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Safety Based Limits for the Control of Impurities in Drug Substances and Drug Products: A Review

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Abstract

Safety based impurity limits are key to the effective reduction and control of impurities in medicinal products. Impurity limits now have a greater focus on daily exposure limits, with the introduction of various approaches, such as permitted daily exposure (PDEs), acceptable intake (AIs), threshold of toxicological control (TTCs) and staged TTCs all aimed at defining a virtually safe dose (VSD). This in turn led to the introduction of less than lifetime (LTL) limits for mutagenic impurities, which is based on an application of Haber's law which states that concentration and exposure times are both critical for assessing likely safety risk to patients. Surprisingly, LTLs have not been applied to the other specific classes of impurities or indeed general impurities.

A recent publication has suggested that a LTL limit for general impurities of 5 mg or 0.7% (whichever is lower), for clinical studies with durations of less than 6 months is warranted. ICH S9 indicated that there was no additional impact on patient safety for impurities where the parent drug substance is extremely toxic and impurity levels (even mutagenic impurities) for oncology products could be controlled at higher levels. However, there has been little regulatory appetite for broadening this entirely pragmatic approach to other therapeutic areas, where life expectancy is equally short, i.e. rare diseases.

Keywords: Haber's law; Duration of dosing; Safety-based limits; Acceptable daily intakes; Acceptable intakes; Permitted daily exposure; Virtually safe dose; Less than lifetime limits

Introduction

Paracelsus, the medieval physician, who is often viewed as the father of modern toxicology, was the first person to appreciate that "the dose makes the poison". This essentially means that very toxic materials can be used therapeutically at very low concentrations and conversely even safe materials can be toxic if overdosed. This in turn led to Haber's law, which basically states that, the incidence and/or severity of any toxic effect is dependent on the total exposure to the toxic agent; that is, the exposure concentration (c) (or dose) multiplied by the duration time (t) of exposure (i.e. c×t). This law is often utilised in setting exposure limits for toxic components. The major caveat, is that establishing acceptable daily intakes (ADIs) for long-term exposures to a toxic substance when only data from short-term studies are available, does require the use of an uncertainty or safety factor.

For example, cancer risk estimates are typically based on the average lifetime daily dose (LDD), which in turn is derived from the total cumulative exposure, using Haber's law, i.e. c×t. Gaylor [1] proposed a modified Haber's law to better extrapolate safe levels based on shorter term exposure intervals and this takes the form of:

$$c^3 \times t = c'^3 \times t'$$

where c and t are the known safe exposure levels(c) based on the longer exposure duration (t) and c' and t' are the projected safe concentration (c') based on the pre-defined shorter exposure duration (t'). Haber's law is equally germane to impurities as it is to medicinal products.

Impurities in New Drug Substances and New Drug Products (ICH Q3a/ ICH Q3b)

One of the first international guidance that used safety based limits for impurities was the international conference on harmonization (ICH) Q3A [2]. This provided an overview of the typical impurities that were found in new drug substances and their controls. Impurities were evaluated based on both chemistry considerations, including "classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical

procedures"; and safety considerations, including "specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies".

Impurities were further delineated into identified and unidentified classes, both of which were included as specification tests [3]. This includes unidentified impurities that were known to be present at levels greater than pre-defined reporting, identification and qualification threshold (Table 1). Those unidentified impurities are often defined on the drug substance specification "by an appropriate qualitative analytical descriptive label (e.g., "unidentified A", "unidentified with relative retention of 0.9")".

Table 1: Reporting, Identification, and Qualification Thresholds for Impurities in New Drug Substances [2].

