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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

[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 E55.14 on Measurement Systems and Analysis.

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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.

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F619 Practice for Extraction of Materials Used in Medical Devices
F719 Practice for Testing Materials in Rabbits for Primary Skin Irritation
F748 Practice for Selecting Generic Biological Test Methods for Materials and Devices
F750 Practice for Evaluating Acute Systemic Toxicity of Material Extracts by Systemic Injection in the Mouse
F756 Practice for Assessment of Hemolytic Properties of Materials
F763 Practice for Short-Term Intramuscular Screening of Implantable Medical Device 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

[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.

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toxicokinetic (TK) or toxicodynamic (TD) data or both and 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.

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3.1.17 *intermediates, n*—materials produced during steps in the synthesis of an active pharmaceutical ingredient (API) that shall undergo further molecular change or processing resulting in an API.

3.1.18 *in silico, adj*—expression used to mean "performed on computer or via computer simulation."

3.1.19 *in vitro, adj*—studies that are performed with cells or biological molecules outside their normal biological context, for example, proteins evaluated in solution or cells in artificial culture medium.

3.1.20 *lowest observed adverse effect level, LOAEL, n*—lowest exposure level in a study in which there were statistically or biologically significant changes in frequency or severity of adverse effects between the exposed population and its appropriate control group. (**8**)

3.1.21 *lowest observed effect level, LOEL, n*—lowest dose or exposure level in a study in which a statistically or biologically significant effect is observed in the exposed population compared with an appropriate unexposed control group that demonstrated an effect between the exposed population and its appropriate control group. (**8**)

3.1.22 *margin of safety, MOS, n*—ratio of the HBEL to the estimated exposure. (**13**)

3.1.23 *mechanism of action, n*—detailed description, often at the molecular level, of the means by which an agent causes a disease or other adverse effect. (**16**)

3.1.23.1 *Discussion*—The term "mechanism of action" implies a more detailed understanding and description of events, often at the molecular level, than is meant by mode of action (**17**).

3.1.24 *mode of action, n*—sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in the adverse effect. (**16, 17**)

3.1.24.1 *Discussion*—A "key event" is an empirically observable precursor step that is itself a necessary element of the mode of action or a biologically based marker for such an element (**17**).

3.1.25 *no observed adverse effect level, NOAEL, n*—highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control; some effects may be produced, but they are not considered adverse or precursors of adverse effects. (**8**)

3.1.26 *no observed effect level, NOEL, n*—exposure level at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control. (**8**)

3.1.27 *over-the-counter (OTC) drugs, n*—medicines sold directly to the consumer without a prescription from a healthcare professional.

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

3.1.29 *pharmacodynamics, n*—derived from toxicodynamics; describe and quantify the sequence of cellular and molecular events at the target site leading to a pharmacological response to a drug.

3.1.30 *pharmacokinetics, n*—derived from toxicokinetics; describe and quantify the time course of absorption, distribution, biotransformation, and excretion of a drug.

3.1.31 *point of departure, PoD, n*—dose-response point that marks the beginning of a low-dose extrapolation to derive an HBEL. (**8**)

3.1.31.1 *Discussion*—This point can be a NOAEL/NOEL, LOAEL/LOEL, or BMDL for an observed effect (**18**).

3.1.32 *potency (activity), n*—expression of the relative response of an agent as compared to a given or implied standard or reference.

3.1.33 *qualified expert, n*—individual with specific education and training in toxicology/pharmacology/pharmacotherapy and risk assessment methods that can apply the principles of toxicology to deriving an HBEL.

3.1.34 *reliability, n*—inherent quality of an effect value in a test report or publication relating to a clearly described experimental design, performance of the experimental procedures, and reporting of the results to provide evidence of the reproducibility and accuracy of the findings. (**19, 20**)

3.1.35 *risk assessment, n*—systematic process to organize and analyze scientific knowledge and information used to characterize the potential adverse effects of human exposures to an agent, including uncertainties inherent in the process of inferring risk. (**13, 21, 22**)

3.1.35.1 *Discussion*—According to the National Research Council paradigm, risk assessment consists of four steps: (*1*) hazard identification, (*2*) dose-response assessment, (*3*) exposure characterization, and (*4*) risk characterization (**21**).

3.1.36 *severity, n*—extent to which an effect impairs the functional capacity of an organism, that is, the degree of adversity.

