

Residual Solvents

To Test or Not to Test

Interpreting and Implementing ICH Q3C Requirements

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➤ Introduction

- why limit residual solvents in pharmaceuticals?
- basic toxicology principles
 - dose-effect
 - hazard vs. risk
- how ICH limits/PDE values derived

➤ Translating and Implementing

- calculating actual product thresholds
- comparing calculated thresholds to product levels
- assessing impact of comparison

➤ Conclusions

➤ Patient Safety

➤ Regulatory focus

- ICH impurity guidance(s) for drug products and drug substances
- ISO guidance for impurities/residuals in medical devices (10993-17)
- EPA/OSHA guidance for contaminant/impurity exposure
 - e.g., new EPA proposed EO limits (relevant for health care professionals)

➤ Consumer focus

- Heightened awareness of impurities/ingredients especially in food products
- Awareness also present for medical products
 - Ex., special assessments from FDA and other agencies on product ingredients or impurities driven by advocacy groups

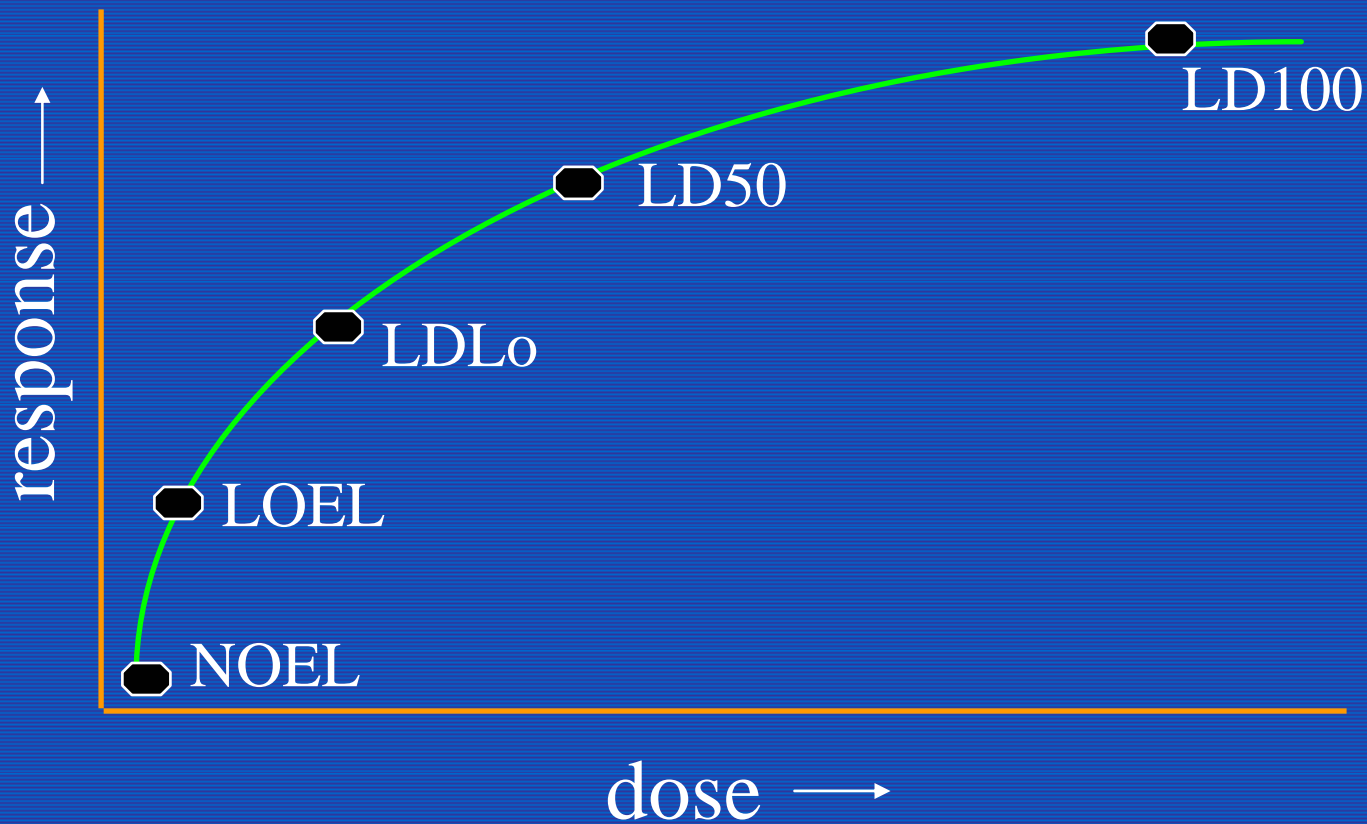


**What is there that is not a
poison?**

**All things are poison and
nothing (is) without poison.
Solely the dose determines that
a thing is not a poison.**

Paracelsus
(1493-1541)

Dose Response



RISK VS. HAZARD

HAZARD: the inherent “toxicity” of an agent.