Maximum Daily Dose[1]	Reporting Threshold[2,3,4]	Identification Threshold[4,5]	Qualification Threshold[4,6]
≤2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0mg per day intake (whichever is lower)
>2g/day	0.03%	0.05%	0.05%

1. The amount of drug substance administered per day;

2. Reporting Threshold: A limit above (>) which an impurity should be reported. Reporting threshold is the same as reporting level in Q2B [4];

3. Higher reporting thresholds should be scientifically justified;

4. Lower thresholds can be appropriate if the impurity is unusually toxic;

5 Identification Thresholds: A limit above (>) which an impurity should be identified;

6 Qualification Thresholds: A limit above (>) which an impurity should be qualified

The reporting threshold was linked to the capability of the supporting analytical methodology [4]. Identification threshold was the limit where the unknown impurity was required to be identified by appropriate analytical methodology. Whereas, the qualification threshold necessitated acquiring and evaluating pre-clinical safety data that "establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified".

Interestingly, although the derivation of the reporting threshold was linked to method capability, the derivation of the identification and qualification threshold limits were never fully delineated, apart from linkage with the maximum daily dose of the product. In addition, for those impurities "known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled". Again, the implicit meaning of this statement was never fully articulated, but it was the genesis for the subsequent guidance on mutagenic impurities, initially termed genotoxic impurities [5].

Similar guidance was provided for impurities typically found in new drug products. These impurities are usually termed degradation products [6]. There was greater delineation of the thresholds in terms of dose (Table 2). However, it was never fully explained why the various thresholds, in terms of maximum daily dose, could not be aligned. Thus there is the confusing scenario that the reporting thresholds are above or below 1g; whereas, the identification thresholds are divided into four (>2g, >10mg-2g, 1mg-10mg and <1mg); whilst the qualification thresholds were also divided into four, but were not aligned with the classes defined in the identification thresholds (>2g, >100mg-2g, 10mg-100mg and <10mg).

Table 2: Reporting, Identification, and Qualification Thresholds for Impurities in New Drug Products [6].

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
>2g/day	0.10%	0.10%	0.15%
>100mg-2g	0.1/0.05%	0.2% or 2mg TDI, whichever is lower	0.2% or 3mg TDI, whichever is lower
10mg-100mg	0.05%	0.2% or 2mg TDI, whichever is lower	0.5% or 200µg TDI, whichever is lower
1mg-10mg	0.05%	0.5% or 20µg TDI, whichever is lower	1.0% or 50µg TDI, whichever is lower
<1mg	0.05%	1.0% or 5µg TDI, whichever is lower	1.0% or 50µg TDI, whichever is lower

1 The amount of drug substance administered per day;

2 Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic;

3 Higher thresholds should be scientifically justified.

The other confusing aspect was that the maximum daily dose (mg/day) and the maximum strength of a product (mg) are often not the same value. Thus for instance, the anti-malarial drug quinine sulfate [7] has a maximum therapeutic dose from the product label of 648mg every 8hours, i.e. 1944mg/day; whereas, the highest dose strength are 324mg/capsule. The analysts testing and releasing quinine sulfate capsules will do so on the commercial product (324mg/capsule), not the maximum

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dose taken by the patient (1944mg/day). In addition, although reporting thresholds are always measured as percentage values and are easily aligned with the data output from the method used by the analyst; identification and qualification thresholds are measured in either percentage values or mg/day values (Table 3).

Table 3: Safety Based Classification of Residual Solvents [11].

Solvent Classification	Comments
1	Benzene, carbon tetrachloride, 1,2 dichloroethane, 1,1-dichloromethane Solvents to be avoided. Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
2	Solvents to be limited. Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.
3	Solvents with low toxic potential in man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day (corresponding to 5000ppm or 0.5%).

The other aspect of having safety based limits for impurities is that it does not reflect the duration of treatment use for that drug and results in the same limits being proposed irrespective of whether the drug is proscribed *pro ne rata* (PRN) or as required, e.g. for constipation, mild pain, etc., or through life time treatments, e.g. for treatment of high blood pressure, etc.