3.1.36.1 *Discussion*—This continuum is a composite of many variables, including degree of impairment to the organism, magnitude, organ effected, incidence, reversibility, pathologic severity, and other factors that give an indication of the severity. Examples of severe effects include carcinogenicity, teratogenicity, neurotoxicity, and death.

3.1.37 *threshold of toxicological concern, TTC, n*—TTC approach is a screening and prioritization tool for the safety assessment of chemicals when hazard data are incomplete and human exposure can be estimated and, thus, for deciding whether exposure to a substance is so low that the probability of adverse health effects is low and that no further data are necessary.

3.1.37.1 *Discussion*—The TTC is not applicable when compound-specific assessment and toxicity data are available or are required under existing regulations (**23, 24**).

3.1.38 *toxicodynamics, n*—describe and quantify the sequence of cellular and molecular events at the target site leading to an adverse response to a chemical.

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3.1.39 *toxicokinetics, n*—describe and quantify the time course of absorption, distribution, biotransformation, and excretion of chemicals.

3.1.40 *uncertainty, n*—refers to a lack of knowledge about specific factors, parameters, or models. (**25**)

3.1.40.1 *Discussion*—It is important to characterize adequately variability and uncertainty in a risk assessment. "Uncertainty includes parameter uncertainty (measurement errors, sampling errors, systematic errors), model uncertainty (uncertainty due to necessary simplification of real-world processes, mis-specification of the model structure, model misuse, use of inappropriate surrogate variables), and scenario uncertainty (descriptive errors, aggregation errors, errors in professional judgment, incomplete analysis)." (**25**) See also Ref (**26**) for a generic list of common types of uncertainties in inputs and methodologies.

3.1.41 *variability, n*—refers to observed differences attributable to true heterogeneity or diversity in parameter values over time, space, or different member of a population (for example, in cumulative exposure dose or dose rate to an individual or group of individuals or in response to exposure). (**25, 26**)

3.1.41.1 *Discussion*—It is an inherent property of a population being evaluated and, while it can be better characterized with more data, it usually cannot be reduced and cannot be eliminated.

4. Significance and Use

4.1 Guidelines for unintended human exposure to active pharmaceutical ingredients (APIs) are required by various global regulations as part of international quality requirements, needed as good product stewardship, and are considered the industry standard.

4.2 Application of the approach described within this guide applies a scientifically justified, data-driven, approach to deriving safe limits for unintended exposures to individual substances. These limits can then be further used to calculate cleaning limits used in quality risk assessment for the manufacture of pharmaceuticals. The HBEL approach considers substance-specific properties (type of effect, potency, pharmacology, safety profile, and so forth). Specific approaches are applicable to different categories of substances and in specific stages in drug development.

4.3 The basis for the HBEL derivation is all available substance-specific data. Interpretation of these data considers the quantity and robustness of the database and the reliability and relevance of the data. Typically, adjustment factors (AFs) are used to address variability and uncertainty in different parameters to determine a safe human exposure limit, although alternative, purposefully conservative, approaches [for example, threshold of toxicological concern (TTC), read-across] may be used as appropriate.

4.4 This guide supports, and is consistent with, elements of the European Commission (EU) Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use (**27, 28**) and guidance from the International Society of Pharmaceutical Engineers (ISPE) (**29**) in which it is mentioned that relevant residue limits should be based on a toxicological evaluation.

4.5 *Key Concepts*—This guide applies the following steps: (*1*) hazard characterization, (*2*) identification of the critical effect(s) including dose-response assessment, (*3*) determination of one or several points of departure (PoD)s, (*4*) application of PoD-specific AFs, and (*5*) calculation of HBELs including justification of selected HBEL (**18**) (see Fig. 1).

5. Procedure

5.1 The procedure proposed in this guide for determination of an HBEL is based on the methods for establishing the permitted daily exposure (PDE) as described in EMA guidance (**14**), the acceptable daily exposure (ADE) value as described in ISPE guidance (**29**), as well as principles outlined in the scientific literature.

5.2 The establishment of an HBEL is a process that requires expertise and needs to be done by a qualified expert and, if possible, should be peer reviewed by relevant subject matter experts. A curriculum vitae (CV) should be available on request that demonstrates the educational background (for example, toxicology, pharmacology, medicine, or other health-related disciplines), certifications such as the Diplomate of the American Board of Toxicology (DABT) or European Registered Toxicologist (ERT), years of experience in the field, and publications related to the field. While all are not required for a "qualified expert," the appropriate documentation in these areas demonstrates the expertise to work in this area. Typically, certification registries require an academic degree in a relevant subject, basic knowledge of the major areas of toxicology, at least five years of relevant toxicological experience, suitability for registration (for example, by published works, reports, or assessments), and current professional engagement in the practice of toxicology (**30, 31**).

