Setting-up of an internal multidisciplinary Vehicle Working Group to increase knowledge on excipients and recommend their use in preclinical in vivo studies

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Introduction

- Enabling formulations for preclinical in vivo studies play a key role for assessing safety, pharmacodynamics, and pharmacokinetics (PK) endpoints of new molecules
- Excipients used in formulations should maximize exposure while avoiding side effects that could influence experimental results
- As new chemical entities are not always sufficiently soluble and/or bioavailable in commonly used vehicles, ‘exotic cocktails’ of various excipients are often used to prepare preclinical formulations
- Limited information has been published on the potential impact of these excipients on commonly used laboratory animals

Methodology

Step 1: Define sources of information
- Publications
  - Vitrin database of excipients (from Lhasa Ltd) containing more than 2000 records on vehicle toxicity data
- UCB data from safety pharmacology (rat Irwin and locomotor activity tests, cardiovascular telemetry) and toxicology studies
- CRO data, experience or guidelines on excipients
- Experience from VWG members and other scientists

Step 2: Define acceptance criteria per study type

<table>
<thead>
<tr>
<th>Study type</th>
<th>Criteria for acceptable vehicles</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPK</td>
<td>No PK interaction that could interfere with the interpretation of the study results, no DMSO (CYP450 interactions), no adverse reactions</td>
</tr>
<tr>
<td>CNS pharmacology</td>
<td>No behavioral changes</td>
</tr>
<tr>
<td>Immunology pharmacology</td>
<td>No interference with antibody response and immunology parameters measured</td>
</tr>
<tr>
<td>Safety pharmacology - CV</td>
<td>No changes in blood pressure or heart rate &gt;10% from baseline, no changes in Qtc &gt;5% (or outside the normal variability)</td>
</tr>
<tr>
<td>Safety pharmacology - Irwin</td>
<td>No behavioral score changes &gt;1 (for parameters scored up to 4) or &gt;2 (for parameters scored up to 8); no adverse signs</td>
</tr>
<tr>
<td>General toxicology</td>
<td>No clinical signs, no changes in clinical chemistry/hematology or histopathological changes outside historical range (other than background)</td>
</tr>
</tbody>
</table>

Step 3: Prioritize excipients to examine first
- 17 excipients selected based on their frequency of use at UCB, risk of side effects, or success in enabling formulations

Step 4: Create a sharepoint site in the UCB intranet and an e-mail address for centralizing users’ questions and concerns

Step 5: Populate results and recommendations across departments and seek feedback

Conclusions and next steps

- These recommendations are mainly based on safety data in rodents. Additional vehicle data related to DMPK or pharmacology, or non-rodent species, would help to ensure that appropriate excipients are used, depending on the purpose of the study
- The proposed recommendations are applicable for excipients used alone, as data on mixture of excipients (‘cocktails’) are rarely available.
- The VWG will continue to investigate more excipients and aims to benefit from the experience and knowledge of partners from pharmaceutical industry, academia, or CROs.

Interested ? Feel free to contact: vehicleworkinggroup@ucb.com or annie.delaunois@ucb.com

Results and recommendations

Standard (first choice) vehicles selected:
- For oral and i.p.: 1% methylcellulose, 0.1% silicon antifoam, 0.1% Tween® 80
- For i.v.: dimethylecetamide (DMSA) 30%

Maximal recommended doses for alternative (second choice) vehicles:

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>p.o.</th>
<th>i.p.</th>
<th>i.v.</th>
<th>Main effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylcellulose (5%)</td>
<td>Chronic</td>
<td>1 g/kg/day</td>
<td>1 g/kg/day</td>
<td>Not used</td>
<td>General toxicology reactions in dogs</td>
</tr>
<tr>
<td>Silicon antifoam (0.1%)</td>
<td>Chronic</td>
<td>0.1 g/kg/day</td>
<td>0.1 g/kg/day</td>
<td>Not used</td>
<td>General toxicology reactions in dogs</td>
</tr>
<tr>
<td>Tween® 80 (0.1%)</td>
<td>Chronic</td>
<td>0.1 g/kg/day</td>
<td>0.1 g/kg/day</td>
<td>Not used</td>
<td>General toxicology reactions in dogs</td>
</tr>
</tbody>
</table>

Objectives

- We initiated a multidisciplinary Vehicle Working Group (VWG) within UCB, with representatives of:
  - Non-Clinical Safety Evaluation
  - Non-Clinical DMPK
  - Pre-formulation
  - CNS Pharmacology
  - Immunology

- Objectives of the VWG:
  - Develop our knowledge on potential side effects of excipients in laboratory animals
  - Recommend vehicles for future use in in vivo studies
  - Harmonize procedures across departments and UCB sites
  - Serve as central contact point for questions on vehicles
  - CNS Pharmacology groups
  - Immunology Pharmacology group

Ulcerative and necrotic skin lesions observed in a rat subcutaneously injected with an excessively alkaline formulation (with the courtesy of Dr A. Popovic)