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## ^⟨477⟩ USER-DETERMINED REPORTING THRESHOLDS

### INTRODUCTION

This chapter provides an approach for determining an appropriate numeric value for the reporting threshold (see [Impurities in Drug Substances and Drug Products \(1086\), Glossary](#)) in chromatographic test procedures and is applicable when the chapter is referenced in an individual monograph employing a user-determined reporting threshold. Monographs that employ user-determined reporting thresholds offer flexibility, ensuring the documentary standard is fit for its intended purpose, by permitting users to determine the reporting threshold criterion that aligns with their product-specific implementation of the compendial chromatographic test procedure. USP may specify user-determined reporting thresholds in monographs for chemically derived drug substances and drug products. User-determined reporting thresholds are generally not applicable in monographs for veterinary only products, biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products, and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin. Monographs that specify user-determined reporting thresholds will typically provide a note as supplemental information that is not essential for regulatory compliance, to aid users who are not product application holders in identifying a numeric value for the reporting threshold that may be suitable for a given set of product-specific factors.

For manufacturers with product applications approved by a responsible regulatory authority, the appropriate numeric value of the reporting threshold is that which has been established in the approved product application, if applicable. For other users of the monograph, the information provided in this chapter can support the determination of an appropriate numeric value for the reporting threshold.

### RELEVANT PRODUCT FACTORS

The relevant product factors supporting the determination of an appropriate numeric value for the reporting threshold for either a drug substance or a drug product include the maximum daily dose (i.e., the maximum amount of drug substance administered per day) and the route of administration of the related drug product. For many drug products, the maximum daily dose (MDD) is the essential factor in determining an appropriate numeric value for the reporting threshold. In cases where the responsible regulatory authority has identified a higher risk posed by impurity exposure through specific routes of administration, due to the greater sensitivity of the related organ systems, the route of administration may supersede MDD in importance. Product types that fall into these higher risk categories may include, but are not limited to, ophthalmic products, nasal sprays, inhalation solutions, inhalation suspensions, and inhalation sprays. For these product types, the responsible regulatory authority may require more conservative thresholds for the identification of impurities (corresponding to a lower acceptance criterion for unspecified impurities) than the thresholds described in applicable International Council for Harmonisation (ICH) guidelines. A lower acceptance criterion for unspecified impurities will necessitate a correspondingly lower reporting threshold. This concept is further discussed in *Additional Considerations*. Users should be aware of any drug product guidance issued by their responsible regulatory authority related to special routes of administration to avoid selecting an inappropriate (high) numeric value for the reporting threshold.

Information on the MDD may be found in the drug product's package insert for most drug products sold under a prescription. In many cases, the MDD in the package insert will be unambiguous and definitive; however, for some product types, including but not limited to topical drug delivery systems, expert knowledge may be required to calculate the maximum daily dose. If for any reason definitive information about the MDD is not available, the monograph user may elect to follow the more conservative numeric value for the reporting threshold, i.e., the value associated with the higher MDD, as described in *Maximum Daily Dose Based Reporting Thresholds*.

### MAXIMUM DAILY DOSE BASED REPORTING THRESHOLDS

The numeric values for reporting thresholds corresponding to different maximum daily doses are established in the following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines: Q3A(R2) Impurities in New Drug Substances and Q3B(R2) Impurities in New Drug Products, and are reproduced in [Table 1](#) below.

Table 1

Monograph	Maximum Daily Dose <sup>a</sup>	Reporting Threshold <sup>b</sup>
Drug Substance <sup>c</sup>	≤2 g	0.05%
	>2 g	0.03%

Monograph	Maximum Daily Dose <sup>a</sup>	Reporting Threshold <sup>b</sup>
Drug Product <sup>d</sup>	≤1 g	0.1%
	>1 g	0.05%

- <sup>a</sup> Refers to the maximum amount of drug substance administered per day via the related drug product.
- <sup>b</sup> Reporting threshold is expressed as a percentage of the drug substance.
- <sup>c</sup> Information abstracted from ICH Q3A(R2) Impurities in New Drug Substances.
- <sup>d</sup> Information abstracted from ICH Q3B(R2) Impurities in New Drug Products.

### ADDITIONAL CONSIDERATIONS

The numeric value of the reporting threshold should not exceed the numeric acceptance criterion for unspecified impurities, e.g., the numeric acceptance criterion for any unspecified impurity in a drug substance monograph or the numeric acceptance criterion for any unspecified degradation product in a drug product monograph. To ensure adequate reporting of impurities, a numeric value for the reporting threshold that is less than the numeric acceptance criterion for any unspecified impurity or any unspecified degradation product, as applicable, should be selected.

Lower reporting thresholds can be appropriate for individual organic impurities that are known to be unusually potent or to produce toxic or unexpected pharmacological effects. The thresholds that address potential safety concerns take precedence over reporting thresholds assigned, based on a general assessment of relevant product factors noted above.

The responsibility for ensuring the suitability of compendial chromatographic test procedures down to the level of the user-determined reporting threshold remains with the monograph user. As described in the general informational chapter [Verification of Compendial Procedures \(1226\)](#), documented evidence of suitability of the compendial analytical procedure should be established under actual conditions of use. If the verification of the compendial procedure is not successful, it may then be necessary to develop and validate an alternative procedure as allowed in [General Notices, 6.30 Alternative and Harmonized Methods and Procedures](#).

Organic Impurities procedures in some monographs include a *Sensitivity solution*, which when used in conjunction with a related *Suitability requirement*, verifies that the chromatographic system possesses adequate sensitivity at the time of use. In monographs that specify user-determined reporting thresholds, the concentration of the *Sensitivity solution* will generally be aligned with the numeric value of a reporting threshold that may be suitable; however, when a user selects a lower numeric value for the reporting threshold, they may elect to reduce the concentration of this solution or establish another appropriate system sensitivity check, when supported by proper validation.

As elaborated in [\(1086\)](#), when the impurity test prescribes the limit of total impurities or there is a quantitative determination of an impurity, choice of an appropriate threshold setting and appropriate conditions for the integration of the peak areas is important. Principles from [Chromatography \(621\)](#), [Validation of Compendial Procedures \(1225\)](#), and [\(1226\)](#), such as signal-to-noise ratio, quantitation limit, and quantitation methods, should be observed. The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold. ▲ (USP 1-May-2024)

**Auxiliary Information** - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
<477> USER-DETERMINED REPORTING THRESHOLDS	<a href="#">Antonio Hernandez-Cardoso</a> Senior Scientific Liaison	GCCA2020 General Chapters - Chemical Analysis 2020

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