ICH Q3A [2] and Q3B [6] were always intended to be only applicable to marketed products, but the regulatory expectations during clinical development often exceed what is actually required. For example, it isn't unusual to see the following expectations [8]:

"For phase I expect structure (or identifier) and origin. For phase II expect Limit of Detection and Quantification and actual impurity levels to be established (aligned with ICH Q3A, Q3B, etc)".

However, by phase II the final synthetic route and process of the drug substance are rarely identified or optimised, and the attrition rate of phase II drugs is still very high [9]. What the regulatory guidance enshrined in ICH M3 [10], actually states with respect to impurities is, "If specific studies are warranted to qualify an impurity or degradant, generally these studies are not warranted before phase 3 unless there are changes that result in a significant new impurity profile (e.g., a new synthetic pathway, a new degradant formed by interactions between the components of the formulation). In these latter cases, appropriate qualification studies can be warranted to support phase 2 or later stages of development".

Residual Solvent Impurities (ICH Q3C)

Although residual solvents are mentioned in ICH Q3A [2], a separate guideline, ICH Q3C [11], was developed to provide safety based guidance on the allowable limits of common residual solvents within pharmaceuticals. As there are "no therapeutic benefits from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality based requirements". Additionally, ICH Q3C recommends the use of less toxic solvents. Thus, solvents that are known to be highly toxic (Class 1) should be avoided during the production of drug substances, excipients, and especially drug products, unless their usage can be justified using a risk-benefit assessment [12]. In addition, some solvents with intermediate toxicity (Class 2) should also be limited from a patient safety perspective. Ideally, the least toxic solvents (Class 3) should always be used where practical. Recommended limits for all solvents may change as additional safety data become available. In addition, supporting safety data for new solvents may be added to the guidance.

Although tolerable daily intake (TDI) and acceptable daily intake (ADI) were both in common usage, ICH Q3C (11) introduced a new term, permitted daily exposure (PDE) to avoid confusion of differing values for ADI's for the same substance. In addition to avoidance of class 1 solvents, the concept of "as low as reasonably practicable" (ALARP) was introduced and is applied to class 2 solvents and often to class 3 solvents. Indeed, regulatory agencies will often use process capability arguments to drive down residual solvent levels below the safety based limits [13] derived from ICH Q3C.

Residual Elemental Impurities (ICH Q3D)

Residual elemental impurities were also mentioned in ICH Q3A [2], but again a separate guideline, ICH Q3D (14) was developed to provide safety based guidance on the allowable limits of residual elements within pharmaceuticals. As elemental impurities provide no therapeutic benefit to the patient, "their levels in the drug product should be controlled within acceptable limits" [14].

The ICH Q3D guideline is sub-divided into three parts: the derivation and assessment of toxicity data; the establishment of a PDE for each elemental impurity derived for three different routes of administration (oral, inhaled and parenteral); and application of a risk based approach to control elemental impurities (as per ICH Q9 (12)). One difference from ICH Q3C [11] is that applicants are not expected to tighten the safety based limits based on process capability considerations, as long as the residual elemental impurities do not exceed the PDE values. However, in certain cases, levels below the PDE may be warranted when lower levels have been shown to positively impact on other critical quality attributes (CQAs) of the drug product; for example, element catalyzed drug degradation (this is particularly common with oxidative degradation mechanisms [15]). In addition, for those elements with higher PDEs, lower limits may have to be assessed from a pharmaceutical quality

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perspective. Residual elements are classified into 5 different categories: class 1, 2a, 2b, 3 and others (Table 4).

Table 4: Safety Based Classification of Residual Elemental Impurities [14].

