A Collaborative Approach towards Risk Assessment for Mutagenic Impurities

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Introduction

Currently, ICH M7 guidance on mutagenic impurities (MIs) supports the control of potential MIs during the synthesis of an active ingredient based on a number of approaches. This includes an option based on the "Understanding of process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is needed for this impurity" [1]. Therefore, with a sufficient understanding of the manufacturing process and chemistry, the need to perform analytical and genotoxicity testing is reduced if it can be proven that the MI in question is unlikely to be present in the final active pharmaceutical ingredient (API).

To achieve this, a general, standardised approach is desired to predict the presence or absence of an MI in the API. Currently, a significant amount of effort is required to prove absence analytically, thus use of a "paper-based" methodology would significantly save on time and costs. One such method was proposed by Pierson et al [2], in which the number of stages between the introduction of the MI of concern and final product of the synthesis scheme is used to determine a course of action – i.e. if the MI is introduced early on in a synthetic route, then a chemical rationale can be provided to demonstrate its removal from the final product; if the MI is introduced much later in the route then testing is more likely to be required (Figure 1). However, this is an empirical approach which does not take into account the properties of the MI (for example, reactivity) in relation to the synthesis pathway in question, which could lead to an overestimation, or worst case, an underestimation of the amount of an MI in a final product. Therefore, a new methodology has been developed which builds on the Pierson concept [3], in collaboration with industry and regulators to expand and standardise its use.

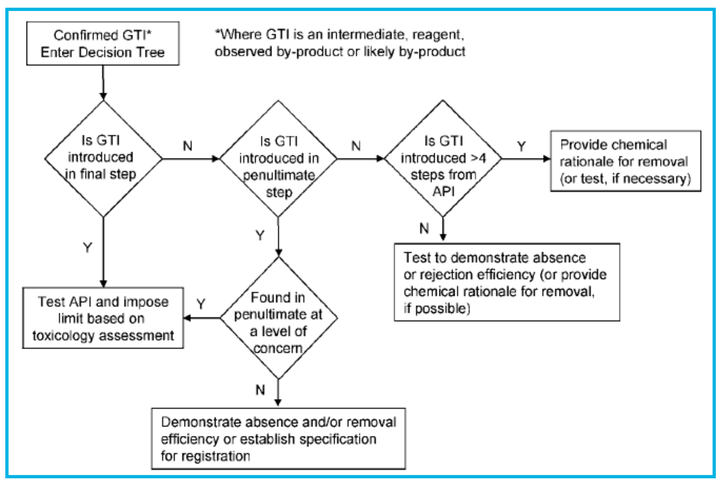


Figure 1: Pierson et al Decision Tree to determine whether to test for an MI.

Concept

A concept was proposed by Andrew Teasdale at AstraZeneca, in which semi-quantitative "purge factors" are calculated to give confidence that a MI is likely to be absent in an end-product. This takes into account the following key factors:

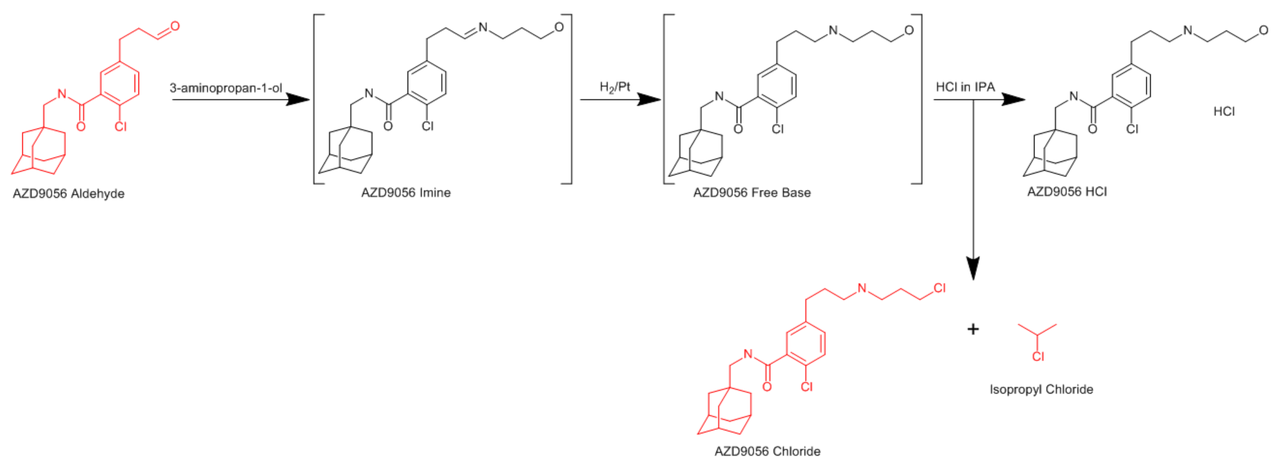
- Reactivity
- Solubility
- Volatility
- Ionisability
- Additional physical processes e.g. chromatography

Each MI of concern is considered at every stage of the synthetic route from its introduction and a score is assigned based on the physical and chemical properties of the MI relative to the conditions of the process (Table 1). These are combined at each step to give a purge factor (proportion remaining) for every stage and an overall purge factor can be determined for the scheme by multiplying all the stage purge factors together. An example using this methodology is shown below (Figure 2) [3]. Others have also applied a similar concept with an additional physical process parameter [4]. However, the approach of Teasdale et al is currently referenced in ICH guidance [1].

