Current Perspective on Toxicology Human Food Safety Assessment

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Presentation Content

• Overview of Human Food Safety (HFS) Assessment
• General and alternative approaches to address toxicology HFS requirement
• Case studies
• Challenges

Human Food Safety Assessment

Ensure that the residues in edible tissues of food animals are safe for human consumption.

Residues: parent drug, metabolite(s), and any substance formed in or on food
Edible tissues: muscle, liver, kidney, fat/skin, eggs, milk
Food animals: may include cattle, swine, chickens, turkey, sheep, goats, fish
Safe: reasonable certainty of no harm
Toxicology Assessment

- Identify and characterize any potential adverse health effects.
- Inform and help prevent adverse health effects.

Toxicology Assessment
Extrapolate toxicity from animals to humans
**Safety Standard**

<table>
<thead>
<tr>
<th>Non-Carcinogen</th>
<th>Carcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasonable certainty of no harm (21 CFR 570.3(h)(i))</td>
<td>No significant increase in the risk of cancer to the human consumer (21 CFR 500.82)</td>
</tr>
</tbody>
</table>

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**Carcinogenic Endpoint**

- DES Proviso of the Delaney Clause: no residue.
- Sensitivity-of-Method (SOM) regulation (21 CFR 500 Part E): no residues means no significant increase in the risk of cancer; define $S_o$, $S_m$, $R_m$ and a regulatory method.
- $S_o$ derived either by a 1-in-1 million linear low-dose mathematical extrapolation or an alternative approach.

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**Non-Carcinogenic Endpoint**

- General approach
- Alternative approach
General Approach

• Include a series of toxicology studies to address various toxicological endpoints of concern (systemic, repro/developmental, genotoxicity/carcinogenicity etc.) with an aim for establishing an acceptable daily intake (ADI).
• Calculate the safe concentration (SC) for each edible tissue based on the current food consumption values.

General Approach

• For an injectable product, sometimes derive an acceptable single dose intake (ASDI) based on allergenicity and/or acute toxicology studies.
• Calculate the safe concentration for injection site muscle.

ADI Determination

• ADI represents residues that may safely be consumed daily in the human diet for a lifetime.
• Toxicological ADI: NOEL÷SF or BMDL÷SF
  - select an appropriate no-observed-effect-level (NOEL) or benchmark dose lower limit (BMDL) from a study showing the most sensitive endpoint in the most appropriate species;
  - select an appropriate safety factor (SF), usually 100-1000).
• If there is a microbiological ADI, then compare it with the toxicological ADI. Whichever the lowest will be the final ADI.
• Determine the need to allocate ADI between the edible tissues, milk and/or eggs.
ASDI Determination

- **ASDI** represents residues that at the injection site may safely be consumed.
- Assumes that consumption of injection site is a rare event.
- Calculated by NOEL÷SF, or BMDL÷SF
  - select a NOEL;
  - select an appropriate SF.

Safe Concentration

- Provide total drug residues allowed in edible tissues
- Calculated using partitioned ADIs and distributed amongst the edible tissues, milk and eggs using food consumption values

\[
SC = \frac{(ADI \text{ or } ASDI \times \text{Average Human BW})}{\text{Food Consumption (g)}}
\]

Food Consumption Values

<table>
<thead>
<tr>
<th>Edible Tissue/Product</th>
<th>Food Consumption (per person)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>300 g</td>
</tr>
<tr>
<td>Liver</td>
<td>100 g</td>
</tr>
<tr>
<td>Kidney</td>
<td>50 g</td>
</tr>
<tr>
<td>Fat/skin</td>
<td>50 g</td>
</tr>
<tr>
<td>Eggs</td>
<td>100 g</td>
</tr>
<tr>
<td>Milk</td>
<td>1.5 L</td>
</tr>
</tbody>
</table>
Alternative Approach

Provide an equivalent assurance of safety

- Scientific justification not to perform all the standard toxicology studies, or conduct focused toxicology studies
- Risk-based, margin of exposure (MOE) assessment
- Weight-of-evidence/body-of-evidence: “white paper” justification based on literature

Alternative Approach

Risk-Based

- Weight-of-Evidence

Equivalent Assurance

- Of Safety

Margin-Of-Exposure

Focused Toxicology Studies

No Need To Provide Complete Toxicology Studies

White Paper Based on Literature

Alternative Approach - Case 1

Risk-Based Assessment for EAZI-BREED CIDR Product

- Approved use in sheep as an insert.
- Progesterone is the API.
Alternative Approach - Case 1

• Toxicology based on allowable incremental increase of progesterone
• No toxicology studies needed
• Supported by the exposure assessment

<table>
<thead>
<tr>
<th>Edible Tissue</th>
<th>Food Consumption Value (g)</th>
<th>Allowable Incremental Increase Limit (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>300</td>
<td>5</td>
</tr>
<tr>
<td>liver</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>kidney</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>fat</td>
<td>50</td>
<td>30</td>
</tr>
</tbody>
</table>

FOI Summary Available at
http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM190797.pdf

Alternative Approach - Case 2

Focused studies for Chemical A
• Primary concerns: potential immunological and hormonal effects
• No need for complete toxicology package, genotoxicology/development/reproductive studies not needed
• Focused studies: subchronic & acute toxicity studies
Alternative Approach - Case 3
Exposure approach for Chemical B
• Risk = Hazard X Exposure
• Residue studies showed comparable tissue residue levels between the treated and untreated target animals.
• The exposure assessment supported the conclusion that no toxicology studies were needed for Chemical B.

Alternative Approach - Case 4
White paper justification for Chemical C
• Literature review: body of evidence showed consistent low toxicity
• Calculated worst-case human exposure because no or incomplete residue chemistry data are available
• Sufficient MOE to alleviate HFS concerns

Future Challenges
Traditional standard toxicology package may not be adequate for addressing HFS concerns for some novel products
• Nanoscale materials
• Synthetic protein/hormone products
• Combination drugs
Nanotechnology Product

• Challenge – unique properties
• ADME may be essential
• Case-by case approach
• CVM is working with the Agency Nanotech Task Force

Synthetic Protein/Hormone Products

Challenge: address oral bioavailability
• In vitro/in vivo toxicology studies addressing endpoints of concerns
• Digestibility by GI tract of target animals and/or humans
• Receptor mediated MOA & human relevance framework
• Exposure consideration
  Allergenicity (protein)

Combination Drugs

Challenges: synergistic effects of residues
• Consider mechanisms of action and target organs for each individual drug.
• Additional toxicology studies on the combination drugs may be needed.
Summary
For sponsor, points to consider when addressing toxicology HFS requirements
• General approach
• Scientific justifiable alternative approach
• Scientific justification not to use default (such as SF, cancer study)
• Encourage open communication as early and as often as needed.

Summary
For CVM, points to consider when addressing toxicology HFS requirements
• Think outside of the box and be innovative
• Case-by-case for novel products involving innovative technology
• Open to alternative approaches that provide an equivalent assurance of safety.

Questions?
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