Approaches for the Safety Evaluation of Excipients

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April 29, 2013

Outline

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  - What is toxicology?
  - Basic principles & information needed to perform an assessment
  - Excipient categories
  - Resources

• Regulations
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  - Testing strategies

• Toxicity studies – design/purpose

• Assessment examples
  - Cyclodextrin
  - Chitosan

Abbreviations

ADME  Absorption, distribution, metabolism, & excretion
AISE  International Association for Soaps, Detergents and Maintenance Products
BID  Bis in die (On a day)
CEFC  European Chemical Industry Council
ECHA  European Chemicals Agency
EMA  European Medicines Agency
FDA  U.S. Food & Drug Administration
GD  Gestation day
GPMT  Guinea pig maximization test
GRAS  Generally recognized as safe
ICH  International Conference on Harmonization
IM  Intramuscular
IP  Intraperitoneal
IV  Intravenous
LNA  Local lymph node assay
MHLW  Ministry of Health, Labor & Welfare
NOAEL  No observed adverse effect level
NOEL  No observed effect level
PO  Per os (oral)
QC  Quaque die (once daily)
SC  Subcutaneous
TSE  Transmissible spongiform encephalopathy
TD  Tar in die (3x daily)
TK  Toxicokinetics
UNEP  UN Environmental Program
What is toxicology?

Toxicology is the study of the adverse effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects.

“All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy.”

Paracelsus (1493-1541)
Basic principles - terms

- **Toxicity**
  - capacity of a compound to cause dysfunction or injury (adverse event)
- **Target**
  - particular tissue, organ, cell, or biochemical process that is disrupted by a compound
- **Mechanism of action**
  - manner in which the compound is able to disrupt a process
- **NOEL (No observed effect level)**
  - exposure level that has no effect on the health of animals – as measured by methods which have a finite sensitivity to measure dysfunction or injury
- **Individual susceptibility**
  - variability in response to a chemical; associated with differences in ADME, genetics, gender, age, and health

**Exposure**

- dependent on dose amount, dose frequency, route of administration, and duration (how long the body is exposed to the compound)
- **Dose**: amount of chemical per body weight
- **Frequency**: daily (QD, BID, TID), weekly, monthly
- **Route**: effectiveness of route, IV > Inhalation > IP > IM > Oral > Topical
- **Duration**:
  - Acute: < 24 hr
  - Subacute: 1 month
  - Subchronic: 1-3 months
  - Chronic: >3 months

**Compound elimination**

I = rapid
II = moderate
III = slow

Adapted from Casarett & Doull's Toxicology, 7th Ed.
Basic principles

- Risk is dependent on exposure and hazard (action/response)
  - Risk assessment is a quantitative estimate on the potential effects of chemical exposure on human health
- There is no risk without exposure
- All substances have the potential to cause adverse events (e.g., water, oxygen)
- Whether a compound is synthetic or naturally occurring does not affect toxicity
  - Dose determines the biological response

Data needed to perform an assessment

- Physicochemical properties
  - solubility, pKa, polymorphs, purity, absorption spectra (phototoxic potential)
- History of use
  - similar medical indication(s), cosmetics, food additive
- Intended use
  - route of administration, duration, special populations (e.g., children), formula concentration
- Regulatory status
  - EU, FDA, Japan
- Quality of existing data
  - old, non-GLP, studies with insufficient detail
  - NOEL/NOAEL determined
- Safety data from structurally similar compounds
- Evidence in published literature

Data needed to perform an assessment

- Role in the formulation (e.g., preservative, solubilizer)
- ADME profile
  - including TK parameters (AUC, Cmax, tmax)
- Existing human data available?
- Updated evaluation available (e.g., phthalates)
- Presence of impurities or degradation products
- Presence of residual solvents (e.g., benzene)
- Specialized toxicity concerns:
  - Allergic or phototoxic potential, genotoxicity, reprotoxicity
- Is it a mixture of variable composition (e.g., polyethylene glycol)
### Examples of excipient toxicological effects

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### Background

- What is toxicology?
- Basic principles & information needed to perform an assessment
- Excipient categories
- Resources...

### Regulations

- Relevant regulations
- Testing strategies

### Toxicity studies – design/purpose

### Assessment examples

- Cyclodextrin
- Chitosan

### Excipient categories

- **Standard, Established (no evaluation required)**
  - Chemicals with a long history of use in drug products

- **Established – modified (targeted evaluation needed)**
  - Standard excipient
    - in a new route of administration
    - at a different (higher) concentration
    - in a different patient population
Excipient categories

- New (novel) (full evaluation required)
  - EU definition (www.emea.europa.eu/pdfs/human/pep/2995106enfin.pdf)
    - excipient being used for the 1st time in a drug product
    - excipient being used via a new route of administration
    - a new chemical entity (NCE)
    - well established chemical which has not yet been used for human administration and/or for a particular human administration pathway

- Human or animal origin
  - Demonstrate compliance with guidance on minimizing risk of transmissible spongiform encephalopathy (TSE)