Elemental Classification	Comments
1	The class 1 elements are As, Cd, Hg, and Pb. They are extremely toxic and they have limited or no use in the pharmaceutical production. Their presence in drug products typically arises from commonly used excipients that are mined, e.g. talc. These four elements require extensive evaluation during the risk assessment process. The risk assessment will determine which components require additional controls, including in some cases testing for class 1 element. However, testing should only be initiated based on risk assessments; i.e. it is not a routine requirement.
2a	The class 2A elements are Co, Ni and V. Class 2A elements have relatively high probability of occurrence in the drug product and they require extensive evaluation during the risk assessment process.
2b	The class 2B elements include Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl. Class 2B elements show a reduced likelihood of occurrence within the drug product because of their low abundance and low potential to be co-isolated with other materials, e.g. in mined excipients. Consequently, they may be excluded from the risk assessment process unless they are intentionally added (i.e. as catalysts) during the manufacture of drug substances, excipients or other components of the drug product.
3	The class 3 elements include Ba, Cr, Cu, Li, Mo, Sb, and Sn. Class 3 elements have relatively low toxicities orally (high PDEs, generally >500 µg/day), but they should be assessed in the risk assessment for inhalation and parenteral routes, unless the route specific PDE is >500 µg/day.
Others	Some of the other elements considered include Al, B, Ca, Fe, K, Mg, Mn, Na, W and Zn. These elemental impurities have low inherent toxicity and PDEs have not been derived. If other elemental impurities are present in the drug product and they are covered by other guidelines and/or regional regulations and practices they should be assessed as part of the risk assessment. A non-comprehensive list includes Al for compromised renal function; Mn and Zn for patients with compromised hepatic function, or quality considerations, for example the presence of W impurities in therapeutic proteins.

ICH Q3D [14] provides a platform for developing an ICH Q9 (12) aligned risk-based control strategy to limit elemental impurities within the drug product. Although, the guidance had highlighted the risk inherent from both drug substance and excipients, the reality based on a multi-product assessment is that the risk is low. Li et al. [16] tested 190 samples from 31 different excipients and 15 samples from eight different drug substances for residual elemental impurities. The results show relatively low levels of elemental impurities are present in the samples tested.

Residual mutagenic impurities (ICH M7)

ICH M7 [5] is focused on DNA reactive impurities that can potentially cause DNA damage, when present at low levels, and thus can potentially cause cancer in man. Importantly, other types of toxic impurities that are non-mutagenic will typically have a threshold mechanism and as such usually do not pose carcinogenic risk in man, at the levels typically seen for impurities.

A Threshold of Toxicological Concern (TTC) approach was introduced to describe an "acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects", this equates to a virtually safe dose (VSD). The methodologies that underpin the TTC are universally considered to be very conservative, as they use a simple linear extrapolation from the TD_{50} dose (i.e. dose giving a 50% tumor incidence) to a 1 in 10^6 likelihood of cancer occurrence.

A default TTC value of 1.5µg/day corresponding to a theoretical 10^{-5} excess lifetime risk of cancer can therefore be justified for mutagenic impurities. Some high potency groups referred to as the "cohort of concern", e.g. aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds; were identified where the default TTC would still pose a significant carcinogenic risk. These high potency compounds were excluded from the TTC approach.

ICH M7 [5] bases acceptable intakes for mutagenic impurities on established risk assessment approaches (see ICH Q9 [12]). As such, acceptable risk during the early development phase is established at a higher theoretically calculated risk level of approximately one additional cancer incidence per million, i.e. 1 in 10^6 risk levels. For later stages in development (Phase III) and for commercial products, the risk level is reduced to one in one hundred thousand, i.e. 1 in 10^5 risk levels. It is worth highlighting, that these risk levels represent a small theoretical increase in risk when compared to the overall lifetime incidence of developing cancer in man, which is greater than 1 in 3.

The initial risk assessment is undertaken on the drug substance synthetic pathway to identify real or potential impurities that may be reactive and thereby mutagenic in nature. In parallel, the formulation and manufacturing process are also assessed for the formation of any reactive degradants (both real and potential), that could be realistically expected to form during long term, real-time storage conditions. In silico structure-based assessments, i.e. Derek Nexus, Sarah Nexus, etc., are used for predicting mutagenicity based upon QSAR (quantitative structure activity relationships) approaches. These findings are then reviewed by toxicology experts to provide any additional understanding as to the relevance of these predictions (both positive and negative), and in the case of contradictory outcomes

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to understand those differences. Based on this assessment, impurities are categorised into five different classes in order of decreasing regulatory concern (Table 5).

