# Vitic Nexus Excipients database – Industry (Pfizer) perspective

**Mazin Derzi[1], Nigel Greene[2], Michelle Marra[3]**

**[1] Drug Safety Research & Development, Pfizer Inc**

**[2] Compound Safety Prediction, Pfizer Inc**

**[3] Pharmaceutical Sciences, Pfizer Inc**

# Content

- **Vitic Excipient Consortium - background**
  - Why Pfizer became involved
- **Vitic Excipients Database for Pfizer**
  - Advantages and disadvantages and key challenges
- **Case studies**

# Excipient Project Consortium

- Is a cross pharmaceutical industry collaboration
- GOAL:
  - To share preclinical safety information on excipients
    - Help reduce need for animal testing – focused on 3Rs
  - To store excipient data in an easily searchable and retrievable format
    - Aid the selection of appropriate vehicles


Pfizer

# Excipient Project

- The Vitic Excipient project was borne out of a collaborative group
  - Large pharmaceutical companies
  - The Fund for the Replacement of Animals in Medical Experiments (FRAME)
  - The Royal Society for the Prevention of Cruelty to Animals (RSPCA)
  - Pfizer is part of the database development steering committee
    - Provided data on excipients for the database
  - Lhasa Limited (a non profit organisation) was utilised as the software developer, intermediary, and independent chair
  - The Excipients database sits on the VITIC nexus platform
    - Includes other chemical databases/information management systems and is a platform supporting other cross industry consortia
      - e.g. Intermediates data sharing and eTox IMI project

Pfizer

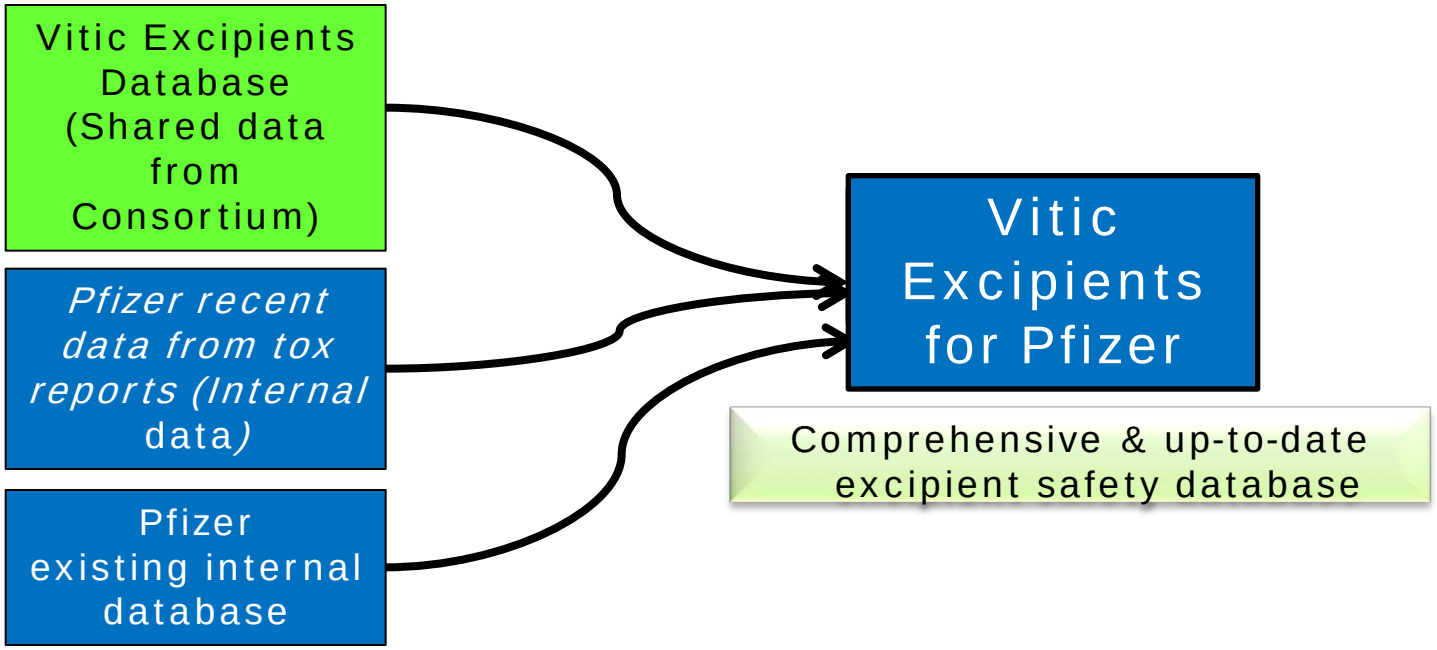
# Why did Pfizer become involved?

