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Standard Guide for Derivation of Health-Based Exposure Limits (HBELs)[1]

This standard is issued under the fixed designation E3219; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide describes the scientific procedures underlying the integrative interpretation of all data concerning an active pharmaceutical ingredient (API) taking into account study adequacy, relevance, reliability, validity, and compound-specific characteristics (for example, potency, toxicological profile, and pharmacokinetics) leading to a numerical value for the API, which is used further in the quality risk management (ICH Q9) of cross contamination during the manufacture of different products in the same manufacturing facilities.

1.2 This guide describes general guidance for calculating and documenting a health-based exposure limit (HBEL). It should serve the involved qualified experts as a reference for HBEL derivations and should harmonize the different approaches and nomenclature to the greatest extent possible.

1.3 This guide should be used for calculating and documenting an HBEL, when required or necessary, for APIs (including biologics), intermediates, cleaning agents, excipients, and other chemicals (that is, reagents, manufacturing residues, and so forth) used for cleaning validation and verification (Guides F3127 and E3106). In scope is the cleaning and cross contamination of surfaces of manufacturing equipment and medical devices but does not include leachables/extractables (21 CFR 211.67, 21 CFR 610.11, 21 CFR 820.70, and 21 CFR 111.27).

1.4 The principles in this guide may also be used as a basis for setting occupational exposure limits.

1.5 The principles in this guide may be applied during the development and commercial manufacturing of small or large molecular weight medicines as well as isolated pharmaceutical intermediates.

1.6 Subsequent-product HBEL values may be set for specific routes of exposure (for example, oral, inhalation, and parenteral) when necessary (for example, because of differences in bioavailability) and for specific patient populations (for example, children) if formulations are manufactured in which one daily dose is not for the 50 kg standard adult but the dosage form is adjusted to a target population with a lower body weight.

1.7 The primary scope of this guide is to ensure the safety of human patients exposed to residual active substances and intermediates via medicinal products. The general principles of this guide can also be applied to the manufacture of veterinary medicinal products. However, there may be certain unique toxicological and pharmacological species-specific differences, such as metabolism and sensitivity, as well as assumptions such as body weight for veterinary medicines that are not addressed in this guide.

1.8 This guide may be used independently or in conjunction with other proposed E55 standards published by ASTM International.

1.9 *Units*—The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.10 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.11 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E1262 Guide for Performance of Chinese Hamster Ovary Cell/Hypoxanthine Guanine Phosphoribosyl Transferase Gene Mutation Assay

E3106 Guide for Science-Based and Risk-Based Cleaning Process Development and Validation

F619 Practice for Extraction of Medical Plastics

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.03 on General Pharmaceutical Standards.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

F719 Practice for Testing Biomaterials in Rabbits for Primary Skin Irritation
F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices
F750 Practice for Evaluating Material Extracts by Systemic Injection in the Mouse
F756 Practice for Assessment of Hemolytic Properties of Materials
F763 Practice for Short-Term Screening of Implant Materials
F813 Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices
F895 Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity
F981 Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Insertion into Bone
F1408 Practice for Subcutaneous Screening Test for Implant Materials
F1439 Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials
F1903 Practice for Testing for Cellular Responses to Particles ***in vitro***
F1983 Practice for Assessment of Selected Tissue Effects of Absorbable Biomaterials for Implant Applications
F2382 Test Method for Assessment of Circulating Blood-Contacting Medical Device Materials on Partial Thromboplastin Time (PTT)
F2808 Test Method for Performing Behind-the-Knee (BTK) Test for Evaluating Skin Irritation Response to Products and Materials That Come Into Repeated or Extended Contact with Skin
F2888 Practice for Platelet Leukocyte Count—An ***In-Vitro*** Measure for Hemocompatibility Assessment of Cardiovascular Materials
F2901 Guide for Selecting Tests to Evaluate Potential Neurotoxicity of Medical Devices
F3127 Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices

2.2 *ISO Standards:*[3]

ISO 10993-1 Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process
ISO 10993-4 Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood
ISO 10993-6 Biological evaluation of medical devices – Part 6: Test for local effects after implantation
ISO 10993-10 Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization
ISO 10993-11 Biological evaluation of medical devices – Part 11: Test for systemic toxicity
ISO 10993-17 Biological evaluation of medical devices-- Part 17: Establishment of allowable limits for leachable substances
ISO 17664 Processing of health care products - Information to be provided by the medical device manufacturer for the processing of medical devices

2.3 *ICH Guidelines:*[4]

ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 4; 31 March 2017)
ICH Q3A(R2) Impurities in New Drug Substances
ICH Q3B(R2) Impurities in New Drug Products
ICH Q3C(R6) Impurities: Guideline for Residual Solvents (Final; 4 October 2019)
ICH Q3D(R1) Guideline for Elemental Impurities (Step 4)
ICH Q9 Quality Risk Management (Step 4)
ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

2.4 *Federal Regulations:*[5]

21 CFR 111.27 What requirements apply to the equipment and utensils that you use?
21 CFR 211.42(d) Design and Construction Features
21 CFR 211.46(d) Ventilation, air filtration, air heating and cooling
21 CFR 211.67 Equipment cleaning and maintenance
21 CFR 211.176 Penicillin contamination
21 CFR 610.11 General safety
21 CFR 820.70 Production and process controls

3. Terminology

3.1 *Definitions:*

3.1.1 *acceptable daily exposure, ADE, n*—this term for a health-based exposure limit (HBEL) is synonymous with the term permitted daily exposure (PDE); see HBEL for details.

3.1.2 *accumulation, n*—progressive increase in the amount of a substance in an organism or part of an organism that occurs because the rate of intake from all routes of exposure from repeated dosing exceeds the organism's ability to remove the substance from the body, ultimately leading to a steady-state tissue concentration higher than that associated from a single dose.

3.1.3 *adjustment factor, AF, n*—numerical factor used in a quantitative risk assessment to represent or allow for the extrapolation, uncertainty, or variability of an observed exposure concentration and its associated health outcome in a particular laboratory species or exposed population to an exposure concentration for the target population (for example, from animals to human patients and short-term exposure to chronic exposure) that would be associated with the same delivered dose.

3.1.3.1 *Discussion*—Synonymous with the terms uncertainty factor (UF), modifying factor (MF), and safety factor (SF). Ideally, AFs are based on quantitative chemical-specific toxicokinetic (TK) or toxicodynamic (TD) data or both and

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

[4] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, 9, chemin des Mines, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

[5] Available from U.S. Government Printing Office, Superintendent of Documents, 732 N. Capitol St., NW, Washington, DC 20401-0001, http://www.access.gpo.gov.

consider factors such as interspecies extrapolation, duration of exposure, intraspecies variability, severity of effect, and others. Often, default AF values are used because of the absence of chemical-specific TK and TD data. For the purposes of this guide, the terms "pharmacokinetic (PK)" and "pharmacodynamic (PD)" are essentially synonymous to "toxicokinetic" and "toxicodynamic" in the context of HBEL setting.

3.1.4 *adverse effect, n*—test-item-related change in the morphology, physiology, growth, development, reproduction, or life span of an animal that likely results in an impairment of functional capacity to maintain homeostasis or an impairment of the capacity to respond to an additional challenge or both. **(1-3)**[6]

3.1.4.1 *Discussion*—A biologically significant pharmacological effect should be considered adverse when establishing an HBEL for an unintended contaminant or residue.

3.1.5 *benchmark dose/benchmark concentration, BMD/BMC, n*—mathematically derived dose of a substance that produces a predetermined change in the response rate of an adverse effect relative to the background response of this effect. **(4-6)**

3.1.5.1 *Discussion*—The BMD or BMC refer to central estimates. The benchmark dose lower limit (BMDL) and benchmark lower concentration (BMCL) refer to the corresponding lower limit of a one-sided 95 % confidence interval on the BMD or BMC, respectively.