Table 5: Different Classes of Potential or Real Mutagenic Impurities Based on Mutagenic and Carcinogenic Potential and Proposed Control Strategies [5].

Impurity Class	Commentary	Control Strategy
1	Known mutagenic carcinogens	Control at or below compound specific acceptable limit, i.e. AIs or PDEs[1]
2	Known mutagens with unknown carcinogenic potential	Control at or below acceptable limits, i.e. LTL[2] or TTC[3]
3	Show alerting structures (un-related to drug substance) with no supporting mutagenicity data	Control at or below acceptable limits, i.e. LTL[2] or TTC[3] Or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Show alerting structures (related to drug substance which is itself non-mutagenic)	Treat as non-mutagenic impurity, i.e. use default ICH Q3A/Q3B limits
5	Show no alerting structures	Treat as non-mutagenic impurity, i.e. use default ICH Q3A/Q3B limits

1. For class 1 compounds, i.e. those which are known mutagenic carcinogens, an AI (acceptable intake) or a PDE (permitted daily exposure) approach has been introduced (ICH M7(R1) (17). These limits are based on either (i) linear extrapolations from TD50 (AI) or (ii) threshold-based PDEs. There are 10 compounds covered by the AI approach and a further 3 covered by the PDE approach.

2. LTL (less than lifetime limits)

3. TTC (Threshold of Toxicological Concern)

It is anticipated that monitoring and control strategies (including analytical methods) will be less developed during earlier clinical phases, where overall development experience is of necessity limited, compared to later clinical phases and commercial manufacture. ICH M7 [5] propose a control strategy using four control options for mutagenic impurities, of these only one includes control of the mutagenic impurity on the API specification (option 1). Options 2 and 3 define some levels of in-process control; whereas, option 4 is centred on process understanding alone, typically termed "Purge Arguments" [18].

It is should be emphasised that these established cancer risk assessments are based on lifetime exposures, i.e. 75 years. Thus, Less-Than-Lifetime (LTL) exposure based limits can be derived both during development and commercial use. LTLs can have higher acceptable intakes of mutagenic impurities and still maintain comparable risk levels, which is obviously an application of Haber's law. Therefore, the carcinogenic effect is predicated on both duration of exposure and dose. Thus for example, "if the compound specific acceptable intake is 15 µg/day for lifetime exposure, the less than lifetime limits (Table 6) can be increased to a daily intake of 100 µg (>1-10 years treatment duration), 200 µg (>1-12 months) or 1200µg (<1month)" [5]. This LTL approach may also be appropriate "in diseases with reduced life expectancy, limited therapeutic alternatives or chronic diseases with late onset" [19].

Table 6: TTC and LTL Safety Based Limits for Mutagenic Impurities [5].

Mutagenic Impurities	Limits (based on LTL)	<1 month	>1-12 month	>1-10 years	>10 years to lifetime
Individual	Daily intake (µg/day)	120	20	10	1.5
Multiple	Daily intake (µg/day)	120	60	30	5

It is worth emphasising that exceeding the default TTC or LTL limits is not necessarily linked with an increased cancer risk in man, given the extremely conservative suppositions employed in the evolution and derivation of the TTC or LTL values. For instance, higher exposure to a potential mutagenic impurity, e.g. formaldehyde, may be reasonable when exposure can be significantly greater from other sources, e.g. endogenous metabolism, food, etc. The most likely increase in cancer incidence is actually much less than 1 in 100,000. In addition, in cases where a mutagenic compound is a non-carcinogen in a rodent bioassay, there would be no predicted increase in cancer risk. Based on all the above considerations, any exposure to an impurity that is later identified as a mutagen is not necessarily associated with an increased cancer risk for patients already exposed to the impurity. A risk assessment would determine whether any further actions would be taken

