Acceptable Intake (AI) and Permitted Daily Exposure (PDE) Data Sharing Project for Pharmaceutical Impurities

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Agenda

• Who are Lhasa Limited?

• Context of the Lhasa Limited AI/PDE data sharing project
  • What are AIs and PDEs?
  • Why share AI/PDE data?
  • What are the benefits?

• The Lhasa Limited AI/PDE data sharing project
  • Goals of the project
  • Who is currently involved?
  • How does the project work?
  • Example database demonstration

• The current status of the Lhasa Limited AI/PDE data sharing project

• How can you get involved?
Who are Lhasa Limited?

- Established in 1983
- Not-for-profit organisation & educational charity
  - Headquarters in Leeds, UK
  - US-based Account Managers
  - Small software development teams in Poznan, Poland and Newcastle, UK
- Controlled by our members; no shareholders
- Creators of knowledge base and database systems
- Facilitate collaborative data sharing in the chemistry-related industries.
Lhasa Limited Members

Full List of Members on Website at:

http://www.lhasalimited.org/membership/current-members.htm
What are AIs and PDEs?

- The synthesis of new pharmaceutical entities involves the use of reactive substances and other reagents.
- Residual chemicals may exert toxic effects and therefore pose risk to human health if present as impurities in the final drug substance.
- Potential sources of impurities include:
  - (Residual) solvents, intermediates or reagents used during synthesis.
  - Extractables and leachables e.g. from medical devices.
- These impurities are the subject of a number of guidelines:
  - ICH M7(R1) (step 4, Mar 2017) – Assessment and Control of DNA Reactive (Mutagenic) Impurities
  - ICH Q3A(R2) (step 4, Oct 2006) – Impurities in New Drug Substances
  - ICH Q3B(R2) (step 4, Jun 2006) – Impurities in New Drug Products
  - ICH Q3C(R6) (step 4, Oct 2016) – Guideline for Residual Solvents
  - ICH Q3D (step 4, Dec 2014) – Guideline for Elemental Impurities
What are AIs and PDEs?

- AIs and PDEs are compound-specific acceptable exposure limits
  - Typically account for the most sensitive site of action, the route of administration, and the toxicity endpoint of relevance.
  - Examples and calculation methodology described further in ICH M7(R1), ICH Q3C and ICH Q3D.
- **AI - Acceptable Intake**
  - Chemical specific risk assessment for the maximum daily human intake level which poses negligible lifetime risk for carcinogenicity
    - “Should be applied instead of the TTC-based acceptable intakes where sufficient carcinogenicity data exist” – ICH M7(R1) (step 4, March 2017)
    - Mutagenic carcinogens (ICH M7 class 1) with a linear dose response and no established threshold mechanism
    - Calculation based on linear extrapolation based on positive carcinogenicity potency data (TD$_{50}$)
- **PDE – Permissible/Permitted Daily Exposure**
  - Chemical specific risk assessment for the maximum daily human intake level which poses negligible lifetime toxicity risk
    - Carcinogens or other toxicants
    - Non-linear dose response, or a mutagenic chemical with a practical threshold dose
    - Calculation based on toxicity data from repeated dose, developmental, reproductive or carcinogenicity studies and the application of uncertainty factors.
Why Share AI/PDE Data?

- Currently sponsors develop AI/PDE limits for chemicals independently
  - May reach different conclusions based on the data and methodology used
    → Potential for different AI/PDE values to be submitted to regulators for the same chemical
  - Very time consuming – requires significant effort to undertake literature review
    → Potential for significant duplication of effort across industry

- Regulators may reach a different conclusion to the sponsor
  - Alternative interpretation of the toxicology data
    → Significant impact on drug development for the sponsor *i.e.* impact on the impurity control strategy.
What are the Benefits of Sharing AI/PDE Data?