- Pfizer is committed to 3R's
  - We see value in sharing our data and gaining access to additional safety information on excipients both in terms of reducing animal testing but also in aiding the selection of appropriate excipients and vehicle formulations
- The safety and efficacy of our products is paramount
  - Pfizer's Drug Safety organization plays a key role evaluating the safety of excipients/vehicle formulations
  - Redundancy is good - multiple records build confidence
- Housing the database within Vitic Nexus allows storage of excipient data in an easily searchable and retrievable platform
  - The database is maintained by Lhasa
  - Database can be accessed via the internet or housed inside your internal firewall


Drug Safety is one arm of a Tripartite governance model for Patient Safety in Pfizer

# Vitic Excipients Database for Pfizer

- **Pfizer extended the database to include more internal excipient safety records.**
- **Pfizer version is a combination of the shared consortium database & internal vehicle safety data**
- **"Vitic Excipients for Pfizer" sits inside our firewall**



# Points to consider when Installing the Database in-house

- **The Good:**
  - Ability to add in-house data that is considered proprietary information
    - Proprietary data on compounds from safety studies
    - Data collected from or during scientific collaborations
    - Including fields that would not be shared externally e.g. study director, etc.
  - Integration with other in-house data systems
  - Satisfy legal requirements around publication of chemical structures prior to patent applications
  - 24/7/365 support for the servers
- **The Bad:**
  - Requires internal resources to maintain and update software which are at the mercy of budgets and prioritization
  - Educating the Help Desk on supporting the application
- **The Ugly:**
  - Getting the initial hardware and installation set up can be painful depending on your IT processes!

Pfizer

# Case studies from the Pfizer user community

**Simon Pegg[2] and Pat Bubucis[1]**

**[1]Drug Safety Research & Development, Pfizer Inc**

**[2]Pharmaceutical Sciences, Pfizer Ltd**

# The problem compound!

- **Compound X**
- **Low solubility, high log D**
- **High exposure required to gain suitable toxicology coverage and understanding**
- **Formulator struggling to formulate at desired concentrations in usual landscape, researches literature (below are examples of some papers & references utilised):**

  - *"Development of supersaturated SEDDs (s-SEDDs) formulation of Pacitaxel with improved oral bioavailability" P. Gao et al Journal of Pharmaceutical Sciences Vol. 92, No. 12 Dec 2003*
  - *"Development of Microemulsion for Solubility Enhancement of Clopidogrel" V. Patel et al Iranian Journal of Pharmaceutical Research (2010), 9 (4) 327-334*
  - "Developing oral solid dosage forms: Pharmaceutical theory & practical practise" Y. Qiu et al. Academic Press (2009)
  - "Preparation & Assessmant of SMEDDs containing Valsartan" R. Advart et al . AAPs Parm Sci Tech Volume 11 Number 1 314-321

# The proposed formulation

- A formulation containing the following components was selected:
- Ethanol
- Tween 80
- PEG 400
- Capmul MCM
- Hydroxymethylcellulose (HPC)

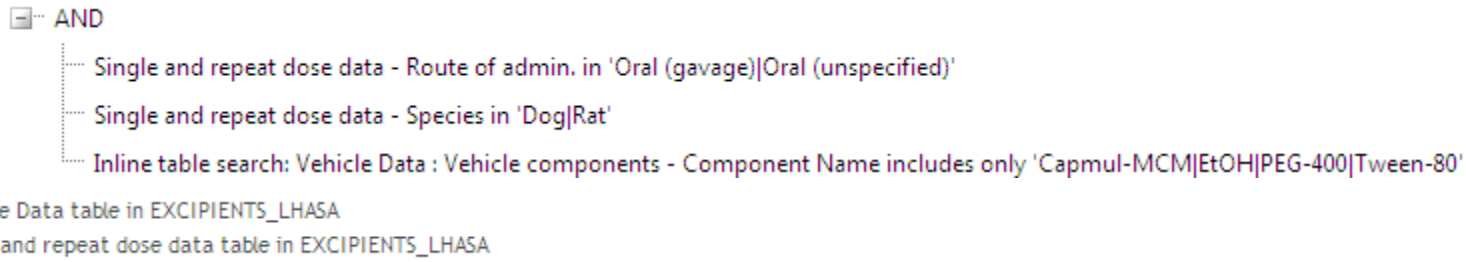
# The solution?

