology challenges

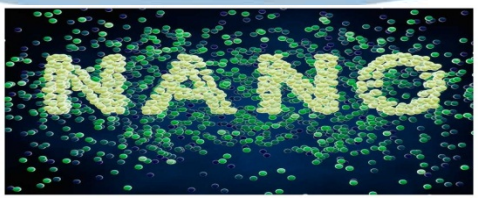
Other Considerations

- Drug interactions
  - Oral contraceptives
- Breakthrough therapy designation
  - Requires preliminary clinical evidence of substantial improvement on at least one clinically significant endpoint over available therapy
  - Request during Phase 2 may be premature
  - Request after Phase 3 results are available



formulations

- Can be:
  - Nanoscale versions of larger materials used in approved products
    - Not considered equivalents
  - Novel nanomaterials
- No guidances issued by CDER focus specifically on nanomaterial-containing products
  - Not regulated differently than small molecules
  - All currently published guidance documents applicable for small molecule drug development apply to nanopharmaceuticals
  - May pose novel challenges for CMC



formulations

- Previously approved drug formulated as nanotherapeutic may have different
  - PK, biodistribution and possible toxicological profile
  - May improve efficacy and reduce toxicity
  - Previously inaccessible areas of body may now be exposed to product
- Need for additional preclinical data may be warranted before human trials for nanoscale versions of approved drugs

Summary

- Clinical trials are needed for prevention indications
  - Approved formulation, new formulation or new investigational agent
  - Exposure response for prevention not known and no validated biomarkers
- Oral lead-in is not absolute
- Other PK/ PD considerations
  - Window of protection
  - PK tail
  - Tissue exposure
- Nano formulations
  - Developed similar to small molecules