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Impurities in drug substances and drug products: new approaches to quantification and qualification ☆

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Abstract

Regulatory requirements for the identification, qualification and control of impurities in drug substances and their formulated products are now being increasingly explicitly defined, particularly through the International Conference on Harmonisation. The implications of the recent guidelines are reviewed, both from their regulatory impact and the impact upon analytical technology. Impurities also have important safety consequences, and suggestions for possible routes to the qualification of impurities which do not involve the need to undertake additional studies are made.

Keywords: Impurities; Drug substance; Drug product; Qualification

1. Introduction

It is important to recognise that all drugs contain impurities. Impurites result from many sources, including from raw materials and reagents, as reaction by-products, and through degradation during manufacture and storage. However, impurities can have safety and efficacy implications and are therefore the subject of considerable attention by both the manufacturer (industry) and regulatory agencies. With some notable exceptions, such as Canada and Germany, very little has been explicitly published by regulatory agencies as guidance for impurity requirements when submitting a dossier for approval of a new chemical entity. Thus, this was an appropriate topic to be considered by the International Conference on Harmonisation (ICH), as well as seeking harmonisation of requirements for both drug substances and drug products. The published drug substance guideline and draft drug product guideline both consider requirements for quality and safety, and delineate requirements for identification, qualificatin and control of impurities. These requirements then define industry's goals for the purity criteria of their products. Meeting these criteria requires careful thought over the analytical technologies to be used in terms of their limits of detection and quantification, and in their selectivity, and requires that due thought be given to strategies and operational tactics for establishing the safety of the impurities

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at their specified levels: this establishment of safety is the process of qualification. In this paper, the focus will be on the quantification and qualification of organic impurities.

2. Definitions of impurities, scope and requirements of guidelines

2.1. Drug substances

The development of the current drug substance ICH guideline commenced immediately following the first ICH conference in 1991 [1] and was finally agreed by the regulatory authorities on 4th May 1995. Very early in the discussions it was clear that to reach agreement it would be necessary to limit the types of drug substances which would be included, and to clearly define what was meant by the term impurity. The guideline was therefore limited to new synthetic chemical entities which had not previously been registered. Impurities were separated into three classes, namely organic, inorganic and residual solvents. Again there were restrictions. Thus, contaminants clearly fall outside the scope of the guideline since they more correctly come under the scope of Good Manufacturing Practice, and, while isomers in general are included, enantiomers are excluded. This exclusion reflects that technological challenges still exist which make the control of enantiomers more difficult than that of typical organic impurities.

Organic impurities may arise from starting materials, intermediates and synthetic by-products, or from reagents or catalysts, or as a consequence of degradation. No distinctions are made. Methods for determination and qualification will be addressed in more detail shortly. Inorganic impurities may result from reagents, ligands or catalysts, as heavy metals or inorganic salts, and from filter aids or chromatography supports. Methods for their control and appropriate limits are generally set by pharmacopoeial precedent and will not be discussed in detail. Residual solvents are inevitable in drug substances since without solvents, the synthetic chemistry, purification, and generation of the desired crystal morphology would be impossible. However, since residual solvents also arise in excipients, and occasionally in the manufacture of drug products, it was decided to draft a separate guideline to address appropriate levels. Drafting of this guideline is at a very early stage, and the requirements will not be discussed further.

Important highlights of the drug substance guideline include; "... identification of all recurring impurities at or above 0.1% is expected in batches manufactured by the proposed commercial process"; "degradation products observed in stability studies at recommended storage conditions should be similarly identified"; and, in recognition of the analytical challenges, "for the purposes of these guidelines, such values [0.05–0.09%] would not be rounded to 0.1% and these impurities would not require identification". A key component of the guideline, and a fundamental concept, is *qualification*. Qualification is defined as "the process of acquiring and evaluating data which establish the biological safety of the individual impurity or a given impurity profile at the level(s) specified". Thus, the pharmaceutical analyst and toxicologist must work hand in hand throughout the pre-clinical and clinical development programme in order to be able to set meaningful specification requirements.

A two tier strategy is agreed for identification and qualification. For drugs administered at up to 2 g per day, the threshold levels are 0.1% w/w or 1 mg per day, whichever is lower. Above 2 g per day, the threshold is 0.05% w/w.