- Initial formulation assessment successfully conducted in terms of concentrations and suitable stability for the formulation
- Formulator opened discussions with Drug Safety representative, both utilised the Lhasa excipient database to check for precedence
- Also the literature references were reviewed by formulator and drug safety to provide further insight and confidence into using the proposed formulation

# How does Drug Safety use Excipients DB?

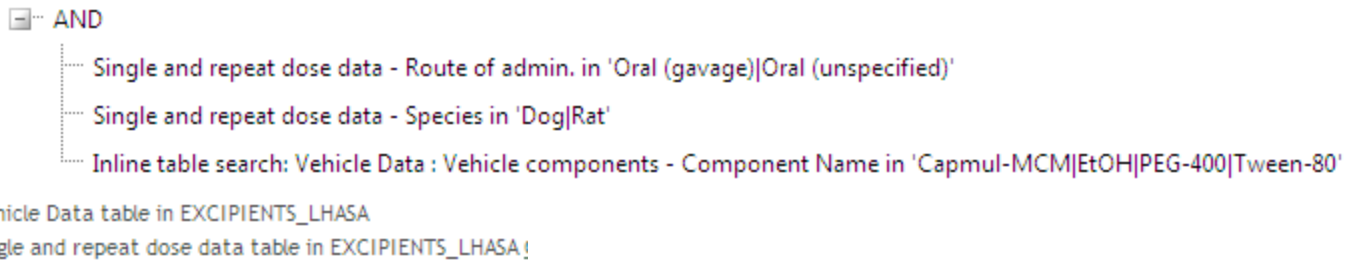
- Look for precedence of vehicles with all or some of the proposed components used by the intended route and species
  - 'in' operator is equivalent to 'OR'
  - 'includes only' returns records with only one or more of the selected values

**Query 1**




There are no records for vehicles containing only Capmul-MCM, Ethanol, PEG-400, and/or Tween-80 used orally in Dog or Rat (proposed SEDDS vehicle not here)

**Query 2**




There are 102 Vehicles with 227 Single & Repeat Dose records that include vehicles with at least one of the selected components used orally in Dog or Rat