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Resources

- International (WHO)
  - International program on chemical safety (IPCS)
  - International agency for research on cancer (IARC)

- European
  - Registration, evaluation, authorization and restriction of chemical substances (REACH; ECHA)
  - International uniform chemical information database (IUCLID; ECHA)
  - Screening information database for high volume chemicals (SIDS; UNEP)
  - Dictionnaire vétal (France, UBM Medica)
  - Die Rote Liste (Germany, Rote Liste Service GmbH)
  - The electronic medicines compendium (eMC; UK, Datapharm Communications Ltd.)
  - eChemPortal (OECD)
  - Human & environmental risk assessment on ingredients of household products (HERA; AISE-CEFIC)
Resources (cont’d)

- United States
  - Inactive ingredient database (IID; USFDA)
  - GRAS substances database (SCOGS; USFDA)
  - National toxicology program (NTP; NIH)
  - High production volume challenge program (HP; USEPA)
  - U.S. Pharmacopeia – National Formulary (USP)

- Japan
  - Japanese standards of pharmaceutical ingredients (MHLW)
  - Japanese pharmaceutical excipients dictionary (JPEC)
  - Pharmacopoeia of Japan (MHLW)

- General
  - Pubmed (US National Library of Medicine)
  - Toxnet (US National Library of Medicine)
  - Cosmetic Ingredient Review (CIR)

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Excipient Regulations

- U.S. (FDA)
  - Guidance for industry: Nonclinical studies for the safety evaluation of pharmaceutical excipients (May 2005)
  - Genotoxic and carcinogenic impurities in drug substances and products: Recommended approaches (Dec 2008, draft)

- European (EMA)
  - Opinion: The potential risks of carcinogens, mutagens, and substances toxic to reproduction when these substances are used as excipients of medicinal products for human use (Oct 2007) (EMEA/CHMP/QWP/1262/2007)
Related Regulations

- **International Conference on Harmonization (ICH)**
  - M3 (R2): Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (Jun 2009)
  - M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (Feb 2013)
  - Q1B: Impurities in new drug products (Jun 2006)
  - Q3C (R5): Impurities: Guideline for residual solvents (Feb 2011)
  - S1A: Guideline on the need for carcinogenicity studies of pharmaceuticals (Jul 1997)

- **International Conference on Harmonization (ICH)**
  - S2 (R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use (Nov 2011)
  - S3A: Note for guidance on toxicokinetics: Assessment of systemic exposure in toxicity studies (Oct 1994)
  - S3B: Guidance for repeated dose tissue distribution studies (Oct 1994)
  - S5 (R2): Detection of toxicity to reproduction for medicinal products and toxicity to male fertility (Nov 2005)
  - S7A: Safety pharmacology studies for human pharmaceuticals (Nov 2000)

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**Regulations**
- Overview of regulations
- Testing strategies
**Toxicity studies – design/purpose**
- Assessment examples
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Excipient – testing strategies

Recommended testing is dependent on the intended duration of use

**Short-term clinical use (≤14 days)**
- Safety pharmacology (ICH guidance S7A)
- Acute study (rodent, nonrodent) (ICH guidance M7)
- Pharmacokinetic: ADME profile (ICH guidelines S3A & S3B)
- Genotoxicity battery (ICH guidance S2)
- 1-Month repeat-dose study (rodent, nonrodent)
  - route of administration for clinical use
  - Includes clinical & anatomic pathology, and TK analysis

**Intermediate clinical use (>2 wk – ≤3 mo)**
- Short-term use studies
- 3-Month repeat-dose study (rodent, nonrodent)
  - route of administration for clinical use
  - Includes clinical & anatomic pathology, and TK analysis
- Additional studies as needed to address specific issues (e.g. studies involving parenteral [IV, IP, SC] route)

**Long-term clinical use (>3 mo)**
- Short-term & intermediate use studies
- 6-Month repeat-dose study (rodent)
  - route of administration for clinical use
  - Includes clinical & anatomic pathology, and TK analysis
- 6- or 9-Month repeat-dose study (nonrodent)
- Carcinogenicity testing (ICH guidelines S1A and S1B)

**Topical, pulmonary, or injectable products**
- All studies listed above using appropriate route of administration
- Sensitization study (GPMT, LLNA)
- IV: in vitro study to evaluate hemolytic potential
- IM/SC: creatinine kinase levels to evaluate possible muscle damage
Background

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Regulations

- Relevant regulations
- Required testing

Toxicity studies – design/purpose

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Safety/Toxicity Studies

Safety pharmacology core battery - GLP

- Assesses pharmacological activity and impact on vital functions
  - Central nervous system: Functional observation battery (FOB), motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature
  - Cardiovascular system: HERS, blood pressure, heart rate, and ECG waveform
  - Respiratory system: Respiratory rate and other measures of respiratory function (e.g., tidal volume or hemoglobin oxygen saturation)
  - Additional (as needed): Renal/urinary and gastrointestinal