2.2. Drug products

Impurities in drug products arise through the ingoing ingredients, and through interactions of the drug substance with excipients and packaging materials, and through degradation. While the drug product guideline is still to be finalised, there is agreement that impurity levels in the ingoing ingredients do not need to be controlled again since they are already the subject of earlier controls. What does need to be controlled is the degradation of the active ingredient, and for the purposes of the guideline, degradation includes the products of interactions of the drug substance

with excipients and with primary packaging materials. Degradation of the excipients themselves is not included. Once again, the scope also focuses upon new chemical entities of synthetic origin, not previously registered.

Identification and qualification levels for drug products still have to be decided. It is recognised that there are significantly greater challenges dealing with drug products. For example, the threshold should be higher because of the interferences that can arise from excipients (Fig. 1). Additionally, the threshold needs to recognise that there can be significant practical challenges in carrying out safety studies, which have real meaning, for low levels of degradation. Finally, the threshold should be higher than that required for the ingoing drug substance in order that the focus is limited to degradation products, since impurities that may have been just below the 0.1% level in the drug substance may be wrongly estimated to be above that level, owing to the greater variance that will inevitably arise in drug product analyses at low levels.

3. Analytical challenges to current methods and potential new methods

While the threshold for identification and qualification of organic impurities is set at 0.1% for the majority of compounds, it is important to recognise that the implication is that a limit of

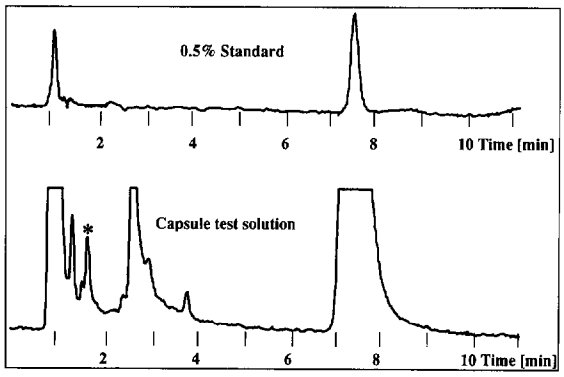

Fig. 1. Chromatograms of a 0.5% standard and an extract of a capsule containing 0.125 mg of a drug substance. The peak marked * is a degradation product.

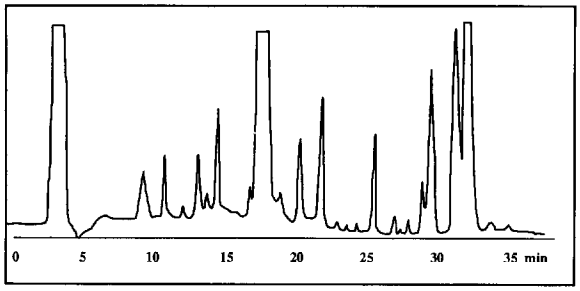

Fig. 2. Gradient HPLC of drug substance plus impurities following pre-column derivatisation with fluorescamine: 12.5 × 0.4 cm containing Asahipak ODP-50 gradient eluted with borate/TBAH buffer (pH 10): methanol (50:50) to methanol/THF (1.5:2) over 25 min. Fluorescence detection with excitation at 280 nm and emission at 475 nm.

quantification (LOQ) of approximately 0.05% will be required: this is described in the drug substance guideline. For a compound that is 98% pure, the 2% of impurities could be composed of between 10 and 20 components at a level of scrutiny of 0.05%. If we want to be sure that each component is present as a single peak only, then we are already at the bounds of peak capacity for conventional isocratic separations [2–4]. In future, it may become essential to increase selectivity through the use of gradient separations, both in HPLC and TLC, or through the use of alternative technologies. TLC is frequently included as an impurity measuring method in pharmacopoeias, although these separations are almost always isocratic. Modern planar chromatography does lend itself to gradient separations, particularly through use of automated multiple development. However, gradient HPLC is the more usual technique, and Fig. 2 shows a gradient HPLC separation of a drug substance plus its impurities where selectivity and detectability were both improved by pre-column derivatisation with fluorescamine (in order to convert mixed anions and cations to just anions which could then be ion-paired).

