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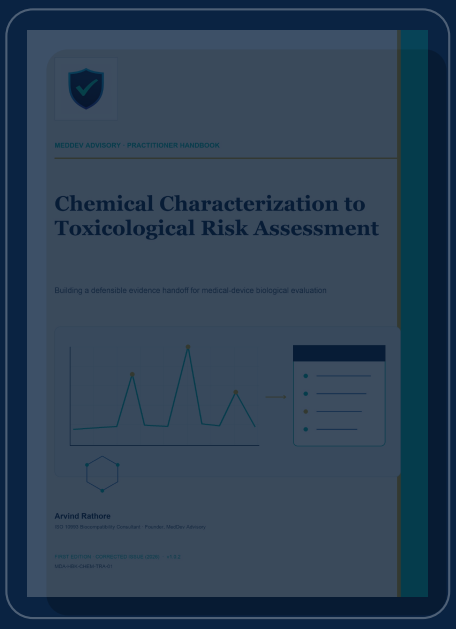
Chemical Characterization to Toxicological Risk Assessment

Arvind Rathore

First edition · corrected issue · v1.0.2 · available by written offer | MDA-HBK-CHEM-TRA-01



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This preview shows selected non-consecutive pages that demonstrate the writing, contents, figures and evidence-control method.

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CURRENT PUBLICATION STATUS

www.meddevadvisory.com/chemical-characterization-toxicological-risk-assessment-handbook

Contents

How to use this book

The operating idea

Treat the chemistry-to-TRA handoff as a traceable chain of decisions:

1. Define the exact device, variants, finished state, use, population and biological question.
2. Assemble enough product-chemistry and process knowledge to know what the study is meant to investigate.
3. Select an article and experimental model that can answer the stated question, with important limitations visible.
4. Understand the analytical coverage, controls, thresholds, identities, quantities, blanks and uncertainty behind the reported results.
5. Translate supported analytical results into reproducible exposure scenarios without confusing experimental extraction with clinical exposure.
6. Give a qualified toxicologist the device, analytical, exposure and uncertainty information required for defensible judgment.
7. Integrate the bounded toxicological contribution with other biological, clinical and post-market evidence.
8. Reopen the assessment when the device, process, use, evidence or source status changes.

This is not a universal algorithm. Some activities overlap or repeat. Its value is that it makes broken links difficult to hide. When the team cannot explain one link, it has found a question to resolve—not a sentence to make more confident.

Reading routes

Commissioning a new chemical-characterization study. Read Chapters 1–8, then Chapters 11–12 before finalizing the brief. The intended toxicologist should be involved before the data package is fixed.

Reviewing a completed laboratory report. Begin with Chapters 2, 5 and 7–11. Continue to Chapters 12–17 if the report will support a qualified TRA.

Preparing or reviewing a toxicologist handoff. Read Chapters 1–3 and 8–17. Pay particular attention to identity confidence, unit lineage, exposure scenarios, unknowns and the distinction between local and systemic questions.

Remediating a weak chemistry-to-TRA file. Read Chapters 1, 3, 7–12 and 17–18. Reconstruct the device and evidence chain before defending the existing conclusion.

Assessing a supplier, material or process change. Read Chapters 2–5, 9–12 and 18. Compare the approved and candidate states at the level that could alter chemical release or exposure, not only at the material trade-name level.

Preparing FDA-facing evidence. Read the relevant scientific chapters first, then the FDA section in Chapter 18. Keep FDA's final guidance, current recognition records and the still-draft chemical-analysis guidance distinct.

Leading RA/QA oversight. Read Chapters 1–3, 7–12 and 17–18. Focus on governance, competence, handoff quality, evidence provenance, change triggers and release decisions.

Current source-status orientation

At the 1 September 2026 baseline:

- ISO 10993-18:2020 remained the current published second edition and had Amendment 1:2022. FDA recognition record 2-298 covered that edition and amendment only partially and identified exclusions that matter to analytical interpretation.
- ISO 10993-17:2023 was the published second edition and had Amendment 1:2025. FDA recognition record 2-303 covered the 2023 base edition partially; the live record did not list Amendment 1:2025 and recorded a transition from the older recognized edition until 20 December 2026.
- ISO 10993-12:2021 had Amendment 1:2025. Its ISO lifecycle record showed Stage 90.60 after the 2026 review closed, while the edition remained published; the public record did not display a confirmation, revision or withdrawal outcome. FDA recognition record 2-314 listed complete recognition of that amended designation and a transition for the prior recognition until 1 July 2029.
- ISO 10993-1:2025 was current. FDA recognition record 2-313 was partial and showed a database entry date of 25 May 2026. Recognition List 066 made the relevant list modification applicable on 24 August 2026. The record permits declarations of conformity to the prior recognized 2018 edition in support of premarket submissions until 1 July 2029, subject to the record's exact scope and qualifications.
- ISO 10993-3:2026 was published on 6 August 2026 and superseded ISO 10993-3:2014 and ISO/TR 10993-33:2015. That publication status does not by itself establish FDA recognition, EU harmonisation, CDSCO adoption or a device-specific endpoint conclusion. This corrected issue does not infer clause-level or method changes; lawful access and qualified review are required before controlled application.
- FDA's September 2023 ISO 10993-1 guidance was final and nonbinding. FDA's September 2024 Chemical Analysis for Biocompatibility Assessment document remained draft and not for implementation.
- The current consolidated EU Medical Device Regulation text was dated 19 July 2026. The current consolidated version of Commission Implementing Decision (EU) 2021/1182 on MDR harmonised standards was dated 17 June 2026. Exact EN designations, amendments, dates and limitations still require direct review; harmonised-standard use remains voluntary and any presumption is limited to what the applicable listing covers.
- India's Medical Devices Rules and current CDSCO material require a separate, current pathway assessment. FDA recognition or EU harmonization does not automatically establish Indian acceptance.

These statements are orientation, not a substitute for the live records. A source can change between publication of this book and a real project decision. The controlled source register supplied with the publication records the public status sources, limitations and review triggers.

