
Guidance for Industry

Q3C Impurities: Residual Solvents

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
December 1997
ICH**

Guidance for Industry

Q3C Impurities: Residual Solvents

Additional copies are available from:
Center for Drug Evaluation and Research (CDER),
Division of Drug Information (HFD-240),
5600 Fishers Lane, Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>

or

Office of Communication, Training, and
Manufacturers Assistance (HFM-40),
Center for Biologics Evaluation and Research (CBER)
1401 Rockville Pike, Rockville, MD 20852-1448,
<http://www.fda.gov/cber/guidelines.htm>;
(Fax) 888-CBERFAX or 301-827-3844
(Voice Information) 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
December 1997
ICH

TABLE OF CONTENTS

<i>I. INTRODUCTION (1)</i>	1
<i>II. SCOPE OF THE GUIDANCE (2)</i>	2
<i>III. GENERAL PRINCIPLES (3)</i>	2
A. Classification of Residual Solvents by Risk Assessment (3.1).....	3
B. Methods for Establishing Exposure Limits (3.2)	3
C. Options for Describing Limits of Class 2 Solvents (3.3).....	3
D. Analytical Procedures (3.4).....	5
E. Reporting Levels of Residual Solvents (3.5).....	5
<i>IV. LIMITS OF RESIDUAL SOLVENTS (4)</i>	6
A. Solvents to Be Avoided (4.1)	6
B. Solvents to Be Limited (4.2)	6
C. Solvents with Low Toxic Potential (4.3).....	6
D. Solvents for Which No Adequate Toxicological Data Were Found (4.4)	7
<i>GLOSSARY</i>	8
<i>APPENDIX 1: ADDITIONAL BACKGROUND</i>	9
<i>APPENDIX 2: METHODS FOR ESTABLISHING EXPOSURE LIMITS</i>	10

Guidance for Industry¹

Q3C Impurities: Residual Solvents

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION (1)

The objective of this guidance is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guidance recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. A complete list of the solvents included in this guidance is provided in a companion document entitled *Q3C — Tables and List*.² The list is not exhaustive, and other solvents may be used and later added to the list.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guidance does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

¹ This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process in July 1997. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Arabic numbers in subsections reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process.

² This guidance was published originally in the *Federal Register* on December 24, 1997 (62 FR67377). At that time the list was included as Appendix 1. In this reformatted version, the list has been removed and made into a companion document, and the remaining appendices have been renumbered.

Since there is no therapeutic benefit 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. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, see Table 1 in the companion document *Q3C — Tables and List*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, see Table 2 in the companion document) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, see Table 3 in the companion document) should be used where practical.

Recommended limits of Class 1 and 2 solvents or classification of solvents may change as new safety data becomes available. Supporting safety data in a marketing application for a new drug product containing a new solvent may be based on concepts in this guidance or the concept of qualification of impurities as expressed in the guidance for drug substance, *Q3A Impurities in New Drug Substances* (January 1996) or drug product, *Q3B Impurities in New Drug Products* (November 1997), or all three guidances.

II. SCOPE OF THE GUIDANCE (2)

Residual solvents in drug substances, excipients, and drug products are within the scope of this guidance. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug products. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that recommended in this guidance, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. Drug product should also be tested if a solvent is used during its manufacture.

This guidance does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guidance applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short-term (30 days or less) or topical application. Justification for these levels should be made on a case-by-case basis.

See Appendix 1 for additional background information related to residual solvents.

III. GENERAL PRINCIPLES (3)

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.