If single methods fail to provide the necessary selectivity, orthogonal coupling of chromatographic techniques such as HPLC-TLC [5] and HPLC-CE [6], or coupling of chromatographic separations with information rich spectroscopic methods such as HPLC-MS or HPLC-NMR may need to contemplated, but hopefully only as a

development tool rather than a tool for routine QC use. The future may see the significantly increased use of spectroscopic techniques for impurity measurement. NMR has shown values for stereoisomers [7] and for process related impurities [8], but still does not quite show the sensitivity required. Near-infrared spectroscopy is rapidly increasing in use and can detect impurities [9], although more understanding of the technique and demonstrations of true validation for low levels of impurities are required.

One single method that is showing great promise in pharmaceutical analysis is capillary electrophoresis (CE). With its much increased efficiency and great variety of separation modes it may provide sufficient peak capacity, and indeed CE is finding increasing favour for pharmaceutical analysis [10]. CE also adds speed to selectivity, and many of the concerns over the robustness and transferability of CE separations have been dispelled recently through a number of collaborative studies [11,12]. Additionally, while enantiomers are outside the scope of the current ICH guideline, there is no doubt that, when they are potential impurities, their level(s) must be controlled. CE-MECC can provide the necessary detectability to control enantiomers to the 0.1% level [13].

Whichever determination methods are chosen, there then remains the decision as to how to quantify and report. Fig. 3 shows a chromatogram of a drug substance containing its known synthetic impurities all at 0.5% w/w relative to the main component. It is immediately clear that the response to the UV detector is very variable, although this is not unusual. The ICH guideline allows one to quantify unknowns by reference to the response of the main component, although it is acknowledged that some impurities will be underestimated, and others overestimated. Where impurities have been characterised, response factors can then be used to correct for detection characteristics. In situations where responses are very variable, there is the complication of knowing just what components to report. Factors to bear in mind must be the variability of their production (is the impurity close to 0.1% such that at some time it might exceed the threshold?), and the knowledge of the chemistry. For example, it may be preferable to use a standard of a known impurity against which to measure unknowns rather than a dilute sample of the main component. The key thing will be to ensure that a consistent method of detection and quantification is used.

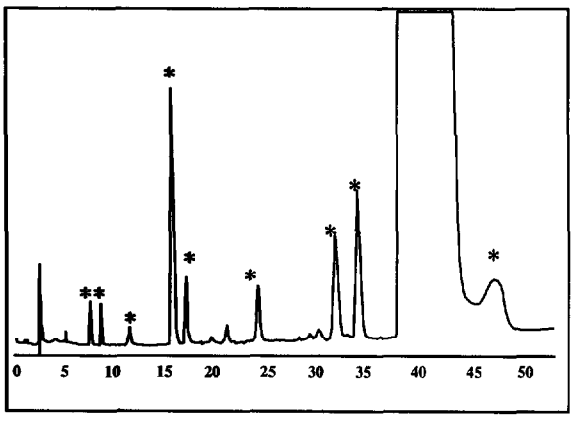

Fig. 3. Chromatogram of separation of drug substance plus impurities all at the 0.5% level.

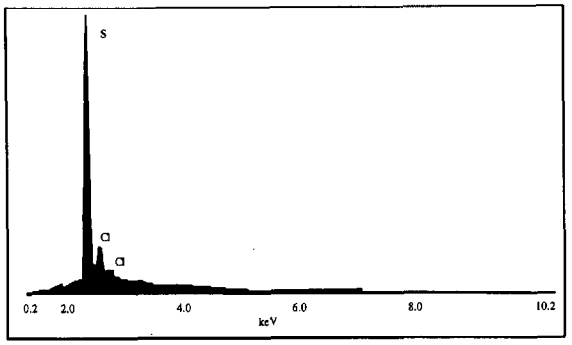

Fig. 4. Scanning electron microscope/energy dispersive X-ray of drug substance containing a hydrochloride salt form.

While inorganic impurities are generally controlled through pharmacopoeial methods, there are times when a greater level of information may be required about inorganic ions associated with drug substances. Atomic absorption and inductively coupled plasma methods are of great value here, as is the sometimes neglected use of a scanning electron microscope with energy dispersive X-ray capabillity. Fig. 4 shows an SEM/EDX of a drug substance, intended to be prepared as its fumarate salt. What was deduced from this information was that the drug substance under investi-

gation was indeed present (from the sulphur peak), but that it contained significant amounts of chloride. It was clear that this sample contained mixed salt forms, the fumarate and hydrochloride salts.