- **Bounded biological-evaluation use** prevents a toxicological conclusion from becoming a universal declaration that the device is safe or that no other evidence is needed.

The decision statement is successful when it can guide laboratory planning, toxicologist scoping, report review, and downstream integration. It should also make it possible to stop. If the device state cannot be established, if the reported units cannot be reconstructed, or if no appropriately qualified reviewer is assigned, the responsible outcome may be a controlled open question—not a forced conclusion.

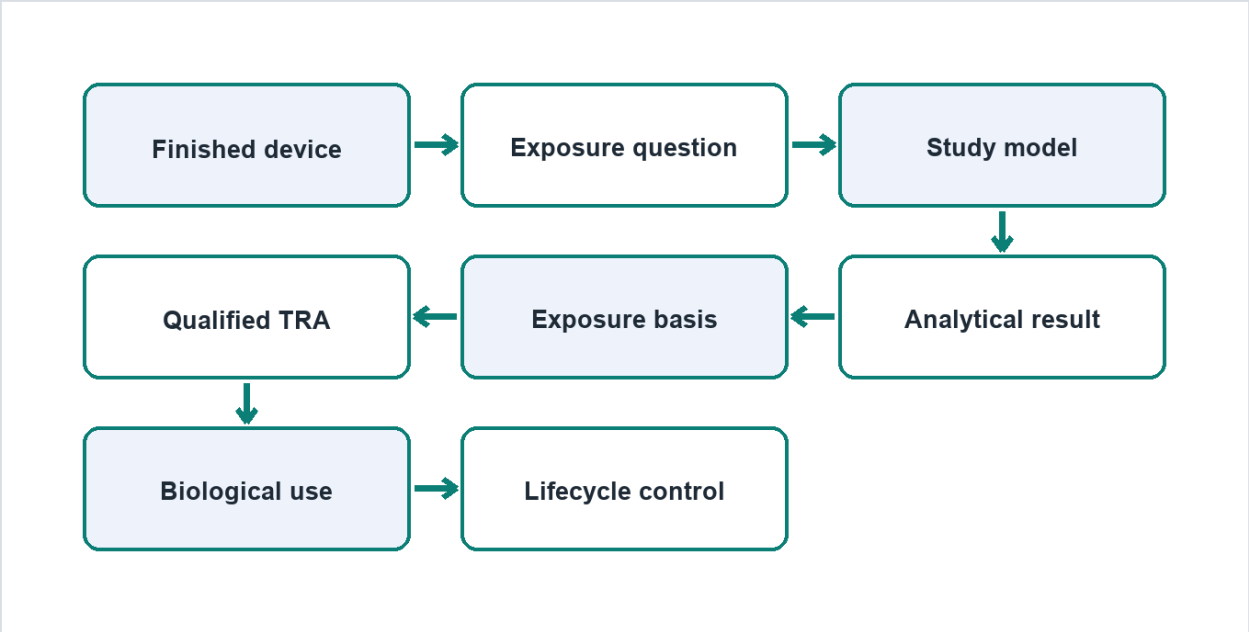

Figure 1. The chemistry-to-TRA evidence chain

Why plausible work still fails

The deliverable is mistaken for the decision

Teams purchase “an ISO 10993-18 study” or “an ISO 10993-17 TRA” as though the title itself defines the scientific job. Standards and current regulator sources inform the work, but a study label does not identify the device question, the represented article, the analytical coverage, the exposure scenario, or the conclusion boundary. A laboratory can complete the quoted scope while the manufacturer’s real uncertainty remains unresolved.

Product reality is compressed into a sample description

The sample form may contain a model name and lot number. The biological-evaluation decision may concern a family with several lengths, coatings, connector counts, colors, manufacturing routes, sterilization conditions, shelf-life states, accessories, or use patterns. Unless the difference between the sample and the decision population is assessed, the sample description becomes an untested family bridge.

Each discipline receives only a reduced output

Engineering sends a product name to the laboratory. The laboratory sends a constituent table to the toxicologist. The toxicologist sends a conclusion paragraph to regulatory. Regulatory places the paragraph into the BER or submission. At every transfer, context disappears: manufacturing state, blank findings, identification confidence, calibration basis, conversions, use frequency, method blind

