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MEDDEV ADVISORY · PRACTITIONER HANDBOOK

The Biological Evaluation Strategy Handbook

Independent practical guidance for medical-device biological evaluation, evidence assessment, risk-based decision-making and documentation

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The fictional cases in this book are composites created for education. Names, configurations, evidence, decisions, and reviewer questions are invented and assumption-based. They are not customer matters, successful submissions, precedents, or recommendations for a real device.

How sources are treated

This book distinguishes five kinds of authority:

1. **Law and regulation.** Binding text within its legal scope. A consolidated text can be convenient for reading, but the authentic legal acts and applicable national rules remain controlling.
2. **Regulator guidance and administrative policy.** An authority's stated approach or current thinking. Guidance can be highly important without becoming legislation. Its scope, date, and nonbinding status matter.
3. **Consensus standards.** Technical publications developed through a standards process. Publication, regulator recognition, EU harmonization, and contractual invocation are separate events. A standard is not automatically mandatory everywhere merely because it is current.
4. **Scientific evidence.** Data and interpretations whose value depends on relevance, reliability, applicability, and uncertainty—not on the prestige of the journal alone.
5. **MedDev Advisory practice.** Original reasoning methods, review questions, and workflow recommendations in this book. These are professional suggestions, not external requirements.

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Author’s note

Biocompatibility work often arrives in fragments. A project team has a material list, a handful of historical reports, a laboratory quotation, several supplier statements, a risk file, and a submission deadline. Every fragment may be useful. None of them, by itself, is a biological evaluation.

My interest in this problem began at the bench. Work in biomaterials, implantable electrochemical biosensors, cytotoxicity, oxidative-stress responses, sterilization effects, and cell–material interactions taught me that a test result is inseparable from the article tested and the way that article was made. A clean number can answer the wrong question. A result that appears reassuring can be irrelevant to the final device. A deviation that looks inconvenient can reveal the very uncertainty the team needs to resolve.

Regulatory documentation exposes the same problem from another direction. Reviewers do not encounter the device in the way its designers do. They encounter a controlled narrative assembled from records. If the narrative does not show what the device is, how the patient encounters it, why the evidence applies, where uncertainty remains, and how the conclusion follows, a technically capable program can still look weak.

This handbook is therefore about decisions and their traceability. It is not a catalog of biological effects, a substitute for the ISO 10993 series, or an instruction to test every endpoint. Its purpose is to help a competent team ask better questions:

- What exactly are we evaluating?
- Which final finished configurations matter?
- How might a patient or user be exposed?
- What does each item of evidence genuinely support?
- Is the apparent gap a safety uncertainty, a missing record, or both?
- What additional information would change the decision?
- Which judgment belongs to a toxicologist, clinician, laboratory specialist, or legal/regulatory expert?
- Can another reviewer reconstruct our reasoning without relying on institutional memory?

A defensible biological evaluation is neither a maximally conservative pile of testing nor a clever attempt to avoid work. It is a proportionate program that makes uncertainty visible, directs effort toward material questions, and explains why the evidence is sufficient for the stated decision—or why it is not.

I have written the book for practitioners who must make that reasoning work inside real organizations. You may begin with a new device, inherit a legacy file, investigate a material change, commission chemistry, respond to a reviewer, or bring scattered evidence into a coherent plan and report. The chapters are arranged as a lifecycle, but the reading routes below allow you to enter at the decision you face.

The book cannot make a device-specific judgment for you. It can make the quality of that judgment easier to see.

Arvind Rathore MedDev Advisory

How to use this book

The operating idea

Treat the biological evaluation as a controlled argument about a particular device in a particular use—not as a binder of test reports.

That argument has a recognizable structure:

1. Define the device, variants, use, population, and contact or exposure boundary.
2. Understand the final finished device and the processes that can shape what reaches the body.
3. Identify biological hazards and material uncertainties within the wider risk-management system.
4. Build an evidence inventory whose provenance can be reconstructed.
5. Judge what each item can and cannot support.
6. Convert unresolved uncertainty into answerable questions.
7. Obtain additional information or testing only where it can change a decision.
8. Integrate the evidence, limitations, controls, and residual uncertainty into a conclusion.
9. Translate the common scientific core into the needs of the relevant jurisdiction and submission.
10. Revisit the evaluation when the device, evidence, use, or post-market knowledge changes.

