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Significance of Impurities in Drug Substance and Product and Role of Analytical Methods

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ABSTRACT

The current practice of characterization and control of impurities in pharmaceuticals is reviewed with emphasis on issues specific to the generic industry. This review includes an overview of FDA, ICH, TGA, TPD and EMEA guidelines related to impurities in Drug Substance and Drug Products. This introduces the identification, characterization and qualification procedures for ANDAs and approaches to the establishment of acceptance criteria for both drug substance and drug product and significance of analytical methods in total process.

Keywords: Acceptance Criteria, Analytical Methods, Characterization, Drug Products, Drug Substance, Impurities, Qualification

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INTRODUCTION

An impurity in a drug substance [1] is any component of the drug substance that is not the chemical entity defined as the drug substance. Similarly, an impurity in a drug product is any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product [2.] The safety of a drug product is dependent not only on the toxicological properties of the active drug substance itself, but also on the impurities that it contains. Therefore, identification, quantification, and control of impurities in the drug substance and drug product, are an important part of drug development and regulatory assessment. ICH Q3A and Q3B address issues relevant to the regulation of impurities in the drug substance and drug product. While many of the concepts and principles outlined in these documents are applicable to Abbreviated New Drug Applications (ANDAs), certain additional or modified restraints need to be considered. When FDA receives an ANDA, a monograph defining certain key attributes of the drug substance and drug product is frequently available in the United States Pharmacopeia (USP). Sometimes, literature information on drug product impurities may also be available. These public standards and literature data play a significant role in the regulatory assessment process of an ANDA.

This review is intended to provide a scientific perspective on drug substance and drug product impurities in ANDAs[3,4.] It provides recommendations for ANDAs on the identification and qualification of impurities for drug substances and drug products. It is also intended to assist in the establishment of impurity specifications for drug substances and drug products.

Listing of Impurities:

The specification for a drug product should include a list of degradation products. Stability studies, chemical development studies, and routine batch analyses can be used to predict the degradation profile for the commercial product. As with the case of the drug substance, the inclusion or exclusion of degradation products in the drug product specification should be rationalized. The rationale may include a discussion of potential degradation pathways, interactions with excipients, forced degradation studies, as well as the observed degradation profile of the batch (es) manufactured during development and by the proposed commercial process. Individual degradation products with specific acceptance criteria that are included in the specification for the drug product are referred to as “specified degradation products”. Specified degradation products can be identified or unidentified. Specified identified degradation products should be included in the list of degradation products along with specified unidentified

degradation products that are estimated to be present at a level greater than the identification threshold given in Table3. Where degradation products are known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation and/or detection limit of the analytical procedures should correspond to the level at which the degradation products are expected to be controlled. For unidentified degradation products to be listed in the drug product specification, the procedure used and assumptions made should be clearly stated in establishing the level of the degradation product. Specified unidentified degradation products can be referred to by an appropriate qualitative analytical descriptive label (e.g., unidentified A, unidentified with relative retention of 0.9).

Table1: International guidelines outlining regulatory requirements for the control and test of Impurities/Degradation products in drug substances and products for human use [5-20]

International agency	Guideline(s)	Issue date/date of coming into effect	Ref.
ICH (USA, EU and Japan)	Q3A(R2): Impurities in New Drug Substances	25 October 2006	5
	Q3B(R2): Impurities in New Drug Products	2 June 2006	6
	Q3C(R5): Impurities: Guideline for Residual Solvents	4 February 2011	7
	Q3D: Impurities: Guideline for Metal Impurities (final concept paper)	29 October 2009	8
	M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (final concept paper)	9 June 2010	9
EMA (Europe)	EMEA/CHMP/CVMP/QWP/450653/2006: Assessment of Quality of Medicinal Products Containing Existing/Known Active Substances	10 July 2007	10
	CPMP/QWP/1529/04: Control of Impurities of Pharmacopoeial Substances	22 April 2004	11
	CPMP/SWP/5199/02 and EMEA/CHMP/QWP/251344/2006: Guideline on the Limits of Genotoxic Impurities	28 June 2007	12
	CPMP/SWP/QWP/4446/00 corr.: Guidelines on Specification Limits for Residues of Metal Catalysts	January 2007	13
	EMA/CHMP/CVMP/QWP/199250/2009: Guideline on Setting Specifications for Related Impurities in Antibiotics (draft)	14 July 2010	14
US FDA (USA)	NDAs: Impurities in Drug Substances	February 2000	15
	Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (draft)	June 2009	16
	NDAs: Impurities in Drug Products	December 2008	17
		November 2010	18
TGA (Australia)	Australian Regulatory Guidelines for Prescription Medicines; Appendix 18: Impurities in Active Pharmaceutical Ingredients and Finished Products	June 2004	19
TPD (Canada)	Impurities in Existing Drug Substances and Products (draft)	September 2005	20