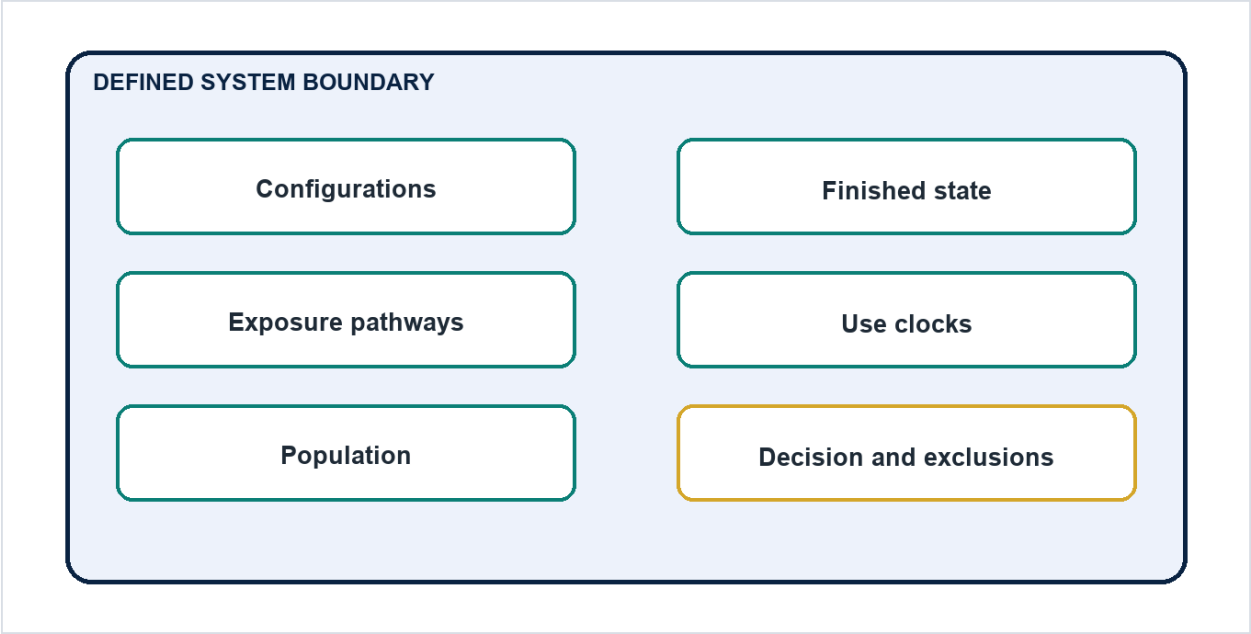

Figure 2. Freeze the device, use and population boundary

Where boundary definitions go wrong

A family name replaces configuration control

A commercial family can contain variants in size, material, color, coating, adhesive, component count, manufacturing route, sterilization, packaging, or use. The label may be convenient for sales and inventory yet scientifically uninformative. Unless the variations are mapped, an article selected from the family cannot be called representative with confidence.

Contact categories replace exposure pathways

A contact description is useful orientation, but it does not capture every route by which a device-related substance can reach a patient or user. A component outside the body may contribute through a delivered-fluid path. A non-contacting ink may be irrelevant—or may sit next to a pathway where transfer requires investigation. A coated surface may expose tissue during insertion differently from long-term residence.

The task is not to classify every conceivable pathway as real. It is to identify plausible, decision-relevant routes and state the evidence supporting or refuting them.

One duration hides several clocks

Device dwell time, material-to-fluid contact time, patient exposure, repeat replacement, cumulative treatment, and delayed release can be different. A catheter assembly may contact a fluid briefly before the fluid enters the patient while remaining connected for hours. An adhesive electrode may be worn for a day and replaced repeatedly over weeks. An implant may create an early insertion exposure and a different long-term interface.

Using one duration label for all these clocks can distort study design and exposure interpretation.

The nominal use case becomes the only use case

The marketing description often emphasizes one device and one procedure. Actual labeled use may involve several units, bilateral use, replacements, accessories, repeat visits, or a course of

constituents. Its meaning depends on article preparation, extraction media, ratio, time, temperature, agitation, replenishment, controls, and method coverage.

An extractables result is neither “unrealistic” by definition nor a direct clinical measurement by default. It can be a powerful source-identification and bounding input when the relationship between the model and the decision is explained. Describing conditions as exaggerated does not automatically prove that the result bounds every clinical release mechanism.

Leachables or use-related release: what transfers under defined use conditions?

A leachables or simulated-use investigation measures substances released under conditions intended to represent part of use more directly. It can support time-specific exposure estimates and reduce uncertainty introduced by translating an aggressive extract. Its strength depends on how well the selected medium, flow, temperature, duration, replenishment, device preparation, and sampling represent the clinical question.

Use-related work is not automatically comprehensive. A clinically relevant condition may release small amounts that challenge analytical sensitivity. It may cover one use period but not repeated use, late release, aging, or a different population. A study can be realistic for one pathway and silent about another.

Degradation: what is created or released as the device changes?

Degradation questions concern products or chemical states created through hydrolysis, oxidation, corrosion, dissolution, wear, metabolism, environmental interaction, or other time- and mechanism-dependent change. The relevant article, medium, stress, time point, and analytical approach may differ from a general new-device extraction.

Degradation can also involve particles, morphology, mechanical performance, and local tissue interactions that are not resolved by a dissolved-constituent assessment. A chemical dataset may inform one part of the evaluation while materials, mechanical, pathology, clinical, or other specialist evidence addresses the rest.