These steps are not a universal algorithm. Some will overlap, repeat, or occur in a different order. Their value is that they expose missing links. If the team cannot explain one link, the program has found work to do.

Seven reading routes

Planning a new biological evaluation. Read Chapters 1–13. When the evidence is ready, continue through Chapters 14–16.

Remediating a legacy file. Begin with Chapters 1 and 3–10. Then use Chapters 14–19 to rebuild the reasoning, document the current state, and prepare for challenge.

Assessing a material, supplier, or process change. Read Chapters 3–8, 9–10, and 18. Do not let the change record become a substitute for the biological-evaluation update.

Managing chemical characterization and toxicological assessment. Read Chapters 2–4 and 9–15. Chapters 11 and 12 deliberately preserve the laboratory and qualified-toxicologist boundaries.

Responding to a regulatory or notified-body question. Read Chapters 6–8 and 14–19. Begin by reconstructing the question, not by defending the existing wording.

Commissioning or conducting laboratory work. Read Chapters 2–4, 9, and 11–13. The purpose is to connect the study design and test article to the decision the result must support.

Leading RA/QA oversight. Read Chapters 1, 5–10, and 14–19. Focus on interfaces, provenance, competency, change control, and release decisions.

Recurring features

Decision Point identifies the choice the team must make and the evidence that should drive it.

Common Failure describes a plausible practice that weakens the evaluation, even when the team is competent and acting in good faith.

What Would Change the Conclusion? prevents provisional reasoning from hardening into an unsupported absolute.

Reviewer's Question tests whether the argument can survive an independent reader who does not share the team's assumptions.

Competence Boundary marks a decision that needs a defined specialist or authorized organizational role.

Jurisdiction Note distinguishes a market-specific presentation or source from the common scientific evidence core.

Case File applies the reasoning to a fictional device without pretending to provide a reusable regulatory answer.

Evidence to Point To identifies the kind of controlled record that would let a reviewer reconstruct the claim.

The chapter checklists are unscored challenge tools. A run of "yes" answers does not prove compliance or biological safety. A "no" answer does not automatically demand new testing. Each answer should trigger a reasoned question about the consequence.

What this book does not replace

It does not replace:

- the current applicable law and regulator instructions;
- authorized copies of relevant standards;
- device-specific guidance and product standards;
- the manufacturer's quality and risk-management procedures;
- current design, manufacturing, supplier, sterilization, packaging, shelf-life, clinical, and post-market records;
- qualified toxicological, clinical, medical, laboratory, statistical, legal, or regulatory judgment;
- a prospective Biological Evaluation Plan or an evidence-based Biological Evaluation Report for the actual device;
- organizational review, approval, and change control.

A note on current edition and jurisdiction transitions

ISO published the sixth edition of ISO 10993-1 in November 2025. FDA recognition record 2-313 shows a database entry date of 25 May 2026, while FDA's Recognition List 066 notice became applicable on 24 August 2026. That notice superseded recognition 2-258 for the 2018 edition; FDA nevertheless records a transition accepting declarations to 2-258 through 1 July 2029. List 066 also added recognition 2-314 for ISO 10993-12:2021 including Amendment 1:2025, with declarations to the superseded record 2-289 accepted through 1 July 2029. On 17 June 2026, the European Commission listed EN ISO 10993-1:2025 and EN ISO 10993-12:2021/A1:2025 as harmonized standards under the EU Medical Device Regulation. These events are related, but they are not interchangeable.

Publication tells you which edition ISO has issued. FDA recognition defines the scope in which FDA will accept a declaration of conformity and records exclusions or cautions. EU harmonization can support a presumption of conformity only for the requirements and within the conditions covered by the listed EN standard. ISO also published ISO 10993-3:2026 in August 2026, but publication alone does not establish FDA recognition or EU harmonization. Applicable law, guidance, device-specific

PART I

Define the evaluation problem

Establish the decision, device boundary, final-finished-device knowledge and exposure model before evidence is judged.

Chapter 1 — Stop Treating Biocompatibility as a Test List

CHAPTER PURPOSE

Establish what a biological evaluation is expected to decide, define its boundaries, and prevent a project from becoming a collection of disconnected reports.