5.3 Documentation describing the procedure to derive an HBEL should be described by the qualified expert in a monograph. The purpose of a monograph is to communicate effectively with the stakeholders and document the scientific data and methods underlying the HBEL derivation to enable its inspection by the regulators. An example template for an HBEL monograph is available in Appendix X1; however, the general format may vary.

5.4 *Hazard Identification and Characterization:*

5.4.1 The purpose of the hazard identification and characterization is to identify the health effects caused by a chemical agent. It involves evaluating the quality and relevance of the available scientific and technical information on the chemical agent, including the mechanism(s) by which an agent exerts its toxic effects; the associated doses, and the route, duration, and timing of exposure. The U.S. Environmental Protection Agency (EPA) has described the five general assessment factors it typically considers in evaluating such data: (*1*) soundness; (*2*) applicability and utility; (*3*) clarity and completeness; (*4*) uncertainty and variability; and (*5*) evaluation and review (**11**).

5.4.1.1 The evaluation of all substance-specific information should result in a comprehensive characterization of the

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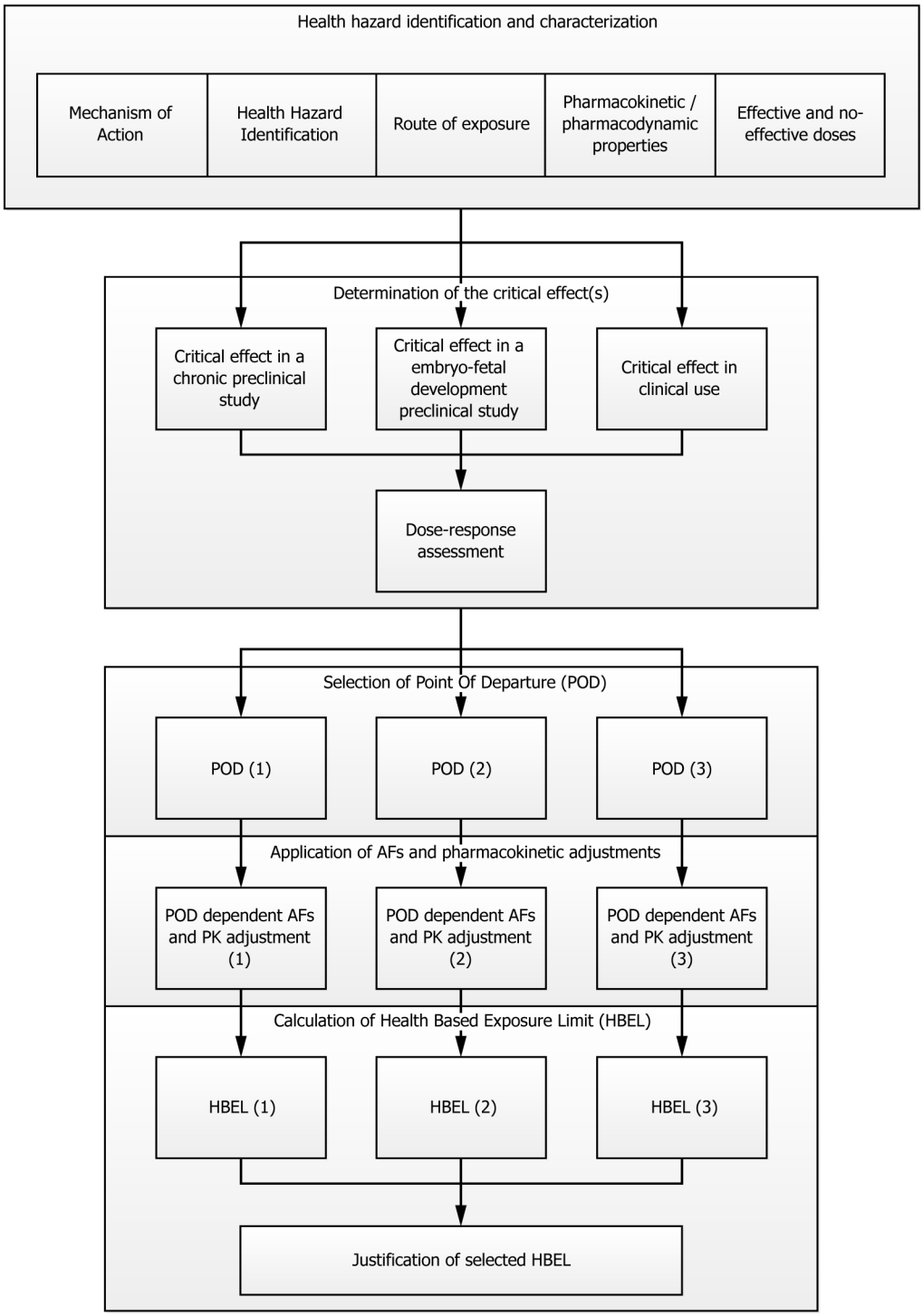