4. Qualification

Qualification is the process by which the safety of impurities at their specification level is underwritten. The normal process of qualification occurs during the pre-clinical studies carried out during development, including components of both genetic and general toxicology. If such studies are to be used to qualify impurities, then it is essential to provide materials with representative impurity profiles. Such profiles should include degradation products. Unfortunately, the provision of material containing both synthetic impurities and degradation products can be challenging, especially if the impurities themselves are likely to degrade. Fig. 5 shows chromatograms of a drug substance with its process related impurities. Unfortunately, attempts to induce the formation of degradation products through simple autoclaving of an aqueous solution resulted in the loss of some of the synthetic impurities.

Any impurity which is also a metabolite can be considered to be qualified. The qualification level

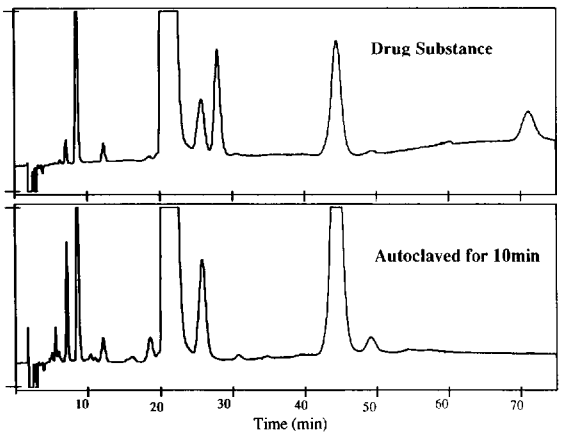

Fig. 5. Comparative chromatograms of a drug substance and an aqueous solution of the drug substance following autoclaving.

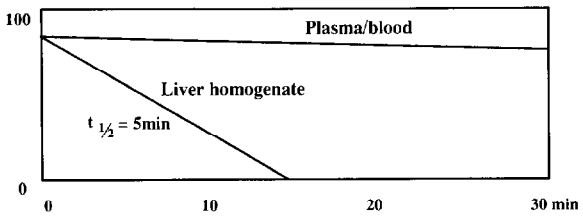

Fig. 6. Rates of hydrolysis of the ethyl ester of a carboxylic acid drug substance demonstrating rapid hydrolysis and little likelihood of sytemic exposure to the ester itself.

will need discussion, but a 1:1 correspondence with the proportion metabolised would not be unreasonable. Drug metabolism studies can therefore provide vital evidence for the qualification processes. There may be opportunities to use ex-vivo metabolism studies to aid qualification without the need to explore further safety studies. Fig. 6 shows the rate of hydrolysis of the ethyl ester of the parent drug. The ethyl ester, produced as a synthetic by-product, had not been included in formal safety studies. While conversion to the parent acid occurred only slowly in plasma or blood, rapid conversion occurred in liver homogenate, thereby demonstrating that there would be no systemic exposure to the ester and assisting in the discussion on impurity qualification.

There are many questions still to be answered. The drug substance guideline requires control of impurities suspected to be more toxic, at levels less than 0.1%. A reasonable level is not suggested. Another question relates to the qualification of enantiomers — deliberately excluded in the guideline. However, can an impurity detected by an achiral method at, for example, 0.15% be considered to be below the threshold for qualification if it can be shown to comprise two enantiomers, each at 0.075%?

5. Conclusions

The establishment of guidelines for impurity levels in drug substances and products now provides the quality criteria for manufacturers. The key aspect is that the impurity profile of a new chemical entity must be shown to be qualified.

With a qualification threshold of 0.1%, or lower for high dose compounds, the pharmaceutical analyst must give careful thought to the analytical technology. Especially in the development phases, it may be necessary to utilise methods with high selectivity, including hyphenated techniques. The importance of qualifying impurity profiles also relevant to the development scientists to ensure consideration is given to the impurities present in batches being used in safety studies, although there are opportunities to carry out metabolism studies to help in the qualification processes.

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