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Letters to the Editor

A Tool for the Semiquantitative Assessment of Potentially Genotoxic Impurity (PGI) Carryover into API Using Physicochemical Parameters and Process Conditions

Introduction

The threat posed by genotoxic impurities (GIs) in drug substances generally arises from the use of electrophilic agents (alkylating agents) within the synthesis. Such reagents are used in the buildup of the molecular structure through carbon−carbon and carbon−nitrogen bond formation, and their use is essentially ubiquitous, given the current methodology available to the synthetic chemist. This suggests that any synthetic drug therefore possesses a latent GI-related risk. Yet this is a very simplistic assessment that fails to take into account the inherently reactive nature of the agent of concern and its likely fate in the manufacturing process downstream of its point of introduction. It is a paradox that the very reactivity that renders the agent a concern from a safety perspective is the same property that will generally ensure its effective removal in the downstream process.

Since the advent of the EMEA Guideline (EMEA/CHMP/QWP/251344/2006) covering the control of GIs, regulatory authorities have demanded proof that any GI is controlled in line with limits expressed in the guideline and its Q&A supplement (EMEA/CHMP/SWP/431994/2007 Revision 2). Such proof has generally taken the form of extensive analytical data; chemical-based arguments alone have often proved to be unacceptable despite, in many cases, the compelling nature of the assessment concerned. A significant amount of effort has therefore been expended in many cases 'to prove a negative'.

The challenge is therefore to develop an approach that allows the likelihood of potential carryover of a GI to be assessed before exhaustive analytical testing is performed. Pierson et al[1] sought to examine this on the basis of the number of manufacturing stages away from the final product the agent is introduced. Such an approach, although useful, is empirical and may only partially eliminate regulatory concerns. AstraZeneca presents a tool developed to bring a degree of quantitation into the PGI fate assessment. This is based on the principle of assessing key physicochemical properties of the agent of concern, relating them to the downstream processing conditions through the application of a standard system of scoring them to establish a 'purge factor'. This has been applied to a number of processes for which data was already available, and has exceeded our expectations in its robustness to date; a case study example is included below.

Methodology

The following key factors were defined in order to assess the potential carry-over of a GI: reactivity, solubility, volatility, ionisability, and any additional physical process designed to eliminate impurities such as chromatography. For clarification, the solubility term relates to the solubility of the GI in question in the solvent system used during the isolation (crystallisation) of the desired product. For each of these terms a score is assigned on the basis of the physicochemical properties of the GI relative to the process conditions. These are then simply multiplied together to determine a 'purge factor' for each stage of the process. The overall purge factor is a multiple of the factors for individual stages. The values assigned are illustrated in Table 1.

Table 1. **Physicochemical parameters and associated standard purge factors**

physicochemical parameters	purge factors
reactivity	highly reactive = 100 moderately reactive = 10 low reactivity/unreactive = 1
solubility[a]	freely soluble = 10 moderately soluble = 3 sparingly soluble = 1
volatility	boiling point >20 °C below that of the reaction/process solvent = 10 boiling point ±10 °C that of the reaction/process solvent = 3 boiling point >20 °C above that of the reaction/process solvent = 1
ionisability	ionisation potential of GI significantly different to that of the desired product[b]
physical processes - chromatography	chromatography - GI elutes prior to desired product = 100 chromatography - GI elutes after desired product = 10 others, evaluated on an individual basis

[a] This relates to solubility within the context of a recrystallisation process whereby the impurity in question, if highly soluble, will remain within mother liquors and hence be purged from the desired product. [b] This relates to a deliberate attempt to partition the desired product/GI between an aqueous and organic layer, typically achieved through the manipulation of pH to change the ionised/unionized state of one of the components.

Case Study

To illustrate the effectiveness of such an approach a case study is provided. This illustrates both the outcome of the predictive purge factor and the real measured values. The synthetic scheme for the process concerned is presented in Figure 1. The PGIs concerned are the AZD9056 aldehyde, AZD9056 chloride, and isopropyl chloride.

