

Bridging Justifications: Supporting the Safety of Excipients in Generic Drug Products

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Disclaimer

The opinions expressed in this presentation are those of the speaker and may not reflect the position of the U. S. Food and Drug Administration

Outline

- Excipient safety review in generic drug applications
- Bridging justifications for excipients in generic drugs
 - What is their utility?
 - What are important factors to consider?
- Case Studies
 - Excipient grade, dose, duration, route of administration, patient population



Excipient safety review: OGD Pharm/Tox

- Bridging justifications are a subset of the safety assessments conducted by OGD Pharm/Tox team
- Excipient safety review is conducted on a consult basis:
 - Consulted by OGD and Office of Pharmaceutical Quality (OPQ) on a fraction of OGD's applications
 - When there is a safety question (i.e. exceeds approved level, question of excipient grade, route)
- P/T and Clinical reviewers evaluate safety of excipients
 - Clinical informs context of use for product, clinical safety
 - Pharm/Tox evaluates available nonclinical safety information

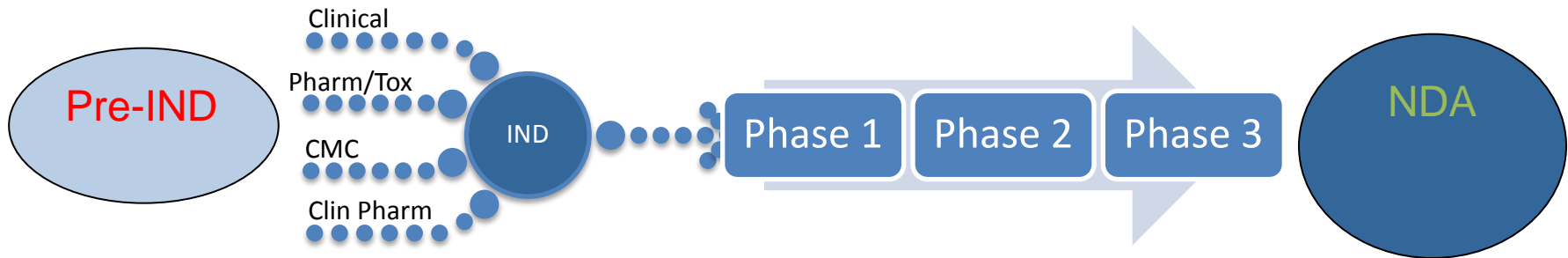


Excipient Safety Assessments

- The review is focused on safety of the proposed excipient for the patient population
- Considerations
 - Route, dose, duration of use, existing safety info
 - Patient population: drug toxicity, disease
- Ultimate Question: Will this excipient change the safety profile of the proposed drug when compared to the Reference Listed Drug (RLD)?

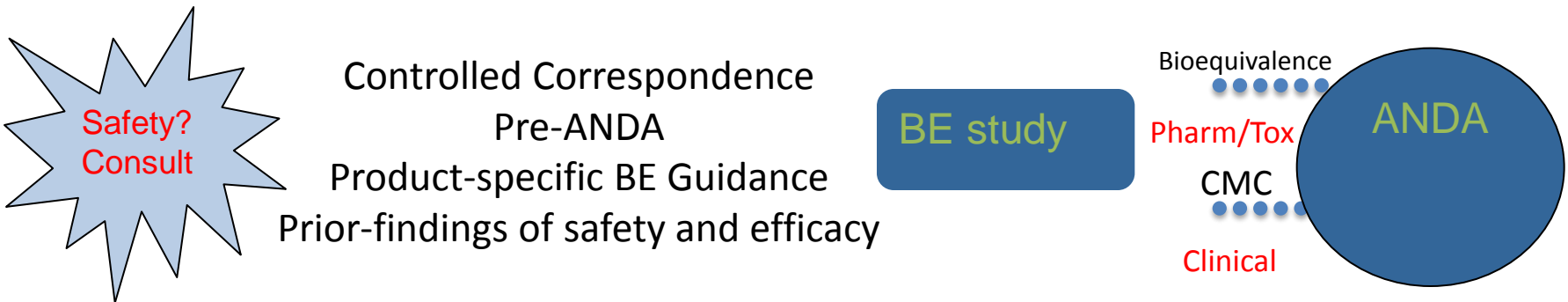
Why this approach?