NOTE 1—This figure represents an example where three possible PoDs have been selected based on three distinctive critical effects, followed by PoD-specific application of AFs and calculation of three HBELs.

FIG. 1 Process Underlying the Calculation and Final Selection of an HBEL

hazards and understanding of the safety profile of a substance. Evaluation of the quality and validity of toxicological data are frequently conducted following the reliability scoring categories and codes developed by Klimisch et al (19). Such an evaluation is to ensure that the data being used to identify potential critical effects are of sufficient quality and validity to address the hazards of the chemical. Determining data quality may be more relevant when deriving an HBEL based on data from secondary literature searches than from using proprietary innovator data, which are typically based on original good laboratory practice (GLP) guideline studies. It is recommended if using the Klimisch criteria that the studies used to derive the critical effect should have a Klimisch score of either 1 (reliable without restriction) or 2 (reliable with restriction). Data with

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a Klimisch score of 4 (reliability not assignable) are used, a justification should be provided. Data with a Klimisch score of 3 (not reliable) should not be used. In lieu of the original studies, secondary data sources that extract information from highly reliable studies (such as found in product package inserts, investigators brochures, and so forth) are acceptable to use for identifying the critical effect. The ToxRTool Excel spreadsheet is a useful tool for evaluating studies and scoring their reliability using the Klimisch criteria (**32**).

5.4.1.2 Data quality evaluation of human epidemiological studies is far more complex given the wide variety of study designs (for example, randomized clinical trials, nonrandomized cohort studies, case-control studies, case-crossover studies, cross-sectional studies, and pharmacovigilance studies), each with a potential for biases (that is, confounding, information bias, and selection bias) that could introduce systematic errors in a study, a variety of critical appraisal tools, and elaborate methods to synthesize multiple study results through systematic reviews and meta-analyses. Nonetheless, there is no consensus or "gold standard" tool for these evaluations and no single tool that works across study types (**33-35**). Use of human data from clinical epidemiological studies that follow good epidemiologic practice guidelines (for example, GRADE, PRISMA, and CONSORT) or high-quality systematic reviews (for example, Cochrane Database Systemic Reviews) are to be preferred.

5.4.2 Drugs that have recently become off-patent have been evaluated and approved according to the up-to-date methods used to assess their safety and efficacy. Conversely, drugs that have been off-patent for decades may not have been assessed with the same rigorous methodology, especially in the preclinical phase. This may result in a data gap for certain potential adverse health effect end points that need to be addressed while assessing the data quality and reliability during calculation of an HBEL. In addition, nonclinical evaluations may be abbreviated for certain indications, such as oncology, thus also resulting in data gaps (ICH S9). To assure consistency of the HBELs, it is important to select the PoD that is reliable, while appropriately modifying certain AFs to address potential data gaps.

5.4.3 Another gap that is present when assessing certain older generic drugs is accessibility of the primary data. In many cases, only a summary is available, with no details about NOAELs identified during the nonclinical and clinical trial studies, the route of administration, or the doses is accessible. In the absence of access to the nonclinical and early clinical trial data, human data (for example, late-stage clinical trials, post-marketing surveillance/pharmacovigilance, and occasionally case reports) may be used as the PoD since a suitably large number of patients and patient populations may have been treated over the intervening years since approval. In those cases, it may be sufficient to select the PoD based on the clinical doses used to treat human patients. However, it is important to note whether susceptible subpopulations have been identified or purposefully excluded from the treatment (for example, women of child-bearing potential because of developmental toxicity concerns).

