Regulatory Toxicology and Pharmacology 84 (2017) 116–123

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

Management of organic impurities in small molecule medicinal products: Deriving safe limits for use in early development

James Harvey [a, *], Andrew Fleetwood [b], Ron Ogilvie [b], Andrew Teasdale [c], Phil Wilcox [a], Steven Spanhaak [d]

[a] GlaxoSmithKline R&D, Park Road, Ware, Hertfordshire, SG12 0DP, United Kingdom
[b] Pfizer, Ramsgate Road Sandwich, Kent, CT13 9N, United Kingdom
[c] AstraZeneca, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NX, United Kingdom
[d] Janssen R&D, Turnhoutseweg 30, 2340 Beerse, Belgium

ARTICLE INFO

Article history:
Received 17 October 2016
Received in revised form
21 December 2016
Accepted 22 December 2016
Available online 27 December 2016

Keywords:
ICH Q3A
ICH Q3B
ICH Q3C
ICH M7
Impurity safety
Non-mutagenic impurities
Impurity qualification
1 mg/day
TTC
Haber's law

ABSTRACT

Management of organic non-mutagenic impurities (NMIs) in medicinal products is regulated by the ICH Q3A, B and C guidelines that are applicable at late stages of clinical development (Phase III onwards) and as a consequence there is no guidance for the assessment and control of NMIs in early clinical trials. An analysis of several key *in vivo* toxicology databases supports the ICH Q3A defined concept that a lifetime dose to 1 mg/day of a NMI would not represent a safety concern to patients. In conjunction with routine (Q)SAR approaches, this 1 mg/day value could be used as a universal qualification threshold for a NMI during any stage of clinical development. This analysis also proposes that modification of this 1 mg/day dose using an established methodology (i.e. Modified Haber's Law) could support 5 mg/day or 0.7% (whichever is lower) as an acceptable limit for a NMI in a drug substance or product in early clinical studies (<6 months). Given the controlled nature of clinical development and the knowledge that most toxicities are dose and duration dependent, these proposed NMI limits provide assurance of patient safety throughout clinical development, without the requirement to commission dedicated *in vivo* toxicology impurity qualification studies.

1. Introduction

Management of organic impurities in small molecule medicinal products is regulated by a number of guidelines (ICH Q3A(R2), 2006; ICH Q3B(R2), 2006; ICH Q3C(R5), 2011; ICH M7, 2016). Prior to the introduction of ICH M7 in 2016 historically the ICH Q3 guidelines discussed the control of what were known as "genotoxic" and "non-genotoxic" impurities. More accurately the ICH Q3 guidelines now provide guidance on general limits for non-mutagenic impurities (NMIs) that are applicable to new drugs at late stages of clinical development (i.e. Phase III see ICH M3) and marketed drug products. Whereas the ICH M7 guideline provides guidance on general limits for mutagenic impurities (MIs) that are applicable to new drugs at all clinical stages of development.

Arriving at a specification suitable for late clinical phase and commercial product is an iterative process in which analytical methods will be developed and validated, a synthetic route suitable for commercial process will be developed, proposed commercial specifications will be set and manufacture will take place at increasing scale. For the earlier phases of development, not all of this process will have occurred, and it is routine and frequently necessary practice to apply a differing set of specifications for earlier phase clinical trial materials. ICH Q3 A/B are stated not to be generally applicable for NMIs in early phase clinical materials. This paper reviews the principles that support the impurity qualification thresholds described within ICH Q3A and suggests how modifications of these thresholds could be used to support impurity qualification in early phase clinical trials. This paper was initiated as a result of an European Federation of Pharmaceutical Industries and Associations (EFPIA) workshop organized in Brussels, May 2012, however, the views stated in this paper do not necessarily represent an EFPIA or company position but are the personal views of the

* Corresponding author. David Jack Centre for R&D, Park Road, Ware, Hertfordshire, SG12 0DP, United Kingdom.
E-mail address: James.S.Harvey@GSK.com (J. Harvey).

http://dx.doi.org/10.1016/j.yrtph.2016.12.011
0273-2300/

authors.

Given the controlled nature of clinical development, and the knowledge that most toxicities are dose and duration dependent, it is proposed (in alignment with the less than lifetime threshold of toxicological concern in ICH M7) that in most circumstances NMI limits in drug substance or drug product can be higher in early stages of clinical development compared to the limits expected for late stage development outlined in ICH Q3A/B. This document supports the concept defined in ICH Q3A that a lifetime dose of 1 mg/day to a NMI would not represent a safety concern. This suggests that the control of such an impurity to <1 mg/day (as opposed to the % qualification limits outlined in ICH Q3A/B) is unlikely to represent a safety issue during any stage of clinical development. Acceptance of this lifetime 1 mg/day limit for a NMI, allows the examination of whether this value can be modified using established methodology (i.e. Modified Haber's Law) to derive an acceptable limit for a NMI in Active Pharmaceutical Ingredient (API) of 5 mg/day or 0.7% (whichever is lower) for early clinical studies (<6 months). The latter % limit allowing for an increased margin of safety for impurities in potent low dose drugs that may exhibit similar pharmacology to the parent, as well being aligned with expectations around quality. Different considerations apply to drug product, and these are discussed in the document to derive acceptable limits of 5 mg/day or 2% (whichever is lower). Acceptance and adoption of such approaches for both drug substance and product may negate the requirement to commission dedicated *in vivo* toxicology impurity qualification studies described in ICH Q3 A/B in early stages of drug development without compromising patient safety. From an industry point of view this would be a beneficial development in support of the 3Rs principles (reduction, refinement, replacement of animal use).