Reader output

A concise evaluation charter that identifies the product, decision, intended use, evidence boundary, open questions, and accountable owner.

Key figure concept

The evidence funnel: product reality → exposure and biological questions → relevant evidence → uncertainty → justified action and documented conclusion.

Biological evaluation begins before anyone selects a laboratory or opens a report template. It begins with a decision: *What must this team be able to conclude about this particular device, for this particular use, at this particular point in its lifecycle?*

That question sounds elementary. In practice, many weak files never answer it. They start with an endpoint list, inherit a testing table from an earlier project, or assemble certificates and study reports under a broad heading called “biocompatibility.” The documents may be numerous and technically respectable, yet the file remains difficult to defend because the reader cannot see how the evidence addresses the device that will actually be placed on the market.

A sound biological evaluation is an evidence-based safety argument. It connects the finished-device reality to plausible biological concerns, evaluates the relevance and limitations of available information, identifies material uncertainty, and records why further action is or is not warranted. Testing can be part of that argument. It is not the argument itself.

The decision to be made

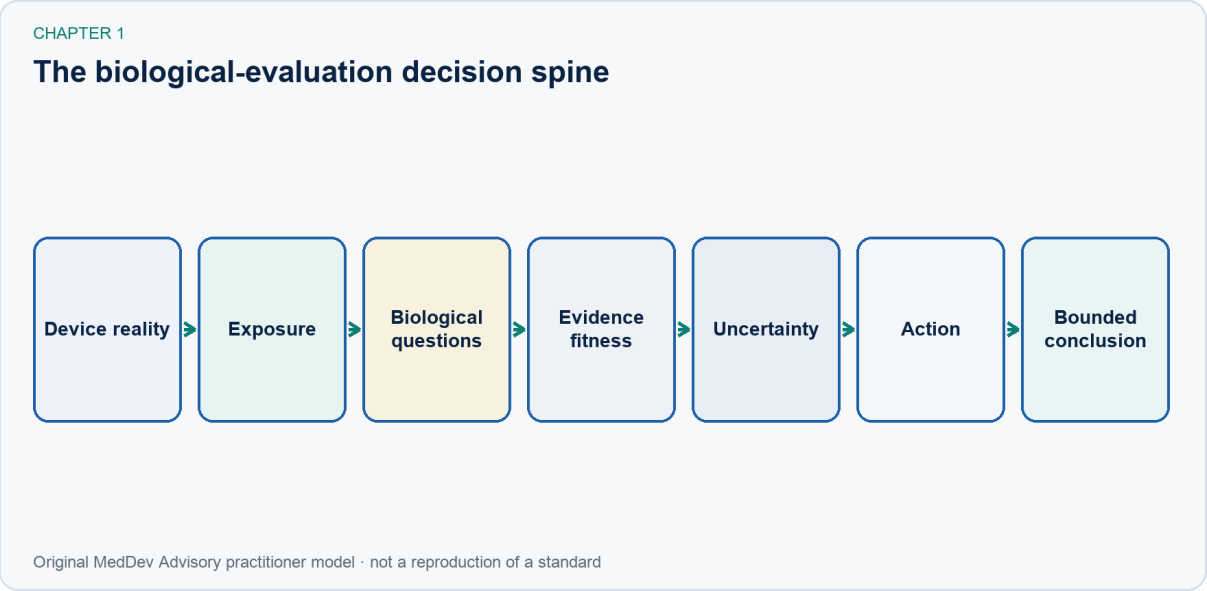

Figure 1. The biological-evaluation decision spine

At the start of a project, write one governing decision in plain language. A useful decision statement identifies:

- the exact device or controlled family being evaluated;
- the intended clinical use and patient-contact conditions within scope;
- the lifecycle event that triggered the work;
- the market or review context relevant to the decision;
- the conclusion or action the team needs from the evaluation; and
- the boundary beyond which the evaluation does not claim to decide.

For example:

> **PRACTICE NOTE**
> Determine whether the available biological-safety evidence remains applicable to the defined commercial configurations of the sterile AsterFlow infusion and catheter family after the specified material, process, sterilization and shelf-life conditions are considered; identify unresolved biological risks and the additional evidence or controls needed before the design review is closed.