5.4.4 Literature searches for hazard characterization should be performed or reviewed by a toxicologist or other qualified risk assessment expert. Verifying the reliability of this information remains a responsibility of the qualified expert. A qualified expert can efficiently determine the literature search strategy based on the type of compound (data-rich or data-poor). The qualified expert can also determine where the data gaps occur and may either try to obtain the data, fill in the gaps as well as possible (for example, read-across, mechanism of action, and so forth), use approaches such as the Threshold of Toxicological Concern (TTC), or apply a larger AF because of increased uncertainty from lack of data (**18**). Ideally, high-quality clinical datasets are available and should be evaluated as they are generally more relevant than nonclinical studies for most adverse health effect endpoints (exceptions being developmental and reproductive toxicity, carcinogenicity) to the calculation of a human HBEL.

5.4.5 The following end points are typically available for review on a commercial stage API:

5.4.5.1 *Nonclinical Data*—A variety of dose-response and mechanistic nonclinical data are collected during API development to support a drug filing. These include single-dose safety pharmacology studies (for example, cardiac, neurobehavioral), repeated-dose studies (including developmental and reproductive toxicity studies), local tolerance, sensitization, and carcinogenicity studies. During data collection, factors related to the mechanism of action such as target receptors, potency, pharmacological effect(s), and the indication(s) for the drug product will have been characterized. The compilation of all relevant toxicological data of the substance should permit the identification of the critical effect(s) and the dose-response relationships of the observed effects in relevant nonclinical species and relevant routes of exposure. Some consideration for identifying the critical effect could include the type of effect measured, severity and reversibility of effect, human relevancy of the effect, duration of exposure (generally more weight is applied to longer versus shorter studies), species selected, route of administration, number of animals tested, type of endpoints measured, and appropriate statistical analysis.

5.4.5.2 *Human Data*—As described in 5.4.5.1, a variety of epidemiology data may be collected during development and post-approval in patients and often healthy human volunteers that support the safety and efficacy profile of an API. Where available, these human data are often of higher relevance than animal data for the same endpoints, for example, the pharmacokinetics, pharmacological effects, and adverse clinical effects (**36**). Characteristics of a robust clinical dataset for an API could include:

(1) Information on pharmacological effects and its dose dependence, the indication, and range of therapeutic doses (including those for sensitive subpopulations);

(2) Adverse effects observed at therapeutic doses and, optimally, also the dose dependence of these effects, including adverse effects at sub- and supra-therapeutic doses;

(3) Pharmacokinetics in humans including all available absorption, distribution, metabolism, and excretion (ADME) parameters in healthy and patient populations; and

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(4) Information on effects and precautions/contraindications for specific subpopulations, such as patients with severe renal or liver impairment, pregnant women, children, or the elderly.

5.5 *Identification of the Critical Effect(s):*

5.5.1 The purpose of this step is to identify the effect most likely to be relevant for the target population (patients) and target route of exposure (oral, parenteral, other). The "critical effect" has been defined as the "most sensitive adverse effect that is considered relevant to humans" (**37**) or the "first clinically significant adverse effect that is observed as the dose increases" (**29, 38**) and "the first adverse effect, or its known precursor, that occurs to the most [relevant or] sensitive species as the dose rate of an agent increases" (**39**). The critical effect shall be clinically relevant (**1-3, 40**). To evaluate the clinical relevance of an adverse effect, the similarity of effects between animal species and humans and demonstration of homology between the animal model and humans are evaluated (**41**).

5.5.2 For an API with a favorable therapeutic index, there is a large margin between doses that cause a pharmacological effect and doses that cause adverse effects. In such cases, the critical effect is often identified as the intended pharmacological activity. This follows the assumption that all effects, both intended pharmacology and unintended toxicity, are considered adverse in a potential cross-contamination scenario. In this context, "critical effect" means the lead effect that is undesired but not necessarily adverse in nature. In the context of setting HBELs, pharmacological effects are considered adverse (**37**).

5.5.3 Each identified critical effect will generally necessitate application of different AFs, meaning that the effect occurring at the lowest dose identified might not always lead to the derivation of the lowest HBEL value. It is recommended that each of the relevant, reliable, critical effects should be used to derive an HBEL (**18**).