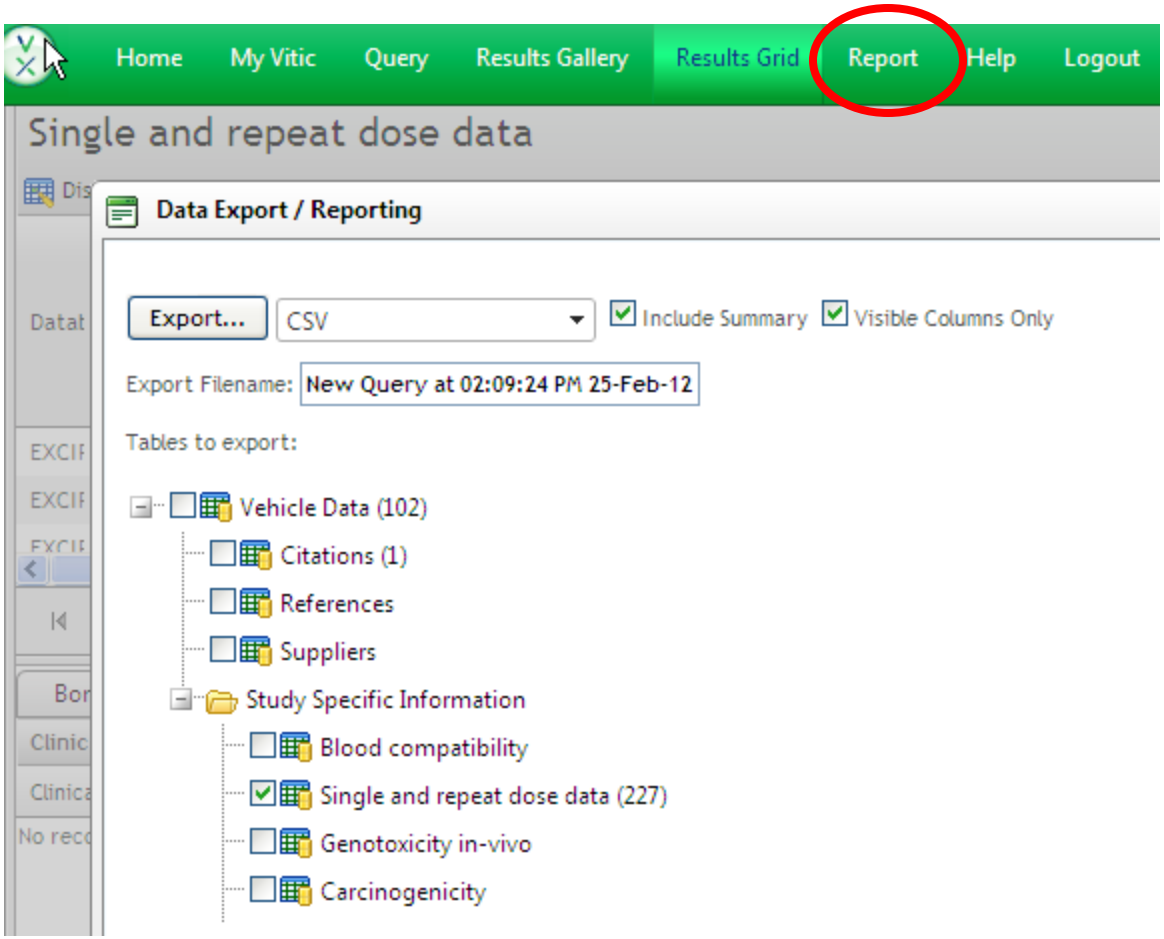
# How does Drug Safety evaluate search results?

- **Review query results in the 'Results Grid'**
- **Compare relevant vehicle/excipient doses for each species to those in the proposed vehicle**
  - Calculate individual excipient doses from concentrations & dose volumes
  - Consider dose frequency and treatment duration
- **Are comparable doses well tolerated based on relevant parameters?**
  - Check results of parameters displayed in both top (scroll to right) and bottom (view individual tabs) sections of 'Results Grid'

| Vehicle name | pH | Dose volume | Dose units | Frequency of admin. | Treatment duration (VC) | Route of admin. | Species | Tolerability |
|---|---|---|---|---|---|---|---|---|
| Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No in | 2 | ml/kg | 1/day | 3 Days | Oral (gavage) | Dog | Not tolerated |
| Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No in | 0.25 | ml/kg | 1/day | 1 Days | Oral (gavage) | Dog | Tolerated with findings |
| Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No in | 1 | ml/kg | 1/day | 3 Days | Oral (gavage) | Dog | Not tolerated |
| Capmul-MCM (40%), Medium-chain-triglycerides (20%), Propylene-carbonate (20%), Vitami | No in | 3 | ml/kg | 2/day | 7 Days | Oral (gavage) | Dog | Tolerated with findings |
| Capmul-MCM (45%), Polyoxyl-40-castor-oil (36%), EtOH (10%), Triethylcitrate (9%) | No in | 2 | ml/kg | 1/day | 7 Days | Oral (gavage) | Dog | Tolerated without findings |

# Use Reports to help evaluate & share results

- **Export query results to a CSV file via the Report option**
- **Open in Excel and save to computer for further manipulations**



# Example - Excel filters & doses for Oral_Dog_Capmul

- Filter 'Vehicle Name' by Capmul (Text Filter → Contains → Capmul)
- Insert a column and calculate Capmul ~ml/kg (bodyweight) dosages
  - Multiply concentration by dose volume (pay attention to units)
  - Sort column in ascending order (Note that dosage in last row was administered twice daily)
- Filter 'Species' by Dog and filter 'Tolerability' to exclude 'Not tolerated'
- Compare Capmul dosages / durations to those for proposed vehicle