NDA: Safety of drug product is qualified with data during drug development



ANDA: Bioequivalence; Reliance on prior findings of safety and efficacy

- Less qualifying data
- Most ANDAs aren't reviewed by P/T or Clinical disciplines



Bridging arguments are reviewed during a P/T consult for an ANDA 6

Bridging Justification

An approach for safety assessments where toxicology data for one or more compounds is applied to a different compound

When justified, the approach uses a body of information to extrapolate safety in cases where specific data do not exist

Bridging justifications are used in CDER Pharm/Tox for excipient safety review in the context of an ANDA or NDA





Pharm/Tox review of excipients

- OGD P/T reviews bridging justification using the approaches detailed in the guidance “Nonclinical Studies for Excipients”
- The context of the drug drives the necessary nonclinical studies
 - Important: route, dose and duration

Guidance for Industry
Nonclinical Studies for the
Safety Evaluation of
Pharmaceutical Excipients

Short-Term Use (14 days or less)	Intermediate Use (14 to 90 days)	Long-Term Use (90 days or recurrent)
Acute Toxicology	Studies from short term	Studies from short and intermediate use columns
ADME	3-month repeat dose tox in 2 species	6-month general toxicology study (rodent)
Genetic toxicology		9-month general tox (non-rodent)
1-month general tox*		2-year carci study (2-species)
DART (devel. and repro)		

Bridging Justifications in FDA's Excipient Guidance

- “Large polymers that differ from previously characterized excipients only in molecular weight (chain length) can be adequately characterized in an abbreviated manner using less safety data, provided that the new excipient and the previously studied excipient are sufficiently similar with regard to physical state, pharmacokinetics, and levels of unreacted monomers and other impurities.”
- “We will consider such excipients on a case-by-case basis”



Why Bridging Justifications?

- Use all available data to fully inform safety
 - Can inform target organs, safety signals, tolerability

- Applicant’s justification is essential for review by OGD
 - Data and justification are a pivotal for our review
 - Essential for meeting review timelines
 - Important to understanding the excipient class

- Reduce animal usage



How does DCR approach bridging?

Questions to ask:

- What is the nature of the excipient class?
- Has this been reviewed before? If yes, how?
- What justifies applying safety info between grades?
Similarities and differences: Manufacturing, impurities, properties that impact safety
- Is the referenced safety information for the correct route and duration for the current context?
- Do any gaps remain after applying the bridged data?



Building a Bridge

Existing information

Approved: product for chronic use
 Approved amount
 Excipient characteristics
 General human exposure
 Pharm/Tox information (context)

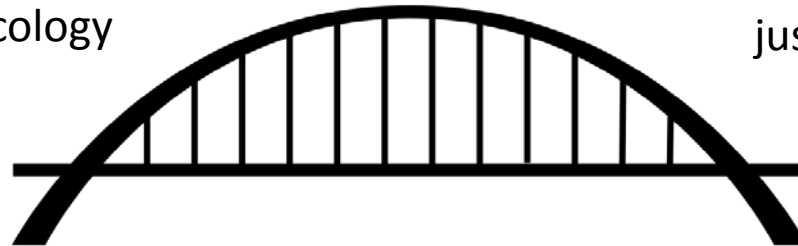
- Genetic toxicology
- General toxicology
- Reproductive toxicology
- Carcinogenicity

Duration
 Dose
 Route
 Properties
 Prior exposure
 P/T data

Proposed Generic Drug

Product for chronic use
 Proposed amount exceeds
 Information on similarities and differences of excipient
 General human exposure
 Pharm/Tox information (context)

- Existing data, relevance and justification to support bridge



- Address relevance of information, any data gaps, and focus on the context of use for the proposed product



Important Factors for a Bridge

- **Data**
 - What safety data exists, and what is being bridged?
 - Clear statement of physical/chemical properties
 - Differences from other excipient if intending to “bridge”
- **Route of Administration**
 - Route should be relevant to the proposed product
- **Dose relation**
 - How are doses in studies relevant to your proposed product?
- **Chronicity**
 - Chronicity of approved product and accompanying studies will be compared to your proposed product
- **Consider context of use, including patient population**

OGD P/T Experience Bridging Justifications

- OGD Pharm/Tox has reviewed several dozen ANDAs that involved bridging justifications (2014-2016)
- On occasion, we send an Easily Correctable Deficiency (ECD) to request further information for the bridging justification during our review
- P/T Team is reviewing bridging justifications within ANDAs without a disproportionate amount of deficiencies

Case Studies

Cases are a composite of past experience

- Highlight important elements in bridging justifications

Case 1: Bridging excipient grade and amount

Case 2: When context differs (duration, route)

Case 3: Grade and patient population

Case 4: Bridging a route of administration

Case 1: Higher amount of a polymer



- A CNS stimulant: chronic oral product for children to adults
- Consulted on the safety of 80 mg copolymer grade X per day
 - Considerations: physical/chemical properties of copolymer, available supportive data, presence in FDA-approved products
- Pharm/Tox data
 - This grade is poorly absorbed and well-tolerated in general tox studies (up to 6 months in rodent alone)
 - Negative across several genetic toxicology studies
 - No safety signal in developmental and reproductive tox data