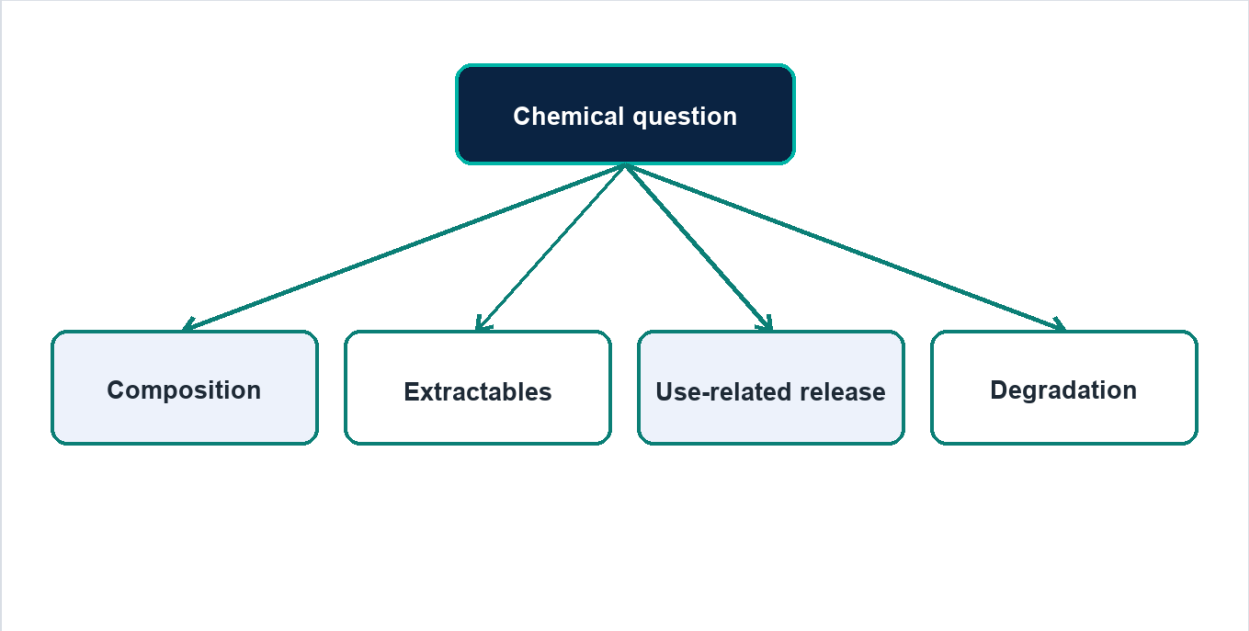

Figure 4. Different chemical evidence answers different questions

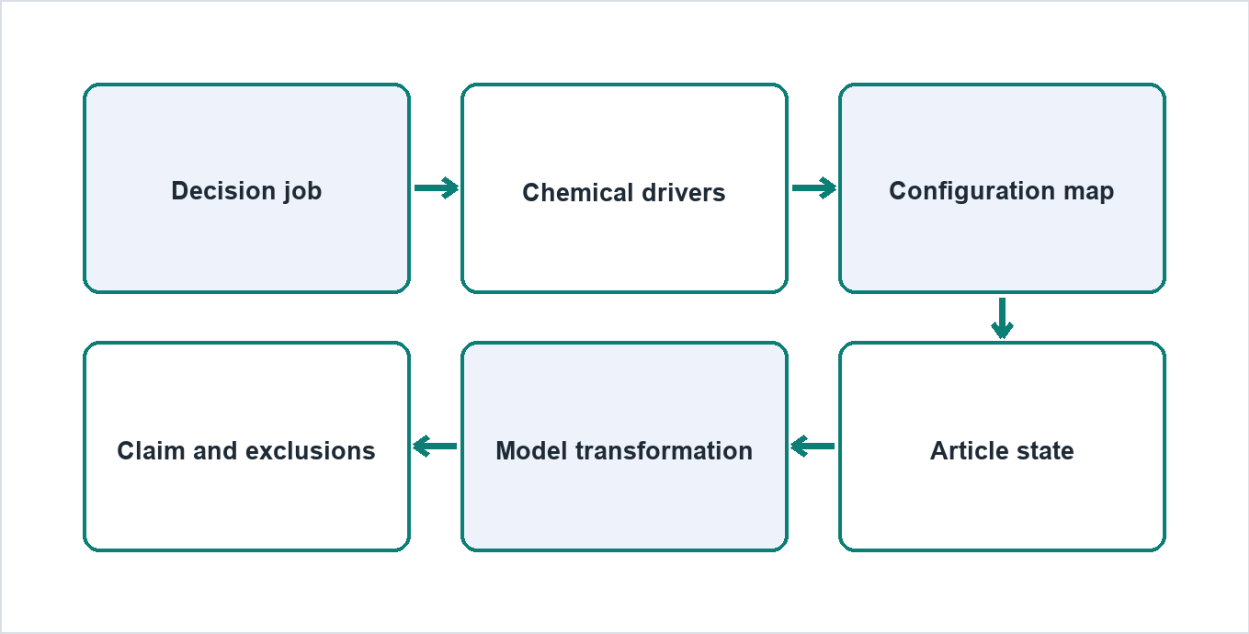

Figure 5. Question-led representative-article selection

Why familiar selection rules fail

Largest is treated as worst for every contributor

The longest fluid path may contain the most tubing but fewer connectors. The greatest implant surface may have a lower coating-to-mass ratio. The larger adhesive patch may deliver more total material while the smaller size is used in a lower-body-mass population. “Largest” should be translated into the specific dimension it challenges.

Unique constituents are diluted by family averages

A colorant, coating, adhesive, printing step, lubricant, or supplier may appear in only one configuration. A high-total-mass article without that contributor cannot represent the unique chemical question. Pooling across configurations can conceal which article produced a result and can dilute a unique feature.

The study state is assumed from the product name

A sample may be assembled from production components but unsterilized, outside final packaging, unaged, or processed through a development route. The report’s use of a commercial model name does not prove that the article reflects the released state.

Cutting and disassembly are treated as neutral

Preparing a device for extraction can expose non-clinical surfaces, disrupt coatings, open sealed interfaces, remove barriers, change surface area, or exclude assembly interactions. These transformations may be scientifically justified. Their effect on the question should be explained.

Component work is described as whole-device evidence

Testing a component can isolate a source and improve sensitivity. It may omit manufacturing residues, interfaces, combined construction, sterilization, packaging, and interactions introduced during assembly. The result should be used for the component question it can answer.