5.6 *Determination of the PoD:*

5.6.1 The PoD determination builds upon the data collection, dose-response assessment, and identification of the candidate critical effects (**28**). It has the dimension of a dose (for example, mg/kg or mg/person). The PoD for the critical effect is used to derive the lowest HBEL relevant for human exposure. In determining the PoD, all relevant end points including nonclinical and clinical data shall be evaluated. Ideally, the PoD is based on the no-observed-adverse-effect level (NOAEL) or the no-observed-effect level (NOEL) of the most sensitive or relevant species or both for the critical effect(s) [ICH Q3C(R6)(**37**). When a NOAEL or NOEL are not available, the lowest-observed-effect level (LOEL) or the lowest-observed-adverse-effect level (LOAEL) can be used as a PoD.

5.6.2 The NOAEL approach has its limitations including: (*1*) the identification of NOAEL values is limited by the doses tested; (*2*) the NOAEL may not represent a true 0 % response (that is, because of sample size considerations, a study may not have sufficient power to detect an adverse effect "signal"); (*3*) the NOAEL is highly dependent on sample size; (*4*) NOAELs are not always available; and (*5*) it does not consider the dose-response curve or data variability and, thus, "wastes" data (**6, 42**). Where feasible, the benchmark dose (BMD) method is preferred to the traditional NOAEL/LOAEL approach as it corrects for these limitations (**4-6, 43-48**). The BMDL is typically considered equivalent to the NOAEL. The BMDL is dependent on the benchmark response (BMR), which is based on the sensitivity of the study, and in many cases, the BMR is considered to be 10 % over background of effect. The goal of a BMD is to fit a model to the dose-response data, and it represents an acceptable alternative to the NOAEL assessment factor approach for deriving an HBEL (**42, 49**).

5.6.3 The typical dosing schedule for a pharmaceutical should be considered during HBEL extrapolation. For APIs administered at least twice daily, the HBEL is expressed as the total daily human therapeutic dose. However, the potential for acute health effects from a single dose (C_{max}-mediated effects) has to be considered, as a single dose may have a clinically relevant effect that is the critical effect. For APIs administered with dosing intervals greater than once daily (for example, routine dosing schedules such as once weekly or once monthly as is commonly seen for biologic drug products and some small molecules), generally a PoD as a prorated daily dose can be used (that is, the single dose divided by the number of days between doses). For APIs that are not routinely chronically administered to an individual patient, but rather on an ad hoc basis (for example, vaccinations, surgical or certain medical procedures), the PoD should be evaluated on the basis of the available data with AFs incorporated as appropriate to reflect potential chronic exposure for derivation of an HBEL. In these cases, or where the dosing schedule is intermittent or otherwise, the PoD is not a dose at steady state, the PK AF may be used instead of daily dose averaging. Where applicable, PK or PD can also be used to inform the derivation of a daily dose or a pharmacologically ineffective dose that can be used as a PoD (**18, 50**).

5.6.4 The body weight and other dosing parameters (for example, body surface area for a topical drug) may change depending on the route of exposure being evaluated for establishing a limit, as well as for the regulatory jurisdiction. For the general population, the body weight used can be conservatively set to a small adult person of 50 kg (**14, 29, 51, 52**). Other jurisdictions may use alternative values for adults and different pediatric populations (**53-56**). The European Medicines Agency (EMA) has stated the "derivation of limits will need to take account of the dose to be administered, which will be influenced by the body weight of the species to be treated" (**14**). If assessing alternative populations or exposure routes (for example, infants), consult an appropriate reference (**53-56**). In a draft document, EMA has suggested consideration of body weight values for three pediatric populations: 0.5 kg for a prematurely born newborn, a 3.5 kg newborn, and 10 kg for a child (**57**).

5.6.5 Regarding body surface area, the EPA guidance provides mean and 95th percentile estimates of the total body surface area for children and adults ((**56**), Table 7.1). For adults, mean total body surface area values are on the order of 2 m^2 (20 000 cm^2). The FDA assumes a 1.62 m^2 body surface area for a human adult of 60 kg, therefore, for a 50 kg adult, the body surface area would be 1.35 m^2 (**58**).

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5.6.6 For certain protein therapeutics, guidance is available for first-in-human (FIH) dose selection, which represents a dose that is expected to have no clinical effect (**59-61**). This includes estimating the minimum anticipated biological effect level (MABEL) from PK/PD modeling. The FIH dose may serve as a surrogate PoD pending collection of clinical data.