I47 =0.3*G47

| | E | F | G | H | I | J | K | M | N | O | S | T | U |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Vehicle name | pH | Dose volume | Dose units | Capmul ~ml/kg | Frequency of admin. | Treatment duration (VC) | Species | Tolerability | No. animals per group | Mortality | Bodyweight | Food consumption |
| 47 | Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No information | 0.25 | ml/kg | 0.075 | 1/day | 3 Days | Dog | Tolerated with findings | 4 | None | Nothing abnormal detected | Nothing abnormal detected |
| 67 | Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No info | 0.25 | ml/kg | 0.075 | 1/day | 1 Days | Dog | Tolerated with findings | 8 | None | No informati | Nothing abnormal |
| 158 | Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No info | 0.5 | ml/kg | 0.15 | 1/day | 3 Days | Dog | Not tolerated | 4 | None | Nothing abnormal | Nothing abnormal |
| 161 | Medium-chain-triglycerides (40%), Tween-80 (40%), Capmul-MCM (20%) | No info | 1 | ml/kg | 0.2 | 1/day | 91 Days | Dog | Tolerated without findings | 10 | None | Nothing abnormal | No informati |
| 162 | Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No info | 1 | ml/kg | 0.3 | 1/day | 3 Days | Dog | Not tolerated | 4 | None | Nothing abnormal | Nothing abnormal |
| 163 | Capmul-MCM (30%), Triacetin (30%), Medium-chain-triglycerides (20%), Tween-80 (20%) | No info | 2 | ml/kg | 0.6 | 1/day | 3 Days | Dog | Not tolerated | 4 | None | Nothing abnormal | Nothing abnormal |
| 164 | Capmul-MCM (45%), Polyoxyl-40-castor-oil (36%), EtOH (10%), Triethylcitrate (9%) | No info | 2 | ml/kg | 0.9 | 1/day | 7 Days | Dog | Tolerated without findings | 2 | None | Nothing abnormal | Nothing abnormal |
| 193 | Capmul-MCM (40%), Medium-chain-triglycerides (20%), Propylene-carbonate (20%), Vitamin-E-TPGS (20%) | No information | 3 | ml/kg | 1.2 | 2/day | 7 Days | Dog | Tolerated with findings | 2 | None | Nothing abnormal detected | No information |

# Then what?

- Repeat the process for each species and each excipient in the proposed vehicle
- Table below shows maximum dosages for vehicles designated 'Well tolerated without findings' with treatment durations relevant to intended use of the proposed vehicle
- Excipient doses in table were well tolerated when administered daily for at least 3 weeks and are higher than in proposed vehicle
  - Ranges might be expanded by reviewing the findings for vehicles designated 'Tolerated with findings'

| | Dog | Rat |
|---|---|---|
| Capmul-MCM | 0.2 ml/kg BW daily 91 days<br>0.9 ml/kg BW daily 7 days | 2.5 ml/kg BW daily 182 days<br>4 ml/kg BW daily 28 days |
| Ethanol | 0.16 ml/kg BW daily 28 days | 1 ml/kg daily 21 days |
| Hydroxymethylcellulose | 100 mg/kg BW twice daily 29days | 200 mg/kg daily 115 days |
| PEG 400 | 1.7 ml/kg BW daily 14 days | 5 ml/kg BW daily 29 days |
| Tween 80 | 0.4 ml/kg BW daily 91 days | 3 ml/kg daily 42 days |

- **Results support safe use of individual excipients at proposed doses**
- **Conduct of dog & rat exploratory toxicity studies with controls is advised to confirm safety of the combined excipients**

# The Outcome

- **Formulation was taken into an exploratory toxicology study that was successful in terms of toleration, and the compound & formulation achieved a suitable/desired exposure**
- **The compound & formulation have now been taken into further toxicology studies including GLP Regulatory Toxicology**

# The next problem compound!

- Compound X, a neutral compound
- Even lower solubility, and even higher log D than last compound
- A one off oral PK/TK study required in rat to address a project specific safety question at an unprecedented high dose
- Formulator struggling to formulate at desired concentrations in usual landscape known for rats

# The Solution?

- Literature precedence did not provide much scope outside the internally known/preferred formulation options. Most used excipients or excipient levels known to cause adverse effects in rat, either from internal experience or via the database
- Formulator utilised the Lhasa excipient database to check for alternative landscape
- Two records showed that oral use of 100% DMSO in rat was well tolerated for 1 day
- Checked with drug safety and endorsed the use of DMSO use based on database confirmation