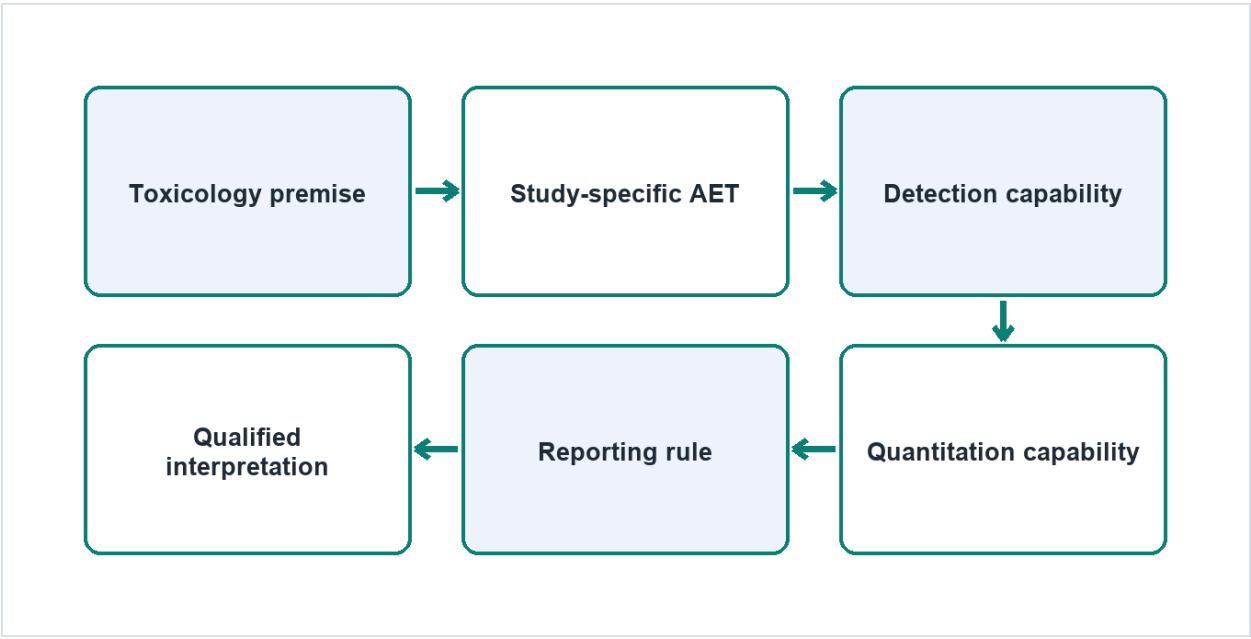

Figure 8. Threshold roles must remain separate

Four roles that must remain separate

Analytical evaluation threshold

An analytical evaluation threshold, commonly abbreviated AET, is used within a chemical-characterization framework to help determine the analytical level above which a detected constituent ordinarily requires identification and quantitation for the intended toxicological process, subject to the governing source, its scope, and appropriate qualifications.

The AET is not a device-safety limit. It is not an exposure limit for a named substance. It does not prove that a constituent below it is harmless, absent, or irrelevant. Its derivation can depend on the selected toxicological premise and on study-specific exposure and analytical inputs. If those inputs do not represent the device and use, the apparent precision of the number is misleading.

This book does not reproduce a protected AET formula or select a toxicological threshold route. Readers must use lawful current sources and qualified toxicological and analytical review.

Limit of detection

An LOD is a method-related expression of the ability to detect an analyte or signal under defined conditions. The exact definition and estimation approach must come from the laboratory's controlled method and applicable sources. An LOD is not automatically a reliable quantitation level, not necessarily uniform across every possible analyte, and not proof that a substance is absent when no signal is reported.

Limit of quantitation

An LOQ is a method-related expression of the level at which quantitation is supported under stated performance conditions. Again, the laboratory must define the term and method. A value reported below an LOQ may carry a different evidentiary status from one above it; a signal below the LOQ is not automatically meaningless. The correct treatment depends on the method, data, purpose, and qualified assessment.

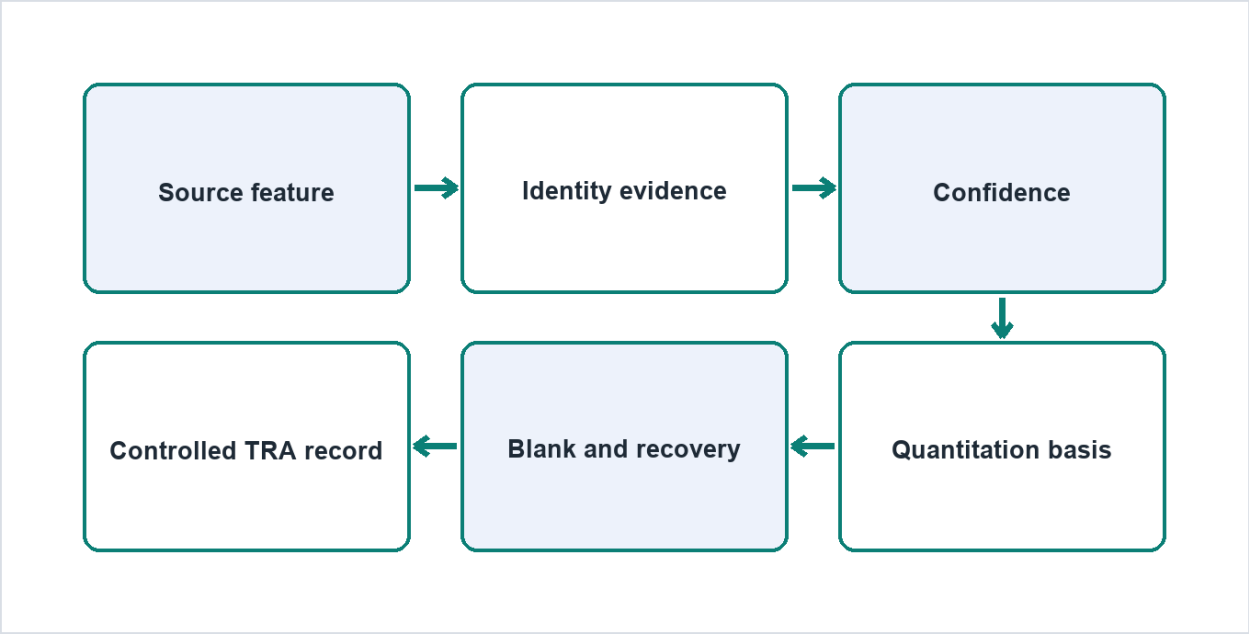

Figure 9. Identity and quantitation lineage

Identity confidence is evidence, not a polished name

A feature begins as an observation produced by a defined method, sample, and data-processing rule. The laboratory may then propose an identity using retention behavior, spectral information, libraries, accurate-mass evidence, elemental information, authentic materials, or other method-appropriate evidence. The exact evidence and confidence language belong to the laboratory's controlled practice.

For review purposes, it is useful to distinguish broad evidentiary states without pretending they form a universal standard hierarchy:

- **confirmed under the stated method:** the report describes direct, method-appropriate evidence against a suitable authentic reference or another justified confirmation route;
- **well-supported proposed identity:** multiple lines of evidence support the assignment, but the report does not claim full confirmation;
- **tentative or provisional identity:** limited evidence supports a plausible assignment and meaningful alternatives may remain;
- **unidentified feature:** a reproducible or reportable signal exists, but a defensible chemical identity has not been established.

These labels are editorial aids only. The controlled record must retain the laboratory's actual terminology and criteria. A device team must never upgrade "tentative" to "identified" because a proposed name is useful for a hazard search.

Identity can also exist at different levels. A report may support a molecular formula but not a unique structure, a chemical class but not a named compound, an isomeric group but not one member, or an element without a chemical species. The downstream assessor needs the level actually supported.