Table2: Categories of impurities to be listed in specifications [5, 6]

Drug substance specification	Drug product specification
Each specified identified impurity	Each specified identified degradation product
Each specified unidentified impurity	Each specified unidentified degradation product
Any unspecified impurity with an acceptance criterion of not more than the identification threshold	Any unspecified degradation product with an acceptance criterion of not more than the identification threshold
Total impurities	Total degradation products

Table3: Thresholds for degradation products in Drug Products [6]

Maximum daily dose [a]	**Reporting threshold [b, c]**
≤1 g	0.1%
>1 g	0.05%
Maximum daily dose [a]	**Identification threshold [b, c]**
<1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg–10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%
Maximum daily dose [a]	**Qualification threshold [b, c]**
<10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg–100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

[a] The amount of drug substance administered per day. [b] 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. [c] Higher thresholds should be scientifically justified.

Setting acceptance criteria for degradation products:

The acceptance criterion for impurities in the drug product should be set no higher than the qualified level. In establishing degradation product acceptance criteria, the first critical consideration is whether a degradation product is specified in the United States Pharmacopeia (USP). If there is a monograph in the USP that includes a limit for a specified identified degradation product, it is recommend that the acceptance criterion be set no higher than the official compendial limit.

If the level of the degradation product is above the level specified in the USP, its qualification is recommended. Then, if appropriate qualification has been achieved, an applicant may wish to petition the USP for revision of the degradation product's acceptance criterion. If the acceptance criterion for a specified degradation product does not exist in the USP and this degradation product can be qualified by comparison to an FDA approved human drug product, the acceptance criterion should be consistent with the level observed in the approved human drug

product. In other circumstances, the acceptance criterion may need to be set lower than the qualified level to ensure drug product quality. For example, if the level of the metabolite impurity is too high, other quality attributes, like potency, could be seriously affected. In this case, we would recommend that the degradation product acceptance criterion be set lower than the qualified level.

Qualification of Impurities:

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) being considered. When appropriate, it is recommend that applicants provide a rationale for establishing impurity acceptance criteria that includes safety considerations.

An impurity is considered qualified when it meets one or more of the following conditions:

1. When the observed level and proposed acceptance criterion for the impurity do not exceed the level observed in an FDA approved human drug product.
2. When the impurity is a significant metabolite of the drug substance.
3. When the observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature.
4. When the observed level and proposed acceptance criterion for the impurity do not exceed the level that has been adequately evaluated in comparative in vitro genotoxicity studies.

Setting impurity specifications for a non-compendial drug substance and drug product [21]

In the case of a non-compendial drug product, sponsors of ANDA submissions are expected to provide a summary of potential impurities, including structure (if known) with an explanation as to whether the origin is degradation and/or process related. As illustrated in Tables below, applicants are encouraged to provide applicable data and a rationale supporting the justification for the proposed levels of these impurities.

Table4: Setting impurity specifications for a non-compendial drug product [21]

Name	Observed: drug product (generic) lot	RLD at expiry	Drug product limits	Justification
Impurity A	≤2.0%	1.5%	NMT 2.5%	Metabolite
Impurity E	≤0.4%	1.0%	NMT 1.0%	Qualified based on RLD
Any unknown impurity	≤0.09%	≤0.05%	NMT 0.20%	ICH Q3B identification threshold
Total impurities	≤2.8%	3.7%	NMT 3.5%	Proposed acceptance criterion are below the levels present in RLD

[a] The maximum daily dose of RLD is 64 mg/day. Therefore the corresponding recommended drug product identification threshold is 0.20%.

This generally encompasses

1) batch analysis of the proposed generic product, 2) qualification data based upon analysis of the RLD and/or literature information, and 3) applicable identification and qualification thresholds based upon the maximum daily dose, and 4) and in the case of the drug product, whether the impurities are degradants.