Theoretical Purge Factors

For each of the three identified potentially genotoxic impurities (PGIs) a theoretical purge factor was calculated. Details of the factors and their derivation are described in Table 2.

Measured Purge Factors

For each of the three impurities experimental purge factors were determined; these are recorded in Table 2.

In the case of AZD9056 aldehyde, this was achieved through tracking the residual level at successive stages. A comparison

(1) Pierson; et al. *Org. Process Res. Dev.* **2009**, *13* (2), 285–291.

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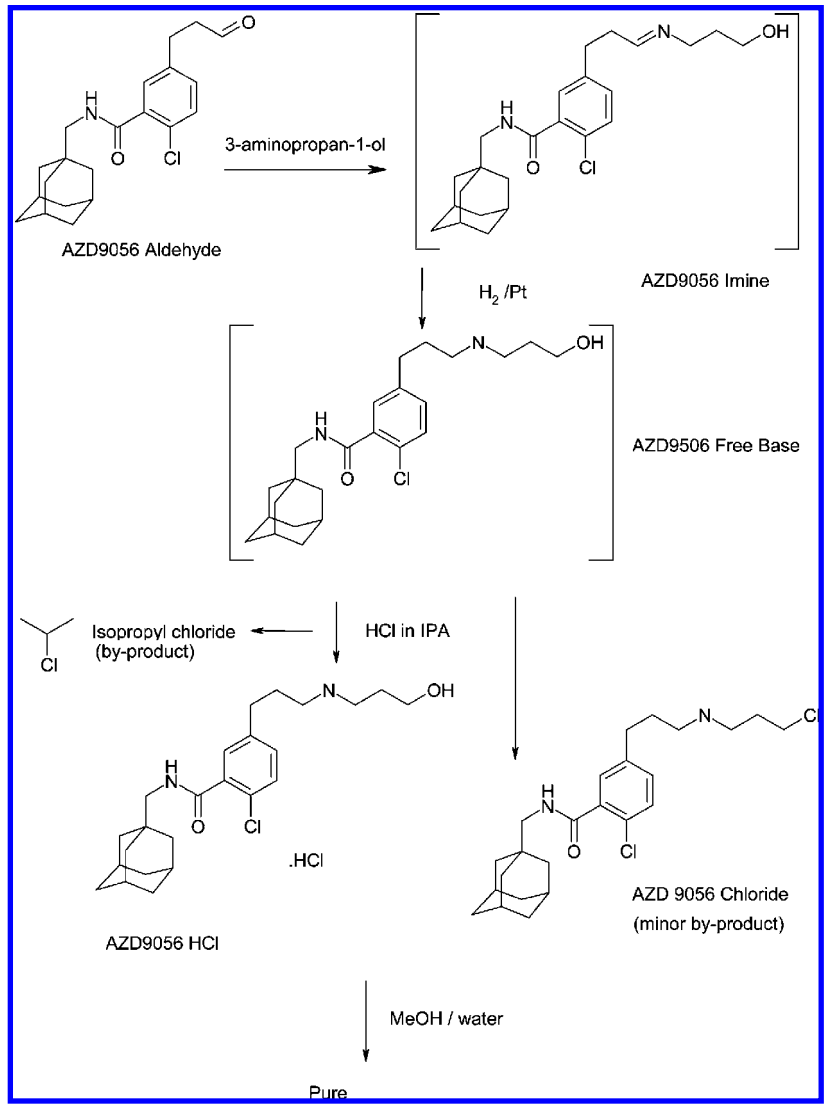