In principle, ICH M7 does not apply to advanced cancer therapeutic indications (covered by ICH S9 (20)), where the drug is itself genotoxic. ICH M7 does not apply to established excipients, flavouring agents and certain biological products, including herbal medicines. Existing commercial products are also exempted, apart from where there are new safety data (including new mutagenic data) for existing impurities; significantly, structural alerts alone do not trigger regulatory concern. However, ICH M7 does cover changes to marketed products, including new marketing applications and post-approval submissions.

Impurities in oncology products (ICH S9)

ICH S9 [20] was developed to provide guidance for nonclinical studies for the development of anticancer pharmaceuticals used in clinical trials for the treatment of patients with advanced disease and limited therapeutic options. During the development of oncology products, supporting clinical studies often involve cancer patients whose prognosis is poor and projected lifetime is short (<2 years).

As such, the guideline objectives are to facilitate and accelerate the development of these anticancer pharmaceuticals

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whilst protecting patients from unnecessary adverse effects. In addition, ethical use of animals, in accordance with the 3R principles (reduce/refine/replace) are paramount. Importantly, the principles described in other ICH guidelines need to be considered in the development of oncology products; whereas, those specific situations where requirements for nonclinical testing may diverge from other guidance are described in ICH S9.

Additionally, the dose levels used in these clinical oncology studies are often at the top end of the tolerable range [21] and often result in adverse effect dose levels. Hence, "the type, timing and flexibility called for in the design of nonclinical studies of anticancer pharmaceuticals can differ" significantly from non-oncology pharmaceuticals. Historically, limits for impurities (see ICH Q3A [2] and Q3B [6]) have been based on a negligible risk to the patient. In oncology products this consideration, whilst important, is not as important as patient wellbeing and exceeding the ICH Q3A [2]/Q3B [6] limits for impurities may be applicable and an appropriate justification should be included in the marketing application.

This explanation should include an overview of the disease being treated, including patient prognosis, the nature of the drug itself (pharmacology, genotoxicity and carcinogenicity, etc.), the total duration of treatment, and the impact of any reduction in impurity levels on manufacturability. Furthermore, the qualification of these impurities may include reflections on the concentration tested in supporting nonclinical studies compared to the levels seen in clinical batches. In addition, TTC, LTL and AI/PDE limits for mutagenic impurities (see ICH M7 [5]) are inappropriate for oncology products and justifications can be used to set higher limits. Interestingly, the guidance does not specifically say that the applicant can default to ICH Q3A [2]/Q3B [6] limits, although this is often inferred. Impurities that are also metabolites can be considered to be suitably qualified.

Interestingly, regulators have been very unwilling to extend the philosophy of ICH S9 [20] beyond oncology products, for instance into rare diseases [22], where lifetime expectancy can be similarly short, i.e. <2 years and where patient expectations are equally high.

New Reflections on Impurities

Harvey et al. [23] used a variety of chemical databases to demonstrate that the 1mg/day impurity level for an unqualified impurity of unknown toxicity, proposed by ICH Q3A [2] (Table 1) is indeed a robust prediction of a virtually safe dose (VSD) for non-mutagenic impurities. Then using the modified Haber's law, where C=1 mg and t=75 years (i.e., 27375 days) and t' is 6 months or 182 days they determined a VSD for this shorter exposure interval of 5 mg/day (i.e. 5 times higher than existing ICH Q3A limit). However, for very potent drugs with effective doses of <1mg, a 5mg/day limit for a related impurity isn't realistic from either a safety or quality perspective. Therefore, the authors also introduced a percentage cut off based on 5x the ICH Q3A qualification threshold of 0.15%; i.e. 0.7%. Thus the proposed limits for drug substances are 5mg or 0.7%, whichever is lower.