Quantitation basis is part of the result

An amount is inseparable from how it was obtained. Common analytical situations include:

- analyte-specific measurement using a suitable authentic standard;

- investigating an unexpected signal or complaint; or
- identifying gaps that require further analytical work.

Avoid a single, permanent “fit/unfit” label detached from purpose. It encourages later users to extend the dataset beyond the boundary that was actually assessed.

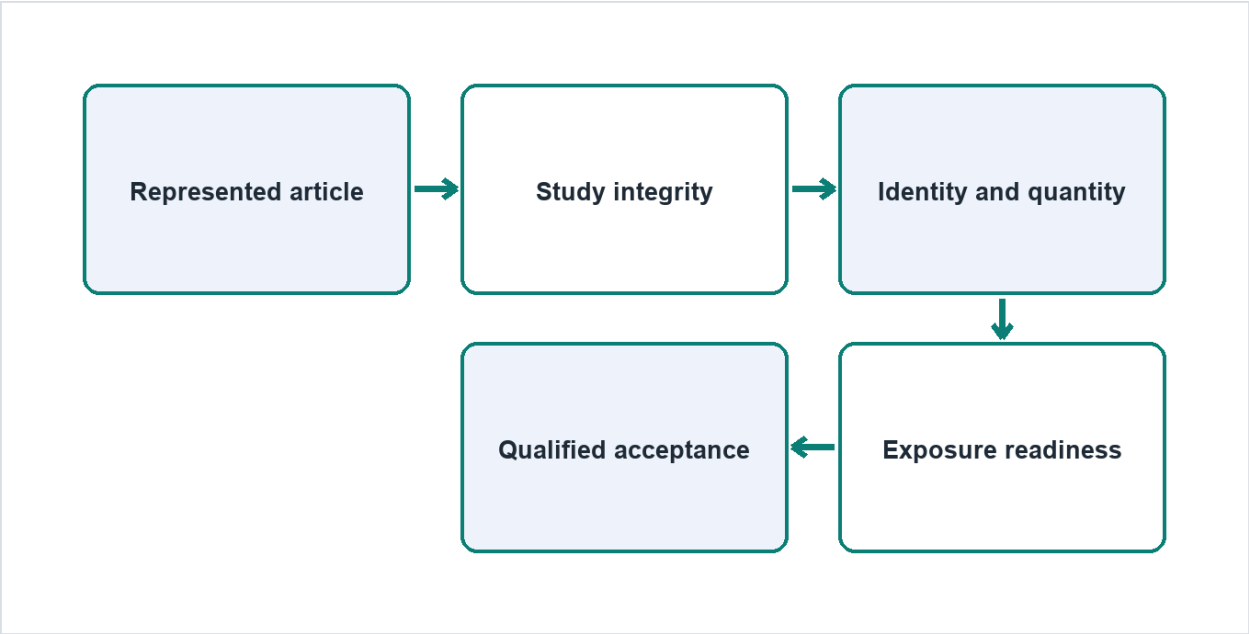

Figure 11. Dataset fitness is decision-specific

Where the handoff breaks

Report completion is mistaken for decision readiness

The laboratory issued a final report, signatures are present, and every planned instrument run is listed. The team concludes that the dataset must be ready for TRA. Report completion establishes that a contracted scope was reported; it does not establish that the scope represented the final device or supplied the information needed for the current toxicological question.

The report is reviewed one table at a time

Reviewers inspect constituent names and amounts without first confirming the tested article, preparation, extraction, or normalization basis. A precise result attached to the wrong article state remains wrong for the decision, however neatly it is tabulated.

Missing lineage is treated as an administrative gap

A lot number, sterilization confirmation, aging condition, or component count may look like document housekeeping. Each can change what the result represents and how it is scaled. If lineage cannot be verified, that uncertainty belongs in the scientific decision.

The toxicologist is expected to repair analytical ambiguity

The handoff includes tentative identities as confirmed substances, estimated concentrations without calibration basis, and totals after undocumented blank subtraction. These are analytical questions. Toxicological expertise cannot convert missing analytical provenance into fact.