Figure 1. **Synthetic process for the manufacture of AZD9056.**

Table 2. **Calculated purge factors**

identity of potentially genotoxic impurity	stage	reactivity	solubility	volatility	calculated purge factor/stage	overall calculated purge factor	measured purge factor
AZD9056 aldehyde	crude (free base) - nonisolated	100	1[a]	1 - in-volatile	100		100
AZD9056 aldehyde	crude (isolated)	1 unreactive	10	1 - in-volatile	10		560
AZD9056 aldehyde	pure	1 unreactive	10	1 - in-volatile	10		2
AZD9056 aldehyde						**100 × 10 × 10 = 10000**	**112000**
AZD9056 chloride[b]	crude (free base) - nonisolated	N/A[c]	N/A	N/A	N/A		
AZD9056 chloride	crude (isolated)	1 unreactive	1	1 - in-volatile	1		5
AZD9056 chloride	pure	1 unreactive	3[d]	1 - in-volatile	3		2
AZD9056 chloride						**1 × 3 = 3**	**10**
isopropyl chloride	crude (free base) - non isolated	N/A	N/A	N/A	N/A		
isopropyl chloride	crude (isolated)	1	10	10	100		
isopropyl chloride	pure	1	10	10	100		
isopropyl chloride						**100 × 100 = 10000**	**38500**

[a] Although highly soluble, since the crude is not isolated, then the aldehyde is not purged. [b] chloride impurity is generated in the crude stage. [c] N/A - factor not applicable in the context of the process under evaluation. [d] Solubility, although low, is greater than that of AZD9056 HCl salt.

of the prediction with the experimental results shows that the calculated purge factor underpredicts the purge capacity of the process by an order of 10. It is interesting to note that in the case of the isolated crude stage, the predicted purge factor of 10 differs significantly from the observed purge factor of 560. Based on this comparison, it could be argued that the use of a scale of 1−10 in terms of the solubility factor should be extended to match that for reactivity (i.e., 1−100). However, it is our belief that the more conservative scale of 1−10 should be retained since this compensates for any variance in processes

such as uncontrolled crystallisation, poor washing and/or inefficient deliquoring of the isolated product. It also ensures that the scoring system tends to underpredict the likely purge capacity of a process, which is preferable to an overprediction. In summary, this clearly demonstrates that even a conservatively calculated purge factor predicts the risk of carryover of significant levels of AZD9056 aldehyde into the AZD9056 pure stage to be low.

With respect to AZD9056 chloride, this impurity is formed at very low levels within the crude isolation stage. The calculated purge factor of 3 (experimental purge factor = 10) accurately predicts that the process has limited capacity to effectively remove this impurity. Thus, in this instance, the results of the prediction would indicate the need to limit formation of the impurity through process control rather than relying on the ability of the process to eliminate it.

In the final example of isopropyl chloride, this impurity is present at relatively high levels (~5%) within the HCl/IPA reagent. However the calculated purge factor correctly predicts that this would be efficiently removed by the process as a consequence of its high volatility and high solubility.

Discussion

These results illustrate that the likelihood of carry-over of a GI can be predicted through a consideration of its physico-chemical properties and the associated process conditions. We believe that such a predictive tool is of value in determining which, if any, GIs are likely to be present in a drug substance and that this is a useful aid in defining the appropriate level of process control or analytical testing that is required to control them. The example of AZD9056 chloride also illustrates that in some circumstances there may be a need to consider a revision to the process to ensure adequate control of a GI, and that this may be rapidly determined using the tool described.

It is hoped that the tool and the case study presented will encourage readers to evaluate this tool to test its validity. We would welcome any feedback, with evaluation and experimental data where possible.

Note Added after ASAP Publication: This paper was published on the Web on Mar 24, 2010, with an error in Table 2. The corrected version was reposted on Mar 31, 2010.

Andrew Teasdale,* Simon Fenner, Andrew Ray, Agnes Ford, and Andrew Phillips

AstraZeneca, Bakewell Road, Loughborough, Leicestershire, England LE11 5RH

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**Author for correspondence. E-mail: andrew.teasdale@astrazeneca.com.*

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