This is not a conclusion. It is a disciplined statement of the work. It avoids promising that the device is “compliant,” “safe,” or “equivalent” before the supporting analysis exists. It also prevents the evaluation from quietly expanding into unrelated questions such as clinical performance, sterility assurance validation, or regulatory submission strategy. Those subjects may interface with biological evaluation, but each requires its own competent assessment.

The decision statement should be narrow enough to answer and broad enough to include all material contributors to patient exposure. If it says only “confirm the catheter material is biocompatible,” it is too narrow. The patient does not encounter a resin name in isolation. The relevant article may include additives, colorants, adhesives, lubricants, coatings, process residues, sterilization-related changes, packaging interactions, aging effects, and substances introduced during use.

Why competent teams still get it wrong

Most failures are not caused by a complete absence of data. They arise because the data were never organized around a controlled question.

The test-first reflex

A familiar table is copied into the plan, and each row becomes a perceived obligation. This can lead to unnecessary animal use, repeated studies, poorly selected test articles, and reports that still do not address the real uncertainty. The opposite error also occurs: a team points to one passing historical study and treats it as permanent proof without checking whether the current device, manufacturing route, or exposure remains represented.

An unstable product identity

Engineering refers to a drawing number. Operations refers to a family name. Regulatory refers to a catalog range. The laboratory tested a configuration described differently again. If these identities are not reconciled, the evaluation may rely on evidence from the wrong article without anyone noticing. “Same product family” is not evidence; it is a proposition that requires a documented basis.

Scope defined by labels rather than exposure

Teams sometimes classify a component as “non-contacting” and stop there. Yet material may transfer through a fluid path, a contacting accessory may be supplied separately, or a processing aid may remain on the finished article. A physical-touch label can be useful, but it cannot replace an exposure analysis.

Evidence treated as interchangeable

A supplier declaration, a resin safety data sheet, a chemical characterization report, a biological study, clinical experience, and complaint data answer different questions. A file becomes fragile when all are placed into one evidence list without stating what each item can and cannot support.

Uncertainty hidden instead of managed

Unknown formulation details, incomplete process records, unexplained analytical findings, or uncertain test-article representativeness are often softened by vague language. Reviewers usually find the gap anyway. A credible evaluation names the uncertainty, estimates its significance, and assigns a proportionate action.

Conclusions inherited without their reasoning

Legacy reports may contain a final sentence but no reconstructable path from device characteristics to evidence and conclusion. Repeating that sentence does not strengthen it. The current team must decide whether the underlying evidence can be understood, verified, and applied to the current product.

A practical reasoning method

The following method is deliberately independent of any single form. It can be used to plan a new evaluation, remediate a legacy file, or assess a change.

1. Freeze the evaluated product identity

Create a controlled snapshot of what is being evaluated. Include the commercial configurations, relevant model or drawing identifiers, patient-contacting and exposure-relevant components, manufacturing sites or routes, sterilization condition, packaging system, claimed shelf life, and important use accessories. Record the effective revision or date for each input.

Do not force premature completeness. Where information is missing, label it as unknown and assign an owner. An explicit unknown is safer than an invented certainty.

2. State the trigger and the decision

Is this a new device, a design transfer, a material or process change, a periodic file review, a response to a regulator, or remediation of inherited documentation? The trigger affects which comparisons matter and how much historical evidence may remain useful.

Then write the governing decision statement. If different stakeholders expect different outcomes, resolve the conflict before the technical review proceeds.

3. Describe clinically realistic exposure

Explain who may be exposed, to what part of the finished device, by which route, for how long and how often, under intended use and reasonably foreseeable conditions relevant to biological safety.

Consider indirect transfer, repeated procedures, multiple units, accessories, preparation steps, and conditions at the upper end of the labeled use envelope.

This is not an invitation to invent worst cases without evidence. It is an instruction to avoid basing the evaluation on an unrealistically benign scenario.

4. Build an evidence map, not a document inventory

For each biological question, identify the evidence that bears on it and record four things:

1. **What the item directly shows.**
2. **Which device, material, process, or exposure it represents.**
3. **Its important limitations.**
4. **How it changes the current decision.**

This turns a folder of reports into a reasoning chain. Evidence may include device specifications, supplier information, manufacturing and sterilization knowledge, analytical data, toxicological assessments, biological studies, published literature, clinical information, and post-market experience. The weight assigned to each item depends on relevance, reliability, completeness, and the uncertainty it resolves.