2. Rationale

2.1. ICH Q3A/B guidance - impurity identification

NMI characterization can take many forms, ranging from an identified relative retention time within a specific chromatographic method to full structural elucidation using techniques such as MS and NMR to definitively identify the exact nature of the impurity in question. The current ICH M3 (R2) guidance expects that structures of impurities that exceed the ICH Q3 A/B identification thresholds should be fully elucidated by Phase III. In the earlier phases of development a balance needs to be struck which ensures patient safety in conjunction with the requirements of ICH M7 and the need to meet the impurity controls necessitated by ICH ICH Q3A/B by the time that late phase development occurs. For example, administration of clinical material containing *unidentified* impurities is considered acceptable if the said impurities have been appropriately qualified in non-clinical toxicology studies (i.e. the lack of structural identification in itself is not considered to constitute an additional risk). With potential MIs being addressed by the thorough evaluation of synthetic API chemistry conducted as part of ICH M7, then standard non-clinical qualification of impurities (in routine toxicology studies on parent drug substance) should be considered robust enough to address non-mutagenic mediated mechanisms of toxicity irrespective of whether the impurity structures have been identified.

2.2. Identification of "unusually toxic" impurities requiring dedicated qualification

Interestingly the ICH Q3A/B guidance (applicable in late stages of development) does consider such a scenario stating that for impurities that are considered "unusually toxic" lower qualification thresholds may be required. It also states an applicant should consider whether there are any "known safety data for this impurity or its structural class preclude human exposure at the concentration present". Establishing whether there is any "known safety data for an impurity" is imperative and is readily achievable using the diverse array of publically available on line toxicology databases that are searchable by chemical name, CAS number or chemical structure (for an extensive list see OECD eChemPortal). However, given that the ICH Q3A/B guidelines do not provide a definition of what constitutes an "unusually toxic" chemical structure, the interpretation of this statement (and any follow on actions) can vary widely depending on the experience of the toxicologists or chemists involved in the assessments.

It is recognised that there are certain rare (with respect to drug substance chemistry) chemical classes that are associated with specific toxicities. These chemical classes are readily identifiable and would require further consideration from an impurity control perspective in line with the ICH Q3A/B statement regarding "safety data" for a "structural class". Examples include (1) polyhalogenated dibenzodioxins, dibenzofurans, or biphenyls that are considered to be extremely potent non-mutagenic carcinogens that have a specific regulatory framework regarding acceptable exposure levels (Van den Berg et al., 2006) (2) organophosphates or carbamates with the potential to inhibit acetyl cholinesterase and induce adverse central nervous system effects that have been studied in detail and assigned a class specific threshold of concern (Kroes et al., 2004) and (3) beta-lactams with the potential to bind to proteins and induce anaphylaxis, a class that to date does not have a generic class specific threshold of concern.

In addition, there are examples of exceptionally rare (but nevertheless precedented in drug substance chemistry) chemotypes that would also require further consideration from an impurity control perspective. These chemotypes are readily identified using conventional *in silico* knowledge based approaches (e.g. Derek Nexus). They include structures such as (1) tetrahydropyridines with the potential to reduce dopamine resulting in adverse neurological events (e.g. 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine) and (2) fluoroacetyl compounds that are potent metabolic poisons associated with high acute toxicity, such chemotypes would generally be considered to be "unusually toxic".

In addition to a structural evaluation for the presence of these rare compound classes, there are numerous *in silico* (Q)SAR tools available that allow for the screening of structures for a number of other toxicological endpoints. However the variation in the maturity and robustness of these *in silico* tools with respect to the prediction of known toxicological endpoints makes their routine application for the assessment of impurities problematic. One area where both industry and regulatory authorities have reached a consensus is the use of *in silico* (Q)SAR approaches to predict whether a chemical structure is a potential genotoxic carcinogen (via a mutagenic mechanism of action). The robustness of the various prediction methods (i.e. expert rule-based and statistical (Q)SAR approaches) are well established and underpin the *in silico* screening strategy outlined in the ICH M7 impurity guidance. This ability to predict DNA reactivity (i.e. mutagenicity) via *in silico* approaches is largely due to (1) a strong mechanistic understanding of specific functional groups and their mutagenic potential (Ashby and Tennant, 1991) and (2) the large publically available experimental datasets that were used as the basis for the development of the *in silico* systems (Benigni et al., 2008).

In contrast, the majority of the *in silico* (Q)SAR approaches relating to the prediction of whether a chemical structure has the potential to induce organ level toxicity, reproductive toxicity or non-genotoxic carcinogenicity are less robust. The limitations of such *in silico* approaches reflects the complexity of modeling