# Search Excipients DB for DMSO administered orally to rats

- Recent search shows 5 vehicles with DMSO with 9 associated S&R records
- Now shows 5 S&R records with 100% DMSO

AND

- Single and repeat dose data - Route of admin. in 'Oral (gavage)|Oral (unspecified)'
- Single and repeat dose data - Species = 'Rat'
- Inline table search: Vehicle Data : Vehicle components - Component Name = 'DMSO'

5 records in the Vehicle Data table in EXCIPIENTS_LHASA

9 records in the Single and repeat dose data table in EXCIPIENTS_LHASA

Home | My Vitic | Query | Results Gallery | Results Grid | Report | Help | Logout

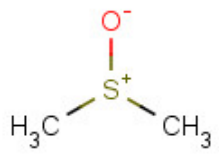
## Single and repeat dose data

Display settings

| Vehicle name | pH | Dose volume | Dose units | Frequency of admin. | Treatment duration (VC) | Route of admin. | Species | Tolerability |
|---|---|---|---|---|---|---|---|---|
| DMSO | No information | 10 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated without findings |
| DMSO | No information | 10 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated without findings |
| DMSO | No information | 10 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated without findings |
| DMSO | No information | 5 | ml/kg | No information | 7 Days | Oral (unspecified) | Rat | Tolerated without findings |
| DMSO | No information | 5 | ml/kg | No information | 4 Weeks | Oral (unspecified) | Rat | Tolerated without findings |
| Glycine-solution (50mM), HP-B-CD (28%), DMSO (5%), Methylcellulose (1%), NaOH | 9.0 | 5 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated without findings |
| Water (55.25%), PEG-400 (25%), DMSO (10%), SBE-B-CD (9.75%) | No information | 10 | ml/kg | 1/day | 2 Days | Oral (gavage) | Rat | Tolerated with findings |
| Water (60%), SBE-B-CD (30%), DMSO (10%) | No information | 10 | ml/kg | 1/day | 7 Days | Oral (gavage) | Rat | Tolerated without findings |
| Water (90%), DMSO (10%) | No information | 10 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated with findings |

Structure Explorer

DMSO




Glycine-solution (50mM), HP-B-CD (28%), DMSO (5%), Methylcellulose (1%), NaOH

# A deeper look for Drug Safety concerns

- All 100% DMSO records were tolerated without findings
- Top 3 have more supporting data, e.g., GLP status, # animals, strain, bodyweight, food consumption, clinical signs, and or gross pathology

## Single and repeat dose data

Display settings

| Vehicle name | pH | Dose volume | Dose units | Frequen of admin. | Treatme duration (VC) | Route of admin. | Speci | Tolerability | GLP status | No. animals per group (both sexes) | Strain | Sex | Mortality | Bodyweight | Food consumptic |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DMSO | No infor | 10 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated without findings | GLP | 10 | Wistar | Male/female | None | Nothing abn | Nothing ab |
| DMSO | No infor | 10 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated without findings | GLP | 4 | Wistar | Male/female | None | Nothing abn | No informa |
| DMSO | No infor | 10 | ml/kg | 1/day | 1 Days | Oral (gavage) | Rat | Tolerated without findings | GLP | 6 | Wistar-Han | Male/female | None | Nothing abn | No informa |
| DMSO | No infor | 5 | ml/kg | No infor | 7 Days | Oral (unspecif | Rat | Tolerated without findings | No inforr | | No informati | Male/female | No inform | No informati | No informa |
| DMSO | No infor | 5 | ml/kg | No infor | 4 Weeks | Oral (unspecif | Rat | Tolerated without findings | No inforr | | No informati | Male/female | No inform | No informati | No informa |

1 Page size: 50 9

Bone marrow exam | Clinical chemistry | Clinical signs | Electron microscopy | Gross pathology | Haematology | Histopathology | Immunotoxicc

Gross pathology Display settings

| Gross pathology - Organ affected | Gross pathology - Observation |
|---|---|
| Nothing abnormal detected (NAD) | |

# The Outcome

- **Formulation was taken into an exploratory TK/PK toxicology study to check the desired safety objective**
- **Study was successful in terms of toleration, and compound & formulation helped provide the required information to progress the project forwards.**