

ICH
M17

Have you got it **covered?**

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Lhasa Limited provides solutions to assist in the meeting of the ICH M7 guideline.

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Lhasa Limited provides an integrated solution to aid experts in meeting the ICH M7 guideline, including: Derek Nexus, Sarah Nexus, Vitic, Mirabilis and Zeneth.

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This suggested framework makes use of Lhasa software as well as expert assessment to identify, classify and control potentially genotoxic impurities.

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Lhasa has worked hard to ensure that its ICH M7 solution provides the right level of information to support expert assessment.

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Lhasa has been creating scientifically robust expert software to improve efficiency and aid regulatory submission for over 30 years.

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Lhasa develops software for toxicity, metabolic fate, purge factor calculation and chemical degradation.

Introduction to ICH M7



The ICH M7 guideline provides a practical framework that can be applied to the identification, categorization, qualification and control of potentially genotoxic impurities to limit potential carcinogenic risk.

The guideline requires the use of two complementary (Q)SAR prediction methodologies (one expert rule-based and the other statistical-based).

Drawing on over 30 years of experience, Lhasa Limited scientists have developed integrated, independent, transparent and scientifically robust software that facilitates the assessment of impurities under ICH M7. The requirement for expert review under ICH M7 means that this process can never be fully automated; however, Lhasa's

ICH M7 workflow can automatically calculate an ICH M7 classification for all relevant impurities in a synthetic route which can then be used as the starting point for expert review. Tools are provided that permit intervention by experts to modify the calculated ICH M7 class, add additional supporting data and record their expert analysis, thereby providing an end-to-end solution for the computational assessment of impurities under ICH M7. The products that make up this solution are described on the following page.