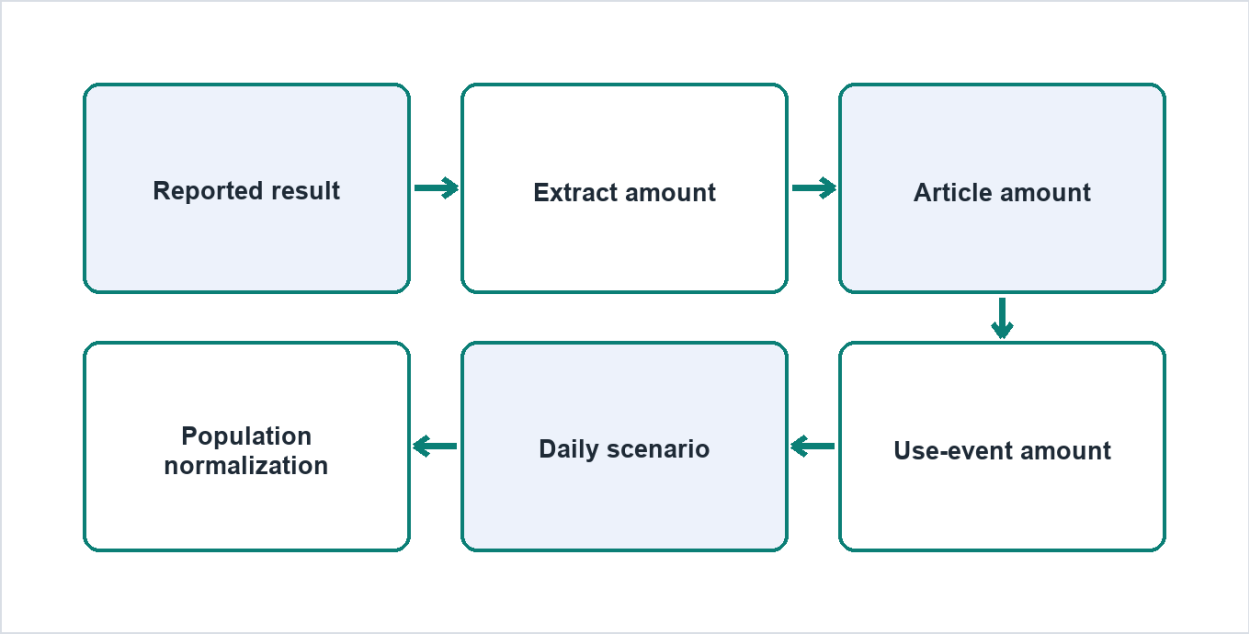

Figure 12. Traceable exposure-unit chain

Where exposure models go off course

Units disappear after the first calculation

The laboratory reports micrograms per milliliter. A spreadsheet produces micrograms per kilogram per day, but intermediate units are hidden. Reviewers cannot see whether milliliters, article count, daily use, and body mass canceled correctly.

The article denominator is assumed

A pooled extract contains several devices, components, or cut pieces. The reported concentration is divided by the number in the vessel even though the articles differ, only part of each article was tested, or the laboratory already normalized the result. The same divisor may be applied twice.

Extraction is confused with release

A study designed to generate potential extractables under defined conditions is treated as a direct clinical leachables measurement. The numerical conversion may be reproducible, but the conceptual bridge is unsupported.

“Worst case” is attached to a single input

Lower body mass, higher device count, complete release, longer duration, and maximum article contribution are combined automatically. Some combinations may be possible; others may describe no real use pattern. A scenario must be plausible and decision-relevant, not merely the product of every largest numerator and smallest denominator.

Time is averaged before the biological question is understood

A high first-day exposure is spread across months, or an intermittent exposure is treated as continuous. Averaging can erase a relevant peak. Conversely, treating a finite course as lifelong daily use can distort applicability. The toxicological question determines the time construct.

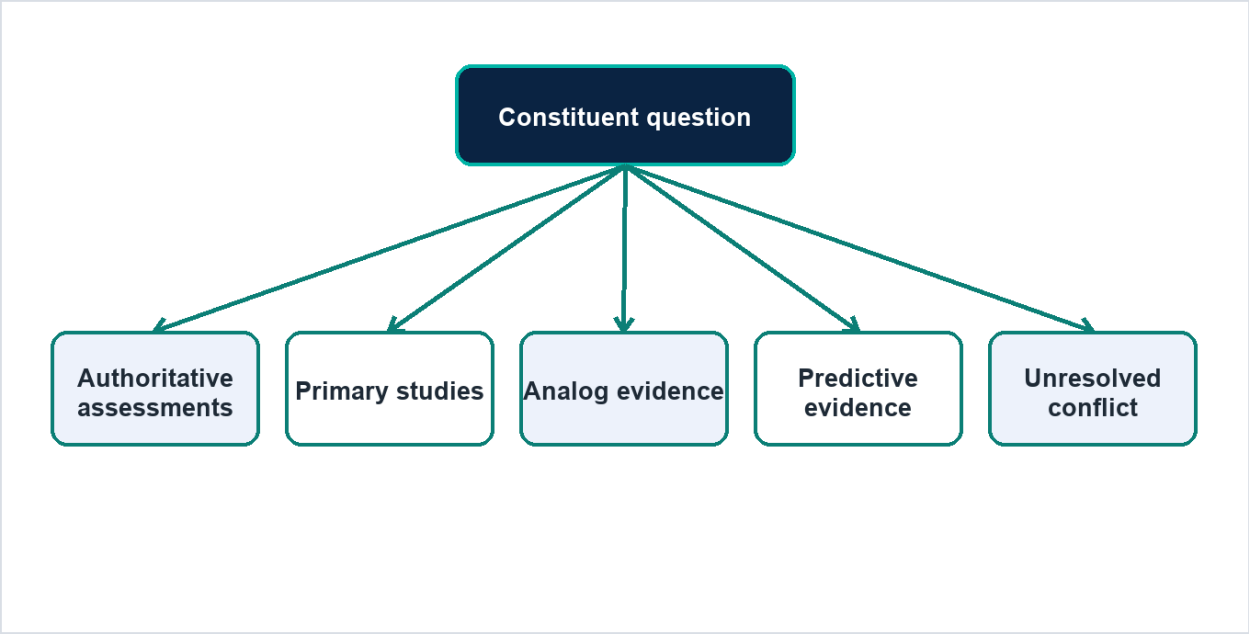

Figure 13. Hazard evidence must retain context

Where hazard research loses its footing

The search begins before identity is stabilized

A tentative library match is entered as a confirmed substance. The researcher finds extensive information for that name, but the underlying analytical feature could be an isomer, salt, reaction product, mixture, or different compound. Research volume cannot compensate for identity error.

A CAS number is treated as unique truth

Registry identifiers are helpful but not infallible. Different forms, hydrates, salts, stereochemistry, mixtures, or commercial substances may be confused. A name and CAS number should be checked against formula, structure, analytical evidence, source material, and device context as appropriate.

A source hierarchy becomes a mechanical ranking

An authoritative assessment can provide a valuable synthesis but may address an occupational or environmental scenario unlike the device exposure. A primary study may be more directly relevant but require detailed quality appraisal. Source type informs confidence; it does not eliminate applicability review.

A limit is copied without its derivation

The spreadsheet records a value and unit but omits critical effect, point of departure, route, duration, population, uncertainty factors, averaging basis, date, and issuing body. The number becomes impossible to interpret or update responsibly.

Secondary summaries replace the underlying evidence

A commercial database or review article may help locate sources. If its summary is used without verifying the primary or authoritative record, qualifiers and revisions can disappear. Access convenience should not determine evidentiary authority.