Table5: Setting impurity specifications for a non-compendial drug substance [21]

Name	Origin	Observed: drug substance (generic) lot	RLD at expiry	Drug product limits	Justification
Impurity A	Degradant (Hydrolysis)	0.20%	1.5%	NMT 0.5%	Metabolite
Impurity B	Process impurity	0.10%	0.01%	NMT 0.15%	ICH Q3A qualification Threshold [a]
Impurity C	Process impurity	0.09%	0.07%	NMT 0.15%	ICH Q3A qualification Threshold [a]
Impurity D	Process impurity	0.11%	0.02%	NMT 0.15%	ICH Q3A qualification Threshold [a]
Impurity E	Degradant (Oxidation)	0.30%	1.0%	NMT 1.0%	Qualified based on RLD
Impurity F(RRT 2.55[b])	Process impurity	0.30%	0.50%	NMT 0.50%	Qualified based on RLD
Any unknown Impurity		0.07%	0.05%	NMT 0.10%	Proposed acceptance criterion are below the levels present in RLD
Total Impurities		1.4%	3.7%	NMT 2.0%	

[a] The maximum daily dose of RLD is 64 mg/day. Therefore the corresponding recommended drug substance identification and qualification thresholds are 0.10% and 0.15%, respectively.

[b] Impurity F is also present is the reference listed drug. This is based on both products exhibiting a peak with the same retention time on the HPLC, identical UV spectra (PDA), and similar mass spectra (MS-electrospray).

This example depicts several important points that should be considered by applicants in their submissions in the context of the implication of impurity specifications to pharmaceutical quality. A fundamental point is that impurity specification limits in a generic product can often be adequately justified based upon a demonstration that the proposed limits are equivalent or more stringent, to the actual levels of the impurity observed in the RLD. As further illustrated in this example, this reasoning may also be extended to cases where there is a specified impurity of unknown structure (e.g. Impurity F at RRT 2.55), provided the unknown impurity is present in the RLD and sufficient evidence of comparability of structure is provided in the submission (e.g., via similar retention times, mass spectra, UV spectra). Noteworthy, is the fact that in some circumstances, a proposed limit of the known impurity exceeding the observed levels in the

innovator may be deemed acceptable, particularly where there is adequate qualification data, such as in the instance of an impurity being an active metabolite (e.g. Impurity A).

Analytical methods:

The safety and quality of the generic drug product/drug substance can be impacted by the presence of impurities. The nature and quantity of these impurities is governed by a number of factors, including the synthetic route of drug substance, reaction conditions, quality of the starting material, reagents, solvents, purification steps, and storage of the end product. As the structure of impurities are sometimes unknown, several spectroscopic and micro-chemical techniques have been developed which require minute quantities of material and readily enable the structural elucidation of the impurity. Versatile analytical methods are also available for the detection and monitoring of impurities in drug substances and drug products. The primary criterion of analytical methodology is the ability to differentiate the compounds of interests. The commonly used methods are separation (isolation) and detection and quantification (spectroscopic) in tandem.

The separation methods include thin layer chromatography (TLC), high performance liquid chromatography (HPLC), gas chromatography (GC), and capillary electrophoresis (CE). HPLC is the most commonly used method for impurity monitoring in an inexpensive way. TLC can be used to separate a broad range of compounds. The primary difficulties related to the TLC method are limited resolution, detection, and ease of quantitation. Gas chromatography can provide the desired resolution, selectivity, and quantitation, unless the sample is not volatile. Capillary electrophoresis is a useful technique when very low quantities of samples are available and high resolution is required. Based upon these developments, it is now possible to replace all non-specific assay methods with highly specific and precise separation methods for assay and detection of impurities, thus greatly improving the value of the analytical determination in bulk drug materials.

The spectroscopic methods include ultraviolet (UV), infrared(IR), nuclear magnetic resonance (NMR), and mass spectrometry(MS). Ultraviolet spectroscopy at a single wavelength provides minimal selectivity of analysis while the availability of diode array detectors offers much more information at various wavelengths to ensure greater selectivity. Infrared spectroscopy provides specific information on some functional groups that may allow quantitation and selectivity. Nuclear magnetic resonance spectroscopy offers fairly detailed structural information on molecules and is a very useful method for characterization of desired product and associated impurities. Mass spectrometry which requires minute amounts of sample, provides excellent

structural information based upon mass ion fragmentation patterns. Thus, UV, IR, NMR, and MS are excellent techniques for characterization and analysis of pharmaceutical compounds and impurities.