Figure 2: Conversion of AZD9056 Aldehyde to AZD9056 HCl. MIs of concern are highlighted in red. The process involves three steps:

1) *Reaction of AZD9056 Aldehyde with 3-aminopropan-1-ol, followed by hydrogenation to give the free base of AZD9056*
2) *Formation and isolation of crude AZD9056 HCl*
3) *Purification of AZD9056 HCl*

For each step the purge factor has been predicted and compared to the measured purge factor. As demonstrated in this example and as designed, the approach under-predicts giving a conservative purge factor



physicochemical parameters	purge factor
reactivity	highly reactive = 100 moderately reactive = 10 low reactivity/unreactive = 1
solubility	freely soluble = 10 moderately soluble = 3 sparingly soluble = 1
volatility	boiling point >20 °C below that of the reaction/ process solvent = 10 boiling point within ±10 °C of that of the reaction/process solvent. = 3 boiling point >20 °C above that of the reaction/ process solvent = 1
ionisability	ionisation potential of MI significantly different from that of the desired product
physical processes: chromatography	chromatography: 10−100 based on extent of separation
physical processes: e.g. other scavenger resins	evaluated on an individual basis

Table 1: Physicochemical parameters and their associated values used to assess the purge factor for a particular MI.

Compound	Step 1 (Predicted)				Step 2 (Predicted)				Step 3 (predicted)				Stage	
	Reactivity	Solubility	Volatility	Predicted Purge Factor	Reactivity	Solubility	Volatility	Predicted Purge Factor	Reactivity	Solubility	Volatility	Predicted Purge Factor	Predicted Purge Factor	Measured Purge Factor
AZD9056 Aldehyde	100	1	1	**100**	1	10	1	**10**	1	10	1	**10**	**10,000**	112,000
AZD9056 Chloride	Not present	Not present	Not present	N/A	1	1	1	**1**	1	3	1	**3**	**3**	10
Isopropyl Chloride	Not present	Not present	Not present	N/A	1	10	10	**100**	1	10	10	**100**	**10,000**	38,500

Collaboration

Lhasa Limited have set up a consortium with industry members with the goal of establishing a software tool which would aid in the generation of "purge factors" and support a standardised, agreed approach for inclusion of these arguments within regulatory submission.

Aims:

- Standardise how calculations are performed
- Collate existing data and knowledge, and promote cross-industry sharing
- Provide an automated software tool

Lhasa Limited are working on three different components which will form a "Purge Tool" (Figure 3).

- The database will facilitate the storage of existing data which could be searched for comparison of "purge factors" for similar impurities
- The reaction knowledge base will predict the reactivity purge factor parameter based on impurity features and reaction types. This will be supported by literature and expert knowledge for regulatory submission
- The interface will bring all this together, allowing the entry of data and calculations of purge factors based on input

This work currently involves focus groups which discuss various aspects of the science, the collection of expert knowledge, and software development.

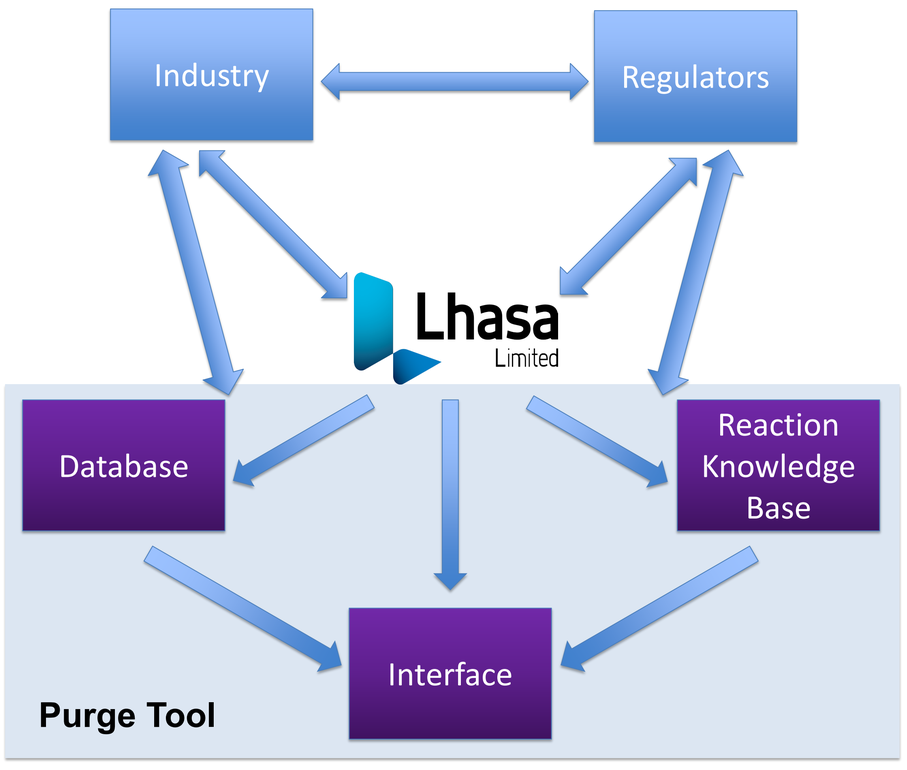


Figure 3: How the collaboration between Lhasa Limited, industry and regulators works and how this feeds into the components of the "Purge Tool" (in purple)

Conclusion

A successful international collaboration has been established with seven large pharmaceutical companies which will guide the development of an *in silico* system for which the concept of purge factors aim to be standardised and accepted by regulators. This work has the potential to save both time and money in regards to regulatory submission and ensures effort is focussed on those impurities which pose a substantive risk. Standardisation will streamline the regulatory submission process, providing clarity and further reduction of costs.

References

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_2.pdf

[2] Pierson et al, Org. Process Res. Dev., 2009, 13, 285-291, http://dx.doi.org/10.1021/op8002129

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[4] Elder et al, Org Process Res. Dev., 2013, 17, 1036-1041, http://dx.doi.org/10.1021/op300268u