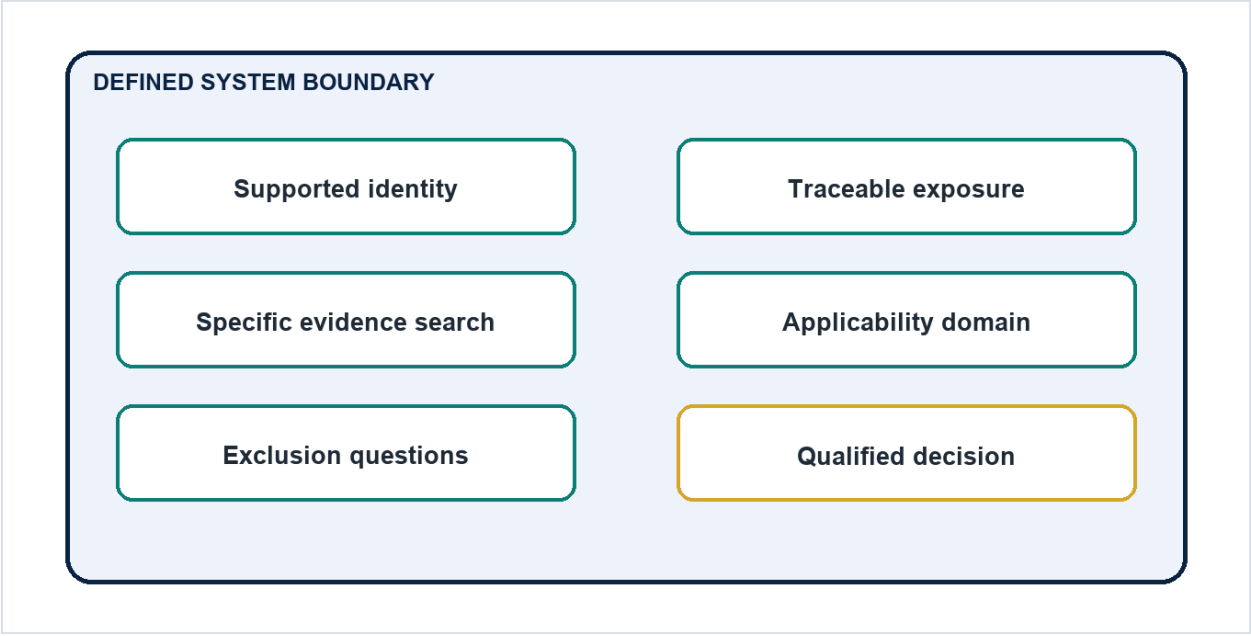

Figure 15. TTC eligibility is a qualified boundary

Where TTC becomes a shortcut

TTC is introduced as a fixed safety limit

A spreadsheet contains one threshold for every detected constituent. The user compares mass per day with the cell and assigns pass or fail. Identity, structure, route, duration, population, and exclusions never enter the decision.

Analytical and toxicological thresholds are merged

An analytical evaluation threshold or reporting rule is described as though it were a final toxicological threshold. Analytical thresholds govern detection, reporting, or investigation under defined assumptions. TTC belongs to toxicological reasoning. The two may interact in study design, but they do not perform the same job.

Unknowns are given an identity by category selection

An unidentified feature is placed into the least restrictive category because no structural alert is known. Absence of an identity means the team may also lack the information needed to assess alerts, exclusions, or domain membership. Ignorance is not favorable evidence.

A structural classification is delegated to software

A program returns a class or threshold route. The team accepts it without checking structure input, ionization or salt form, stereochemistry, mixtures, model version, domain, alerts, or expert interpretation. Automation can assist a controlled analysis; it cannot own the toxicological decision.

Exposure is compared on the wrong basis

The threshold concerns one time, route, or population basis while the device exposure is averaged or normalized differently. A numerical margin appears only because the denominators do not match.

Appendix F — Controlled source baseline and watch list

The release package includes a controlled source register with public source status, checked date, limitation and recheck trigger. The following are the main public starting points; they do not replace lawfully obtained standards or device-specific review.

International standards status

- ISO 10993-18:2020 catalog record and Amendment 1:2022
- ISO 10993-17:2023 catalog record and Amendment 1:2025
- ISO 10993-12:2021 catalog record and Amendment 1:2025
- ISO 10993-1:2025 catalog record
- ISO 10993-3:2026 catalog record — published 6 August 2026; supersedes ISO 10993-3:2014 and ISO/TR 10993-33:2015; consult a lawfully obtained copy and qualified specialists before controlled use
- ISO 14971:2019 catalog record
- ISO/TS 21726:2019 catalog record

United States

- FDA final biocompatibility guidance, September 2023
- FDA draft chemical-analysis guidance, September 2024
- FDA recognition record 2-298 for ISO 10993-18
- FDA recognition record 2-303 for ISO 10993-17
- FDA recognition record 2-314 for ISO 10993-12
- FDA recognition record 2-313 for ISO 10993-1
- FDA Recognition List 066 notice — modifications applicable 24 August 2026
- FDA recognition record 2-268 for ISO/TS 21726
- FDA CDRH chemical-characterization methods dataset
- FDA recognized consensus standards database

European Union and India

- EU Medical Device Regulation, consolidated text dated 19 July 2026
- Commission Implementing Decision (EU) 2021/1182, consolidated text dated 17 June 2026
- CDSCO Medical Devices Rules index
- Medical Devices Rules, 2017 — CDSCO-listed 15 February 2023 compilation, amended in that file through 14 October 2022; read with later final amendments

Immediate review triggers

Reassess affected content if FDA finalizes, revises or withdraws the 2024 draft; an FDA recognition record, list-applicability date or transition changes; ISO publishes or revises a relevant edition; EU harmonisation changes; India issues material new requirements; or credible scientific, regulator, reviewer or customer evidence reveals a defect that could alter the advice.

The public Maintenance Passport and errata record should state what changed, what did not change and what action an entitled reader should consider.

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- Decision-led writing and original figures
- Contents, professional boundaries and source-control discipline

WHAT IT DOES NOT PROVIDE

- The complete handbook, an authorized standard or a customer licence
- A device-specific analytical, toxicological, quality or regulatory conclusion
- A guarantee of regulator, notified-body or market outcome

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