Lhasa Limited software for ICH M7

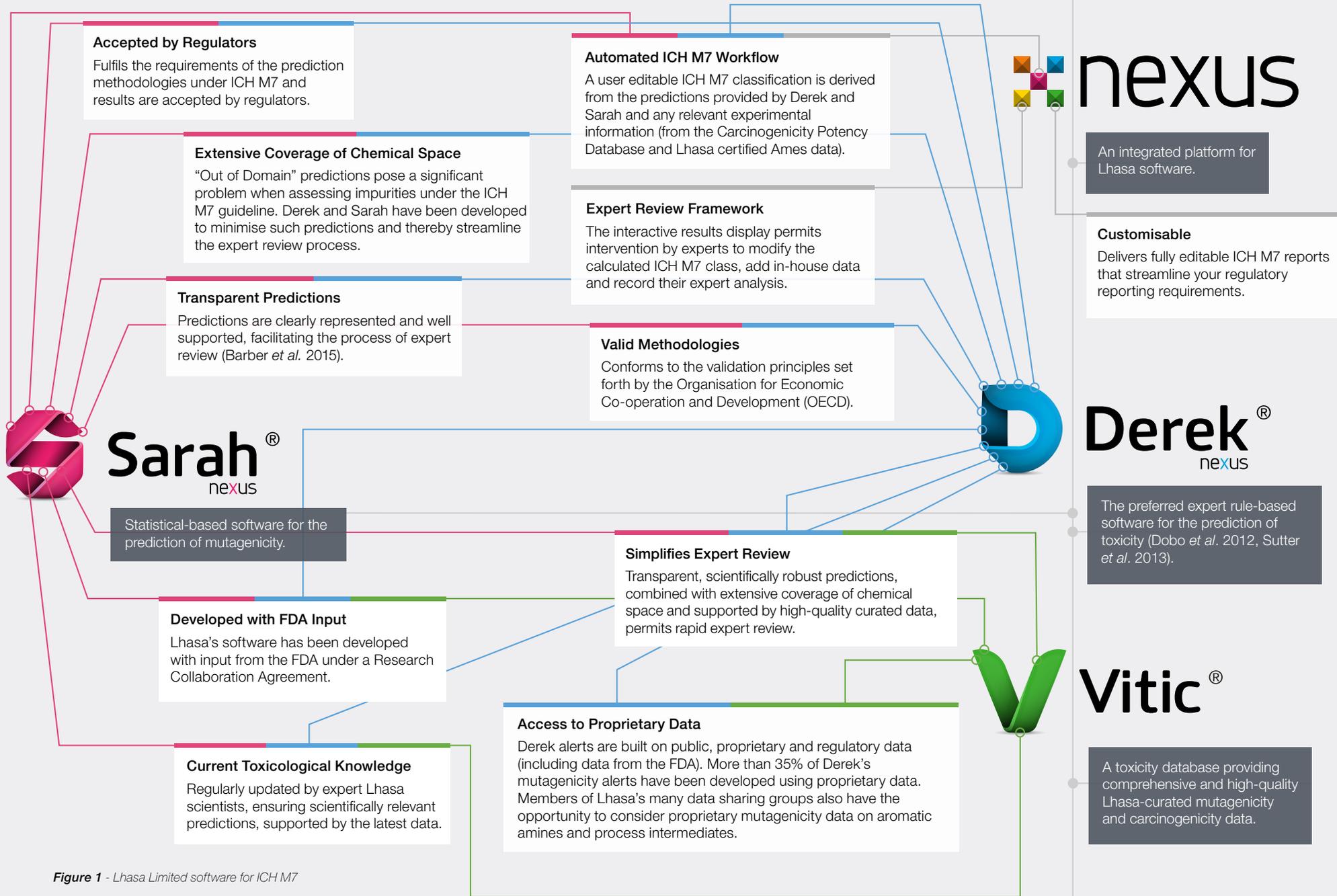


Figure 1 - Lhasa Limited software for ICH M7

Lhasa Limited software for ICH M7

Easy Mutagenic Assessment of Degradants

Predicted degradants can be imported into Nexus for analysis by Derek and Sarah.

Degradation Prediction

Provides insight into relevant degradation pathways, which can be used to guide decisions on the selection of potential degradants to be evaluated for mutagenicity.

Current Degradation Knowledge

Regularly updated by expert Lhasa scientists, ensuring scientifically relevant predictions, supported by the latest data.

Transparency

Provides expert commentary and detailed supporting information for calculated purge factors, enabling improved and justifiable decision making.

Consistent Industry Standard Approach

A common methodology and reporting framework provides standardisation for the inclusion of purge-based arguments in submissions to regulators.

Expert ICH M7 Support

Section 8, Control Option 4 of the ICH M7 Guideline allows for a control strategy that relies on an understanding of process controls in lieu of analytical testing. This risk assessment can be presented as an estimated purge factor for the clearance of the impurity by the process.



Zeneth[®]

Expert rule-based software for the prediction of forced chemical degradation (Kleinman *et al.* 2014).



Mirabilis[™]

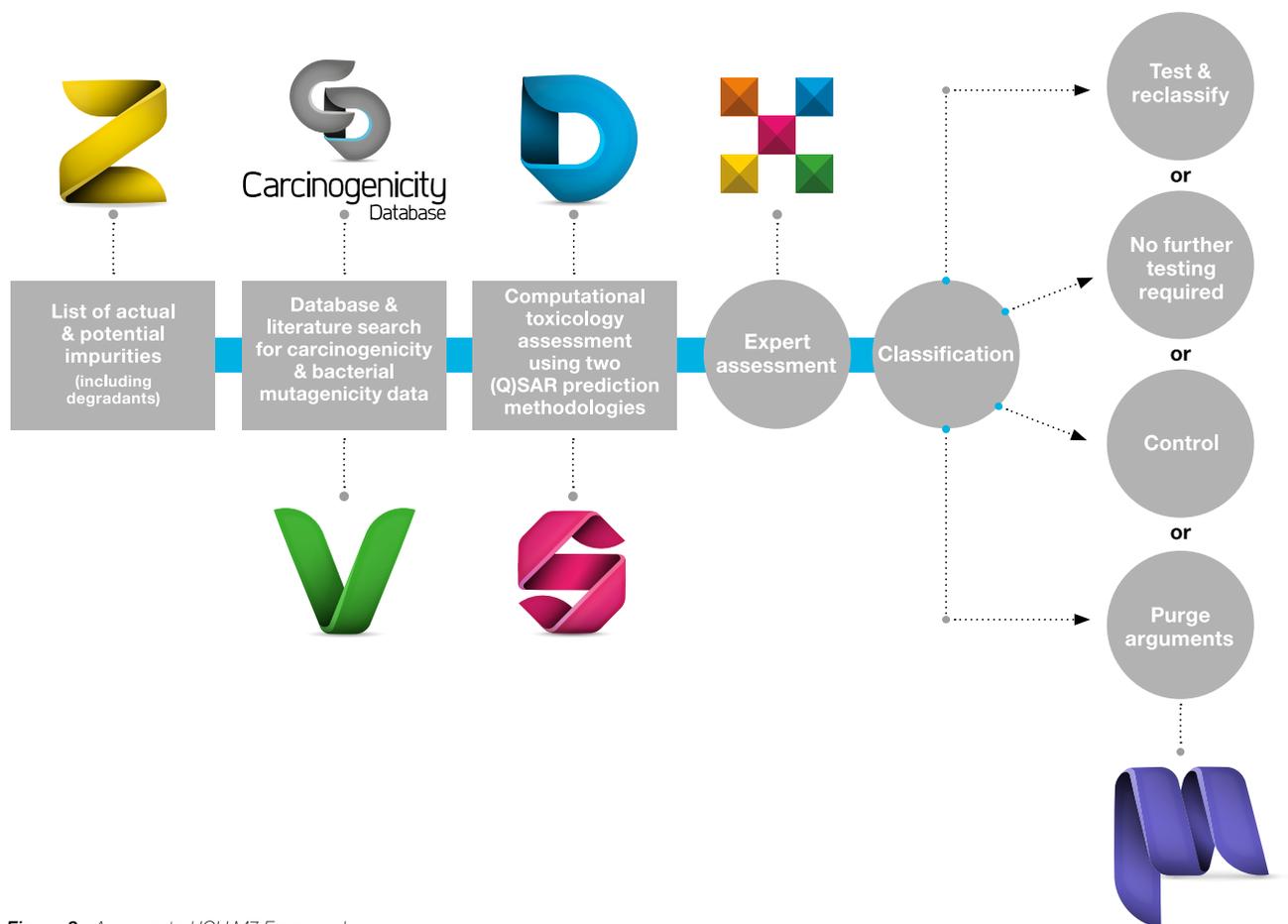
Expert software for the calculation of purge factors of potentially genotoxic impurities in a synthetic route.