• Reduce duplication of effort across industry
  • Saves you a significant amount of time, effort, resource and cost

• Opportunity for cross-industry harmonisation of AI/PDE data and methodology
  • Industry acceptable AI/PDE data
  • Consistent use in regulatory submissions

• Data used in the calculation of an AI/PDE is often from public sources
  • Sharing your effort to generate an AI/PDE monograph rather than proprietary data

• Access to a larger harmonised AI/PDE data pool
  • Benefit from gaining access to the effort shared by other industrial partners.
Goals of the Lhasa Limited AI/PDE Data Sharing Project

1. Share existing AI/PDE data to generate an agreed upon series of AIs/PDEs for common impurities of highest value to you for use in your regulatory submissions
   - Wider in scope than mutagens:
     - Common reagents, solvents, biological reagents, other non-proprietary impurities
     - Include assessments which conclude “An AI/PDE cannot be calculated, therefore use the threshold of toxicological concern (TTC)”

2. Harmonise the shared AI/PDE data and the approach to conduct safety assessments
   - AI/PDE data will be harmonised through intra-project collaborative peer review
   - Aim to have a single harmonised AI/PDE value per chemical which is acceptable to all

3. The AI/PDE data will be made available to project members through a Vitic Nexus database
   - Ease of access to the shared project data → summary data and detailed supporting monograph documents
   - Include other publically available AI/PDE data e.g. the ICH M7 addendum chemicals
   - Collaboratively maintain the database to ensure this is the key AI/PDE data resource

4. Access to this resource will save you a significant amount of time, effort, resource and cost.
Who is Currently Involved?

- Nine organisations are collaborating to establish this project with Lhasa
How Do Lhasa Limited’s Data Sharing Projects Work?

Lhasa and members form a project consortium

Lhasa act as the honest broker and work with the consortium to:

- Agree scientific direction of the project
- Agree technicalities e.g. guidelines for data donation

Collaborative database development with consortium

Consortium members donate agreed data for sharing

Database is released to consortium

Lhasa curate, extract, and host the shared data

Lhasa extract knowledge from the shared data

Lhasa and the consortium promote the efforts of the initiative to industry and regulatory bodies worldwide.
How Does the AI/PDE Project Work? – Data Flow

Consortium members share AI/PDE monographs in agreed format

Vitic Nexus schema:
- Structure, CAS, name etc.
- AI/PDE data
- Peer review status
- Hyperlink

Vitic Nexus database of shared AI/PDE data released to consortium members

User authentication

Watermarked “Peer review pending” or “date-stamped”
How Does the AI/PDE Project Work? – Peer-Review

- Refined monographs re-submitted to Lhasa
- Update AI/PDE data in schema
- Update the peer review status to a "date-stamp"
- Update the hyperlink to the harmonised monograph document
- Include other identified public AI/PDE data

Collaborative refinement and harmonisation

- Peer review comments re-submitted to Lhasa/sent to the sharing organisation

All monographs are available for general peer-review
Lhasa assign members specific monograph(s) for more detailed peer-review

Watermarked “Peer review pending”
Database Demonstration

- Example database: ICH M7 addendum chemicals
Nine organisations are collaborating to initiate this project

Each has shared 2 AI/PDE monograph documents with Lhasa, the honest broker

Lhasa have generated the first database version containing the shared AI/PDE data and monograph documents for 18 chemicals

Database of original AI/PDE data and monographs has been released to the consortium members through Vitic Nexus for intra-project peer-review

AI/PDE monograph peer review is currently on-going → AI/PDE harmonisation.
How Can You Get Involved?

- New consortium members are actively being sought to join future data sharing cycles
  - Share additional AI/PDE monograph data
  - Harmonise through peer review new and existing shared AI/PDE data
  - Expand the database to maximise its value and impact for all

- Contact will.drewe@lhasalimited.org for more information.
Lhasa Limited’s Other Data Sharing Projects

• Lhasa Limited act as the honest broker to facilitate a number of other data sharing initiatives through the Vitic Nexus platform

• More information on these projects can be found at https://www.lhasalimited.org/research-and-collaboration/

• Alternatively please contact businessdevelopment@lhasalimited.org
Summary

- Highlighted the context of the AI/PDE data sharing project
  - What AIs and PDEs are
  - Why we should work collaboratively to share AI/PDE data and what the benefits are for you

- Reviewed the Lhasa Limited AI/PDE data sharing project
  - Goals of the project
  - Who is currently involved and the current project status
  - How the project works and example database demonstration

- Highlighted how you can get involved in future data sharing cycles.
Thank you for your attention

Questions?