RISK: the likelihood of causing adverse effects -
completely dependent on exposure

Can have minimal risk with highly hazardous agents, and visa-versa

Classification of Toxicants

Probable oral lethal dose in humans

<u>Agent</u>	<u>LD₅₀</u> (mg/kg)	<u>Toxicity Rating</u>
Ethyl alcohol	10,000	Slightly toxic (5-15 g/kg)
Sodium chloride	4,000	Moderately toxic (0.5-5 g/kg)
Aspirin	750	
Phenobarbital	150	Very toxic (50-500 mg/kg)
Parathion	7	Extremely toxic (5-10 mg/kg)
Strychnine	2	Super toxic (< 5 mg/kg)
Botulinus toxin	0.00001	

Most Humans Aren't Large Rats!



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➤ Toxicological risk assessment

- 3 broad categories
 - Class 1: known human a/o genotoxic carcinogens or agents with high environmental hazard
 - Class 2: solvents with potentially severe a/o irreversible effects
 - Class 3: solvents with inherently lower hazard potential
- Margin of exposure or “safety” margin approach

animal NOEL or LOEL

apply modifying factors to account for species differences, human variability, etc.

extrapolated “safe” or permissible human exposure level

- ICH PDE values for oral exposure and based on oral animal data
- ICH PDE calculated as “safe”, potential lifetime exposure
- ICH PDE values can change based on new/relevant data
- other methods besides safety margin approach

➤ Based on therapeutic dosing/use of product in humans

➤ Converting PDE to threshold for LVP a/o SVP

- Common sense!, bottom line is the mg/d (PDE) of residual solvent person is exposed to in any one day by the drug product

➤ Consider methanol with PDE of 30 mg/d

- For 50 mL SVP with max daily dosing volume of 200 mL/d (max; 4 x drug product/d)
 - drug product limit (mg) = $PDE / \# \text{ of vials or SVPs} = 30 \text{ mg/d} / 4 \text{ SVPs/d} = 7.5 \text{ mg/SVP}$
 - drug product limit (ppm) = 7.5 mg/50 mL, equivalent to 150 ppm (ppm is mg/L)
 - therefore, individual components (API, excipients, etc,) must sum to $\leq 7.5 \text{ mg a/o } 150 \text{ ppm}$
- For 750 mL LVP with max daily dosing volume of 1.5 L/d (max; 2 x drug product/d)
 - drug product limit (mg) = $30 \text{ mg/d} / 2 \text{ LVPs/d} = 15 \text{ mg/LVP}$
 - drug product limit (ppm) = 15 mg/750 mL, equivalent to 20 ppm
 - therefore, individual components (API, excipients, etc,) must sum to $\leq 15 \text{ mg a/o } 20 \text{ ppm}$

➤ Based on therapeutic dosing/use of product in humans

- **Same concept for other dosage forms (e.g., solid tablets, etc.)**
 - Common sense!, bottom line is the mg/d (PDE) of residual solvent person is exposed to in any one day by the drug product
 - Example: for a tablet, and the 30 mg/d methanol PDE example, assume 2 x 500 mg tablets/d max daily dose
 - then, $30 \text{ mg/d} / 2 \text{ tablets/d} = 15 \text{ mg/tablet}$

- **Class 3 solvents limited at $\leq 50 \text{ mg/d}$; apply same concepts as highlighted above to calculate product limits**

- **Class 1 solvents should be avoided; ppm limits provided if unavoidable**

➤ Compare calculated limits to known information

➤ Supplier information

- Discussed extensively in following presentation

➤ Other sources of published information

- MSDS information
- Other product information specs
- DMF info
- Any relevant patent info
- SBOA info for API's
- Other FOI-able resources

➤ Analytical testing if no relevant data available

- **Comparison indicates actual product levels less than ICH PDE**
 - **Done – Class 2 and 3 solvents**
 - **Consider periodic confirmation for Class 1**
- **Comparison indicates actual product levels greater than ICH PDE**
 - **Consider:**
 - **Risk vs. benefit analysis**
 - **therapeutic benefit and associated therapeutic margin of safety vs. potential risks from solvent; review assumptions in extrapolation**
 - **ICH Q3C PDE values for oral exposure; could be supplemented or modified based on specific product route, duration of therapy, etc.**
 - **other methods of extrapolation may be appropriate (benchmark dose extrapolations, PBPK modeling, etc.); consider less than lifetime exposure (vs. PDE), etc.**

➤ **Comparison indicates actual product levels greater than ICH PDE**

➤ **How important is the duration of therapy?**

- ICH Q3C allows for potential acceptance of residual solvent levels > PDE values in certain cases where the therapy is short term (30 days or less)

➤ **What about dermal products?**

- ICH Q3C allows for potential acceptance of residual solvent levels > PDE values in certain cases with topical application

➤ **Higher levels justified on a case-by-case basis**

Conclusions

- Limits proposed / promulgated primarily from regulatory initiatives
 - no clinical indication of adverse effects from residual solvents in currently approved drug products (yet completely appropriate to remain vigilant)
- Actual product limits calculated using therapy dosing information
- Compare calculated limits to information on product levels
 - Actual product testing necessary if no other relevant information available
- Compare calculated limits to relevant information on actual product levels
 - Options available even if product levels exceed calculated limits



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Thank You