Conventional approach for the characterization of Impurities/Degradation products [22]

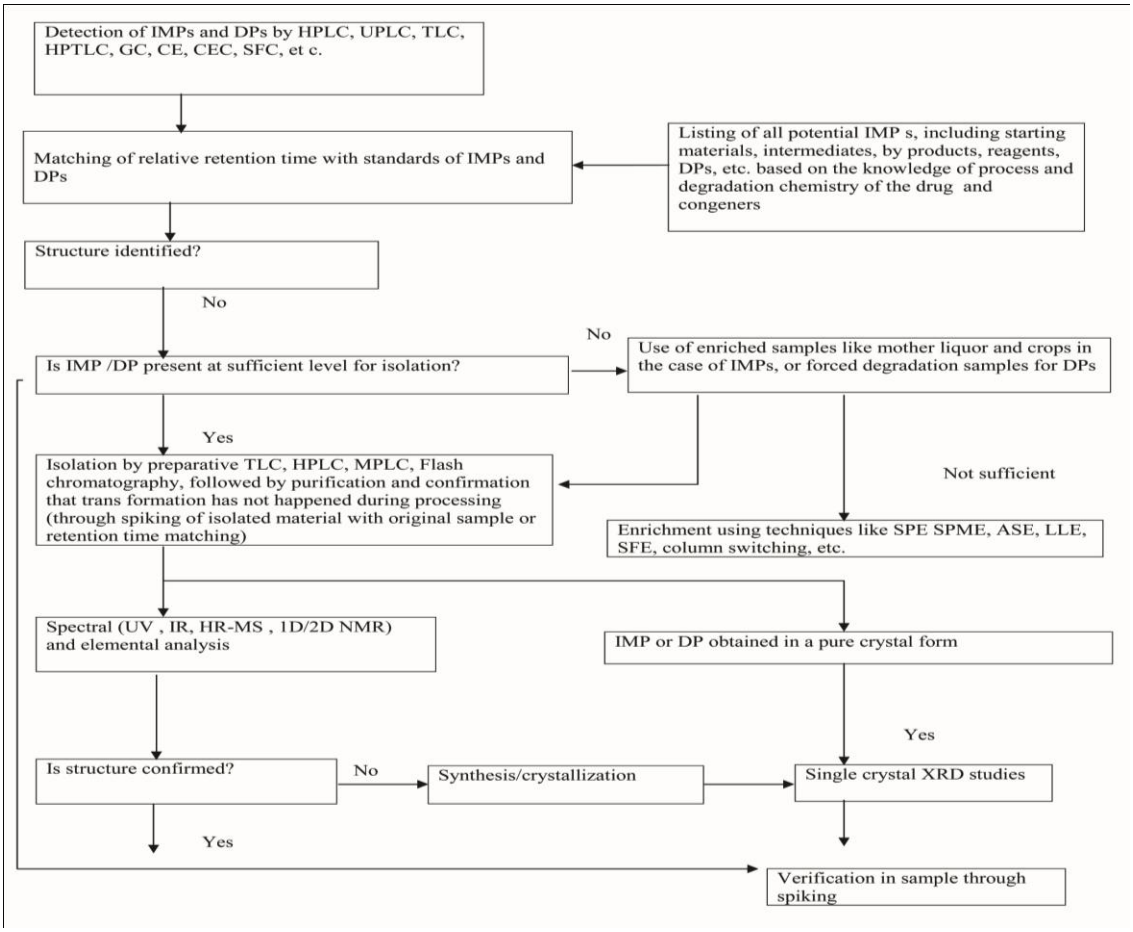

Figure1: Conventional approach for the characterization of Impurities /degradation products

Characterization of Impurities:

Evidently, impurities and degradation products, for which structural characterization has been achieved, are the ones considered as 'Identified'. Majority of the International regulatory guidelines require that any impurity or degradation product at a level greater than ICH identification threshold should be identified. The ICH Common Technical Document (CTD, M4Q(R1) clearly requires characterization information on impurities in new drug substances and degradation products in new drug products under sections 3.2.S.3.2 and 3.2.P.5.5, respectively.

The conventional approach to identification and structure elucidation of unknown IMPs/DPs primarily involves separation and then isolation/enrichment/synthesis, followed by spectral analysis.

CONCLUSION:

Thus we can conclude that, adopting above mentioned steps of analytical process and reporting format we can produce the Control of drug product and drug substance part of the marketing authorization dossier in accordance with international regulatory guidelines.

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