5. Separate facts, assumptions, and professional judgments

These categories should never be allowed to blur.

- A **fact** is supported by a controlled record or cited evidence.
- An **assumption** is a provisional condition used to continue the analysis and must be confirmed or bounded.
- A **professional judgment** is an interpretation made by a competent person using the available facts, uncertainty, and context.

The distinction is especially important when the team relies on family grouping, representative test articles, supplier attestations, bridging, or legacy studies. The file should show which parts are observed and which parts are reasoned.

6. Test the applicability of every important evidence bridge

Whenever evidence from one article is used for another, ask what would have to be true for that bridge to hold. Compare the attributes that could change patient exposure or biological response, not merely the product names. Relevant attributes may include formulation, additives, color, surface treatment, geometry, surface-area relationship, processing, cleaning, sterilization, packaging, aging, use duration, and clinical environment.

Do not declare two configurations “equivalent” merely because the base polymer or supplier is the same. Conversely, do not demand new testing merely because catalog numbers differ. The issue is whether the differences are understood and whether the existing evidence remains informative.

7. Convert uncertainty into a controlled action

An uncertainty should lead to one of four outcomes:

- it is resolved by existing evidence;
- it is bounded and accepted with a documented rationale;
- it requires additional information, analysis, or testing; or
- it prevents the decision and is escalated.

Each open action needs an owner, due point, expected output, and closure criterion. “Obtain more information” is not an adequate action. “Obtain the approved supplier’s current formulation and

The decision to be made

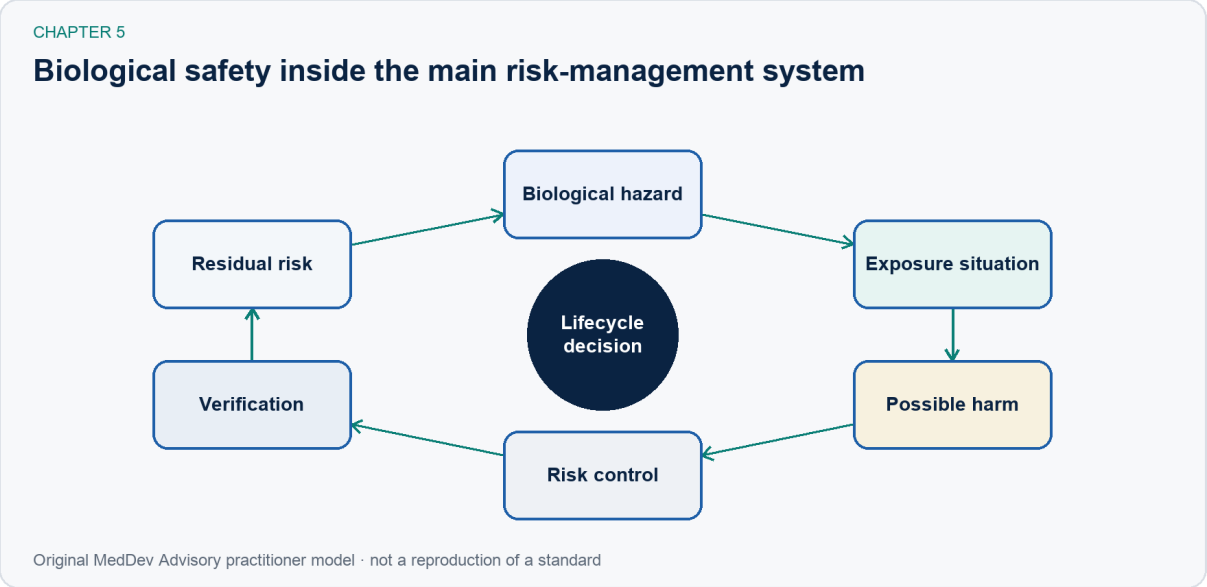

Figure 5. Biological safety inside the main risk-management system

The practical decision is:

> **PRACTICE NOTE**
> How will the biological evaluation inform, and remain traceable to, the device risk-management system without collapsing complex scientific uncertainty into a list of tests or a single unsupported risk label?