Case 1: Higher amount of a polymer

- 37.5 mg of polymer grade X is approved in another product for chronic oral use
- The RLD had different grades of same polymer at higher amounts
- P/T data for polymer grade X lacked 2-species chronic tox but had considerable safety information
- Bridge: The proposed amount (80 mg) was acceptable based on totality of information: Pharm/Tox info, prior use, similarity with other grades at higher levels



Case 2: Data gap for chronic toxicity

- Proposed product: a chronically used tablet in adults
 - Consulted because an excipient was not in the Inactive Ingredient Database or RLD

“Evaluate the submitted Pharm/Tox data to determine if this inactive ingredient is safe for use in this drug product at the level proposed”
- *Applicant justification:*
 - Nonclinical safety justification based on published literature
 - Minimal information exists on specific compound
 - Applicant referred to data on other compounds in same class
 - Available information: genetic toxicology and acute general toxicology on compounds with different molecular size and variable substitutions.

Case 2: Data gap for chronic toxicity

- Evaluated published literature and use in approved products
 - This compound is in an approved *topical* product
 - In an NDA review for an oral drug product, a data gap for chronic toxicology and carcinogenicity was identified, resulting in a Post-marketing Requirement (PMR)
- Held meeting with NDA review team about PMR
 - Published info was inadequate for chronic toxicity assessment
- Consulted with the OND review division regarding excipient data, PMR and potential for 505(b)(2)

Case 2: Data gap for chronic toxicity

- OGD Pharm/Tox confirmed status of PMR and potential path forward with OND division
- Available data were an insufficient bridge for chronic toxicity by the oral route of admin.
- Significant gaps need to be addressed before this compound is qualified for chronic use
 - Applicant may remove excipient from formulation
 - Applicant can address chronic toxicity and carcinogenicity under the 505(b)(2) pathway



Case 3: Grade and Patient Population

- Proposed product: Oral suspension for chronic use
 - Patients age 2 to adult will take this on an intermittent, chronic basis
- DCR is consulted on the safety of the proposed maximum daily intake of 900 mg excipient

Applicant Justification

- Joint FAO/WHO Expert Committee on Food Additives (JECFA),
- Nonclinical tox summary consisted of data from various excipients in class ranging in molecular weight

Case 3: Grade and Patient Population

- Pharm/Tox: Polymer was negative for genotoxicity, low absorption of HMW polymers, NOAELs ID'd in rodent studies for various grades
- Approved levels – 53 mg excipient approved in another oral drug
 - Chronic use, indicated in adults

Gaps identified

- Molecular weight of the excipient grade is markedly lower than grades which are evaluated in available published information
 - Absorption of this lower MW grade is not characterized
- Proposed level is 18-fold higher than approved levels for this route
- Safety in pediatrics is not addressed

Deficiency: Clinical and P/T information on long-term safe use of this excipient grade



Case 4: Bridge for Route of Admin



- Proposed formulation is a “film” that is delivered by the buccal route in an adult population
 - Requires assessment of safety for *both* local and potential for systemic toxicity
- DCR Pharm/Tox was consulted on the safety of nine excipients in the buccal film
 - Polymers (n=3), flavor, preservatives
- Applicant submission was comprehensive
 - Provided controlled correspondences on excipients
 - Comprehensive literature review on excipients
 - Justification for polymers included physical description of excipient and published safety information

Case 4: Bridge for Route of Admin



- DCR reviewed the toxicology report provided by the applicant, controlled correspondences, safety findings from bioequiv. study, FDA databases, the toxicology and medical literature
- Each excipient was reviewed for presence in approved products of a similar context of use
 - Evidence of systemic exposure and local safety in clinical and nonclinical information
- ECD was sent to clarify the composition of the flavor and address the local and systemic safety of flavor components.
 - Qualitative and quantitative composition, synonyms for components
 - CFR citations, information on prior usage
 - Genetic toxicology and available safety information for non-CFR components
 - Information was updated in the DMF

Case 4: Bridge for Route of Admin



- Several excipients were present in a similar approved product
- Flavor was reviewed using the component approach
 - Elements: presence in CFR, similar use in other flavors, local and systemic toxicity
- Polymer Bridge
 - Considered molecular characteristics, prior use in FDA-approved products, available Pharm/Tox and clinical safety experience with this compound and similar grades
 - Low probability of absorption, so also considered relevant oral safety information
- All excipients in the buccal film were acceptable based on evidence of local and systemic safety

Summary

- OGD P/T reviews bridging justifications within ANDAs, per Excipient Guidance and similar to Office of New Drugs P/T
 - Pharm/Tox and Clinical disciplines evaluate excipients based on context of use
- Important elements of bridging justifications:
 - Similarity and difference between excipients
 - Existing nonclinical and clinical data
 - Address data gaps
 - Address proposed context of use
- Each case is unique but similar principles apply. OGD P/T reviews bridging justifications with relative success as a means to ensure excipient safety in generic drugs