Single Dose (rodent/nonrodent) – nonGLP

- Dosed via intended clinical route of administration
- Number of animals/sexdose: 3 (rodent); 1 (nonrodent)
- Predicts the consequences of human overdose situations
- Defines a maximum tolerated dose (acute)
- Parameters: Mortality, clinical signs, body weight, food consumption, clinical pathology (optional), abbreviated anatomic pathology (rodent), toxicokinetics (not usually performed)

Toxicity Studies

Repeated dose (rodent/nonrodent) – GLP

- Dosed via intended clinical route of administration.
  - Number of animals/sexdose:
    - Rodent: 10 (main), 6 (recovery), 6 (TK)
    - Nonrodent: 3-4 (main) + 2 (recovery)
  - Duration (1, 3, 6, or 9 month) should be equal to or exceed the duration of the human clinical trials up to the maximum recommended duration of the repeated-dose toxicity studies.
  - Parameters: Mortality, clinical signs, body weight, food consumption, clinical pathology (optional), abbreviated anatomic pathology (rodent), toxicokinetics (not usually performed)

Genetox battery – GLP

- Bacterial (Ames) assay: test for gene mutations
- In vitro chromosomal aberration assay (e.g., Mouse Lymphoma 5178Y cells; Human Peripheral Lymphocyte assay)
- In vivo rat or mouse micronucleus assay: test for chromosomal damage
Toxicity Studies

- Reproductive toxicity – GLP studies
  - Fertility (rats): effects on mating and implantation
    - Number of animals: 20/sex/dose
    - Males dosed 4 wk prior to cohabitation until females necropsied
    - Females dosed 2 wk prior to cohabitation until gestation day (GD) 7
    - Parameters: Clinical signs, body weight, food consumption, mating and fertility indices, sperm analysis (optional), anatomic pathology (including uterine and ovary observations)
  - Embryofetal toxicity (rodents, rabbits): effects on embryo/fetus development
    - Number of animals/sex/dose: 20 (main) + 2-6 (TK)
    - Dosing: GD6 to GD17 (rat); GD6 to GD15 (mouse); GD6 to GD19 (rabbit)
    - Cesarean: GD21 (rat), GD18 (mouse); GD29 (rabbit)
    - Parameters: Clinical signs, body weight, maternal and fetal (visceral/skeletal) anatomic pathology exam, TK.

- Pre-postnatal toxicity (rats): effects on offspring behavior and maturation
  - Number of animals/sex/dose: 24 mated females
  - Dosing: GD6 to postnatal day 20
  - Parameters: Clinical signs (F0, F1), body weight (F0, F1), reproductive indices (F0, F1), behavioral testing (F1), anatomic pathology (F0, F1), pup viability indices (F1).

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Cyclodextrin

- Sulphobutylether β-cyclodextrin (SBECD)
  - Solubilizing/stabilizing agent
  - Contains a genotoxic impurity that cannot be completely eliminated
  - No suitable alternative cyclodextrin exists
  - Available safety data supports its use in drug products

Agency decision
- Approved, but the supplier had to reduce the level of the genotoxic substance to the greatest extent possible.
- Favorable benefit/risk balance for the drug product as a whole outweighed the potential safety concern of the excipient.

Chitosan

- Polysaccharide polymers with different molecular weights derived from chitin (crustacean shells, insect exoskeleton)

  - Regulatory status
    - Not permitted in marketed drugs
    - GRAS status – direct food additive
    - Permitted in cosmetics
    - Permitted in a medical device (Celox – hemostatic products)

  - Biological activity
    - Hemostasis
    - Reduce blood loss
    - Adhesion reduced
    - Wound healing
    - Reduce liver/blood cholesterol

  (Baldrick; Reg.Toxicol.Pharmacol., 2010)

Available safety data

- Acute toxicity (rat, mouse): oral, IP, SC, IV
- ADME: characterized
- Repeat dose (rat, mice, rabbit, dog): 10 days to 52 weeks
- Genotox data: Limited; not mutagenic (Ames)
- Reproductive toxicity: No data
- Carcinogenicity: No data

- Additional information
  - Cytotoxicity & hemocompatibility: Characterized
  - Local tolerance (eye/skin irritation): No issues
  - SC implantation: No significant reaction
  - Immunoactivity: No findings
  - Human data: Limited; dietary supplement study, no issues

  (Baldrick; Reg.Toxicol.Pharmacol., 2010)
Chitosan

Is it a safe pharmaceutical excipient? Depends on the route

- **Yes**: Oral, Inhalation, Intranasal, Ocular, Dermal
  - Is metabolized to a naturally occurring glucosamine derivative
  - Additional testing – case by case, but it will be limited because of available human data and prior use in the food industry
  - Additional evaluations – part of drug product testing as a formula constituent
  - Sensitization testing to evaluate potential adverse effects in patients with shellfish allergy
  - Genotoxicity testing of form of chitosan to be used in drug product

- **No**: Parenteral (IV, IP)
  - No clear evidence to support safety
  - Potential concern if its use brings it directly in contact with blood: coagulation, thrombus formation, platelet adhesion and cytotoxicity
  - Examination of its potential effects on blood clotting is needed

(Baldrick, Reg. Toxicol. Pharmacol., 2010)