This allows applicants to adopt the existing ICH Q3A guideline which were developed for commercial products and apply them to development products, in much the same way that the ICH M7 guidelines allows LTL limits for mutagenic impurities, for early clinical development. For drug products, similar LTL limits for non-mutagenic impurities can be derived based on a modification of Haber's law. The additional constraint of a percentage limit of 0.7% need not be applied to drug products as the more potent the drug substance becomes, the lower the dose required. The authors therefore suggested a limit of 5 mg or 2%, whichever is lower, for exposure intervals of <6 months, for general drug substance impurities, i.e. non-mutagenic.

In addition to absolute amounts of unknown impurities, the other key focus is those impurities with unusually high and/or specific toxicities. Whilst it is recognised that mutagenic impurities constitute the greatest threat to patient safety and they have been addressed via ICH M7; there are other classes of non-mutagenic impurities that will still give cause for concern. The three principal classes of toxic impurities are

(i) polyhalogenated, dibenzodioxins, dibenzofurans and biphenyls that are non-mutagenic carcinogens, which have specific regulatory framework with respect to acceptable exposure levels [24],

(ii) organophosphates or carbamates that are neurotoxins and have their own threshold of concern [25] and (iii) β- lactam like impurities that have the potential to cause anaphylaxis and which currently do not have any threshold of concern [23].

It is worth highlighting that

(a) These impurities are extremely rare and do not reflect the typical structure of impurities generated by medicinal research [26,27] and

(b) That these structural motifs (if present) would be highlighted and addressed as part of the ICH M7 risk assessment [5], as "the findings from any mutagenic risk assessment are also reviewed by toxicology experts".

Conclusion

Safety based impurity limits are a core consideration of all of the existing ICH Q3 guidance documents. However, there has been an evolution in the approach toward impurities since the publication of the initial guidance [2,6]. Whereas, ICH Q3A [2] and Q3B [6] provide general guidance on impurities in drug substances and drug products, respectively and mainly focus on absolute levels of impurities, i.e. percentage based limits; later guidance focused on individual impurity classes; i.e. residual solvents [11], residual elemental impurities [14] and mutagenic impurities [5] and had a greater focus on daily exposure limits. In

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the latter cases, this led to the introduction of various impurity specific limits, such as PDEs, AIs, TTCs and staged TTCs, all aimed at defining a virtually safe dose (VSD). This in turn led to the introduction of LTL limits for mutagenic impurities.

LTLs are based on an application of Haber's law which states that concentration and exposure times are both critical for assessing likely safety risk to patients. Surprisingly, LTLs have not been applied to the other specific classes of impurities or indeed general impurities. In order to address this deficiency, Harvey et al. [23] have assessed the underpinning data behind the current "1mg or 1%, whichever is lower" limit in ICH Q3A [2]/Q3B [6], and they found this to be based on robust science and they proposed an ancillary LTL for general impurities of 5 mg or 0.7%, whichever is lower, for clinical studies with durations of less than 6 months.

Logically, the toxicity of the parent drug substance also affects how we deal with impurities, even very toxic impurities. Thus, there is limited, if any, additional impact on patient safety for impurities where the parent drug substance is mutagenic, carcinogenic or cytotoxic. Accordingly it was recognised that for oncology products, impurity levels (even mutagenic impurities) could be controlled at higher levels. This "higher level" wasn't defined but is based on an overview of the disease being treated, including patient prognosis, and the nature of the drug itself. Additionally, from a risk based perspective and an understanding of Haber's law, an overt focus on impurity control makes little sense if the life expectancy of the affected patient is short, i.e. less than 2 years [20]. Interestingly, there has been little regulatory appetite for widening this entirely pragmatic approach to impurity control to other therapeutic areas, where life expectancy is equally short, i.e. rare diseases [22].

Conflict of Interest

The author is an individual CMC consultant and declares that there are no conflicts of interest.

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