A Lhasa Limited ICH M7 framework

ICH M7 guideline:

Assessment and control of potentially genotoxic impurities in pharmaceuticals to limit potential carcinogenic risk.

Lhasa Limited provides an intuitive and integrated workflow that can be applied to the identification, categorization, qualification and control of mutagenic impurities to limit potential carcinogenic risk (Figure 2).



Classification		
Class 1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
Class 2	Known mutagens with unknown carcinogenic potential	Control at or below acceptable limits (appropriate TTC)
Class 3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control as above or conduct bacterial mutagenicity assay; if non-mutagenic = class 5; if mutagenic = class 2
Class 4	Alerting structure, same alert in drug substance or compounds related to drug substance which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
Class 5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

Figure 2 - A suggested ICH M7 Framework

Using expert review for ICH M7 submissions

Expert assessment is a fundamental part of the assessment of the mutagenic potential of impurities under the ICH M7 guideline and, as such, Lhasa has worked hard to ensure that its ICH M7 workflow provides the right level of information to support expert analysis, allowing you to come to an informed decision.

Various publications illustrate how an expert can improve performance by evaluating *in silico* predictions (Dobo *et al.* 2012 and Sutter *et al.* 2013).

Whilst expert assessment has been successfully applied in the context of ICH M7, the definition of what constitutes expert analysis has been largely left open. Barber *et al.* (2015) have outlined views on establishing best practice in the application of expert review, and these views can be summarised in the Lhasa ICH M7 decision matrix.

<i>In silico</i> Prediction 1	<i>In silico</i> Prediction 2	
+	+	Likely to conclude positive Very strong evidence would be needed to overturn both predictions.
+	Out of domain or equivocal	Likely to conclude positive Lack of a second prediction suggests insufficient evidence to draw any other conclusion.
+	-	Uncertain Likely to conclude positive without strong evidence to overturn a positive prediction.
-	Out of domain or equivocal	Uncertain Conservatively could assign as positive. May conclude negative if strong evidence showing feature driving a 'no prediction' is present in the same context in known negative examples (without deactivating features).
-	-	Likely to conclude negative Expert review should support this conclusion - e.g. by assessing any concerning features (misclassified, unclassified, potentially reactive...).

The Lhasa ICH M7 decision matrix provides an overview on the likely outcome based on your 2 predictions. Expert review and additional information can however lead to a different expert call (Barber *et al.* 2015).

Why choose Lhasa?

When asked why people choose to work with Lhasa Limited, the common responses are:

1

Over 30 years of experience in developing state-of-the-art *in silico* prediction and database systems.

2

Transparency of Lhasa systems allows trust and confidence in the science presented.

3

All science is developed in-house, providing the opportunity to discuss directly with Lhasa expert scientists.

4

Software is easy to use and well supported.



Our Products

What other software do we produce?



An expert rule-based system for the prediction of toxicology.



An expert rule-based system for the prediction of metabolic fate.



A tool for assessing the relative purging of mutagenic impurities.



A statistical-based system for the prediction of mutagenicity.



A chemical database and information management system.



An expert rule-based system for the prediction of degradation pathways.



shared knowledge • shared progress

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For more information, please contact info@lhasalimited.org

References

• Barber *et al.* (2015) 'Establishing best practice in the application of expert review of mutagenicity under ICH M7' *Regulatory Toxicology and Pharmacology*, vol 73, no. 1, pp. 367-377.

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