3.1.6 *benchmark response, BMR, n*—predetermined change in the response rate of an adverse effect relative to the background response rate of this effect (for example, 10 % response for quantal ("yes/no") or continuous data). **(4-6)**

3.1.6.1 *Discussion*—The BMR is the basis for deriving BMDs and BMCs.

3.1.7 *bioavailability, n*—fraction of a substance that reaches the systemic circulation after administration or exposure.

3.1.8 *carcinogen, n*—agent that is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity.

3.1.8.1 *Discussion*—The induction of benign neoplasms may, in some circumstances, contribute to the judgment that the agent may be carcinogenic. The terms "neoplasms" and "tumor" are used interchangeably **(7)**. Carcinogens that are likely causing tumors by interaction with deoxyribonucleic acid (DNA) (genotoxic) are distinguished from carcinogens causing tumors by other mechanisms not involving genotoxicity (non-genotoxic).

3.1.9 *clinically relevant, adj*—biologically meaningful change in patient health in response to exposure.

3.1.10 *critical effect, n*—first adverse effect, or its known precursor, that occurs in the increasing dose/concentration scale after appropriate adjustment for interspecies differences and interindividual variability. **(8)**

3.1.10.1 *Discussion*—The effect shall be relevant for the target population (for example, unintended exposure to a patient or a healthy employee), that is, it is both statistically significant and clinically relevant. In this context, "critical effect" means the lead effect is undesired but not necessarily harmful in nature. The critical effect may result in the lowest HBEL; however, there are exceptions.

3.1.11 *drug allergy, n*—immunologically mediated drug hypersensitivity reaction.

3.1.11.1 *Discussion*—Of the four types of hypersensitivity reactions, Type I, an immediate IgE-mediated, hypersensitivity reaction is the most common and is a true allergic reaction **(9, 10)**. T-cell mediated (Type IV) hypersensitivity reactions are delayed-type reactions and are the second most common.

3.1.12 *genotoxicity, n*—also genetic toxicity; the effect that results from damage to DNA and altered genetic expression.

3.1.12.1 *Discussion*—The four types of genetic change are gene mutation (change in DNA sequence within a gene), chromosome aberration (changes in the chromosome structure), aneuploidy/polyploidy (increase or decrease in the number of chromosomes), and epigenetics (external changes to DNA such as methylation).

3.1.13 *general assessment factors, n*—factors used to evaluate the quality and relevance of scientific and technical information.

3.1.13.1 *Discussion*—Five general assessment factors include soundness, applicability and utility, clarity and completeness, uncertainty and variability, and evaluation and review **(11)**, with the level of quality assurance applied to the information is commensurate with the intended use of the information and the degree of confidence necessary in that information **(12)**.

3.1.14 *generic drug, n*—drug product that is comparable to a brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use.

3.1.14.1 *Discussion*—Biosimilars are generic biologics.

3.1.15 *hazard characterization (dose-response assessment in U.S. EPA risk assessment framework), n*—qualitative and, wherever possible, quantitative description of the inherent property of an agent or situation having the potential to cause adverse effects **(13)**. It is a description of the potential adverse health effects attributable to a specific compound, the mechanisms by which the agent exerts its toxic effects, and the associated dose, route, duration, and timing of exposure.

3.1.16 *health-based exposure limit, HBEL, n*—dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.

3.1.16.1 *Discussion*—The HBEL, being based on the critical effect, should be protective of all populations by all routes of administration and should be the result of a structured scientific evaluation of all available pharmacological and toxicological data including both non-clinical and clinical data **(14, 15)**.

[6] The boldface numbers in parentheses refer to a list of references at the end of this standard.