5.7 *Application of AFs:*

5.7.1 The purpose of the application of AFs is to adjust for uncertainty and variability in the various parameters measured in the critical study compared to effects that may occur in the population targeted by the HBEL assessment. Synonyms include assessment factors, uncertainty factors, safety factors, and modifying factors [ICH Q3C(R6)] (**14, 62**). Eq 11 in 6.1 provides the basic equation for the determination of an HBEL.

5.7.2 The use of AFs should not be obligatory or limiting but rather follow scientific evaluation of the available dataset taking into consideration possible case-by-case specifics of different substances. It is important to evaluate the database in a holistic manner determining strengths and weaknesses that are relevant to the overall assessment. Each substance and database present a unique set of issues that shall be evaluated critically and thoughtfully (**41**). All factors relating to the data need to be considered in view of uncertainties in and reliability of the data.

5.7.3 AFs address the various uncertainties allowing for extrapolation to a reliable and robust NOAEL in humans (**14**). Uncertainty with the PoD arises from the following: when the study is not conducted in the same species as the target population (that is, rats versus humans), it does not cover the variability in the human population; a NO(A)EL is not available; all relevant effects are not studied; only short-term studies are available; severe effects are observed at the lower dose(s) studied; differences in bioavailability are expected because of differences in the exposure route; or other types of uncertainty are present.

5.7.4 The AFs, with the exception of compound-specific adjustment factors (CSAFs), should not be regarded as absolute values of uncertainty but rather as estimates of those uncertainties. A value is selected from a range, generally from 1–10, based on degree of variability in the data, and data-driven CSAF values in excess of 10 may be occur because of larger than expected variability in PK and PD in the human population. Professional scientific judgment and, if possible, peer review of the available data should be applied to yield a consensus in the selection of each AF. Care should be taken not to adjust for the same uncertainty in two factors. For the selection of the following AFs, the rationale should be provided in detail and justified for each calculation.

5.7.5 Sources of variability, uncertainty, and additional adjustments that are typically addressed in a quantitative risk assessment include, but may not be limited to, the list in Table 1.

5.7.6 The list in Table 1 is rather a compilation of terminology on factors and does not indicate that all should be used for each PoD. The specific AFs used on an organizational basis should be described procedurally to demonstrate consistency between documents.

5.8 *Pharmacokinetic Adjustments:*

5.8.1 *Absorption Factor (α, PK-ABS):*

5.8.1.1 The absorption factor (also called α or PK-ABS) is used to correct for differences in absorption between the route of exposure used in the study that the PoD is from and the route of exposure in the population being assessed (**65**). Eq 1 can be applied to determine α.

$$\alpha = F_{HBEL}/F_{PoD} \quad (1)$$

where:

F_{PoD} = Bioavailability fraction from the administration route used in the study that the PoD was derived from and

F_{HBEL} = Bioavailability fraction for the administration for which the HBEL is being established.

5.8.1.2 For example, if the PoD is from a study in which the route of exposure was IV and the HBEL is being established for the oral route of exposure for a small molecule in which the oral bioavailability is 0.2 and IV bioavailability is 1.0, then note Eq 2-4 (**50**):

$$F_{PoD\text{-}ORAL} = 0.2 \quad (2)$$

$$F_{HBEL\text{-}IV} = 1.0 \quad (3)$$

$$\alpha = F_{HBEL}/F_{PoD} = 1.0/0.2 = 5.0 \quad (4)$$

5.8.1.3 Other parenteral routes (for example, subcutaneous, intramuscular) may not provide the same exposure as the IV route. The bioavailability of other routes should be given as relevant to IV (that is, absolute bioavailability) for a $HBEL_{IV}$.

TABLE 1 Adjustment Factor Terminology from Various Guidelines

Adjustment Factor	AF (**14, 52**), ICH Q3C(R6)	AF (**41, 62, 63, 64**)
Pharmacokinetic adjustments that is, bioavailability correction, bioaccumulation, PK, PD)	---	PK
Interspecies extrapolation (that is, differences in pharmacokinetics and pharmacodynamics between animals and humans)	F1	UF_A
Intraspecies/Interindividual variability (that is, variability in human susceptibility)	F2	UF_H
Exposure length (that is, extrapolation from short-term to chronic dosing)	F3	UF_S
Severity of effect	F4	---
LO(A)EL-to-NO(A)EL extrapolation	F5	UF_L
Database completeness	---	UF_D
Modifying factor	---	MF
Composite adjustment factor	---	UF_C

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