A useful interface map identifies five things:

1. the device, process, use, and patient conditions that can create biologically relevant exposure;
2. the possible adverse consequences that matter to the risk analysis;
3. the evidence questions needed to understand those concerns;
4. the design, process, use, monitoring, or evidence controls that address them; and
5. the conditions under which the current reasoning must be reopened.

The map does not need to repeat every record in the risk file or biological-evaluation report. Its job is to make the handoffs explicit. A person reviewing the risk analysis should know where to find the scientific basis. A person reviewing the biological evaluation should know which risk-management decisions the work is intended to support.

Why competent teams still get it wrong

They start with endpoints instead of causal pathways

A biological endpoint is an area of evaluation; it is not automatically a hazard, a hazardous situation, a harm, or a test requirement. When those ideas are treated as interchangeable, the risk analysis becomes a renamed testing table. It may record that sensitization was “passed” but fail to identify the material constituent, processing residue, repeated exposure, or user subgroup that made sensitization a relevant concern in the first place.

The causal story matters because controls act on causes and exposure pathways. A different supplier specification, improved rinse, lower-extractables formulation, protected fluid path, or restricted use condition may change the risk in ways that another test report does not.

The decision to be made

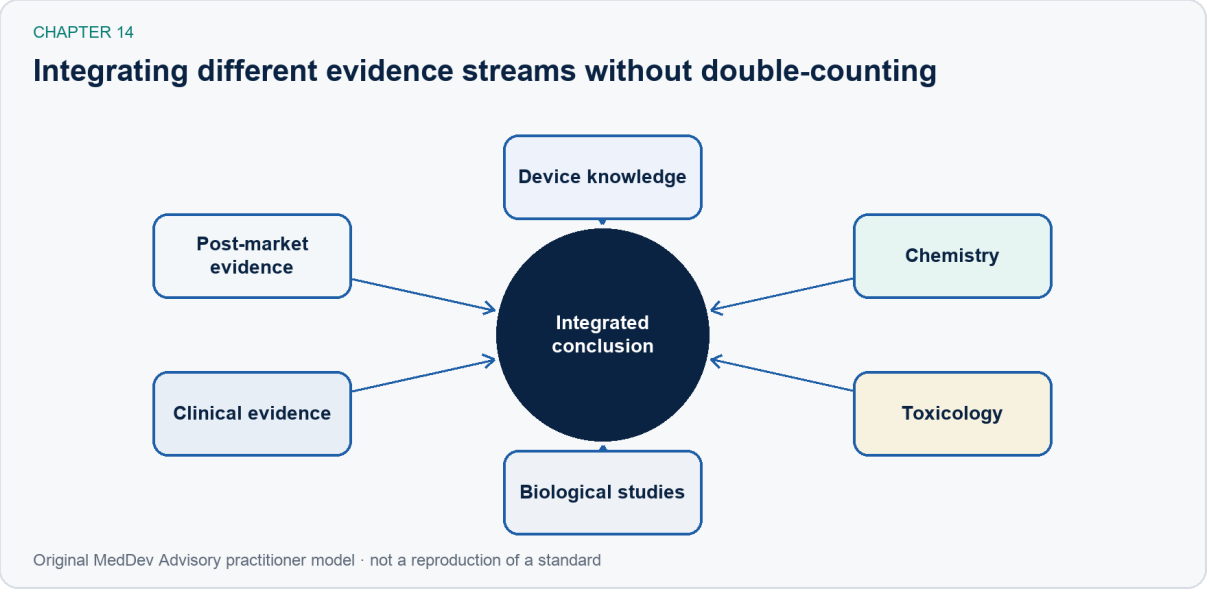

Figure 14. Integrating different evidence streams without double-counting

Integration has one governing question:

> **PRACTICE NOTE**
> For each material biological-safety question, what does the combined evidence establish, which limitations or contradictions remain, how independent are the supporting streams, and what consequence follows for the present device decision?

An integrated evidence map should make five matters explicit:

1. the claim or question being evaluated;
2. the distinct contribution of each relevant evidence stream;
3. the shared data, assumptions and device states on which those streams depend;
4. the effect of conflicts, gaps and uncertainty; and
5. the bounded decision, action or escalation supported at that point.

The map is not a scoring system. It should not award points for the presence of each evidence type. Some questions may be resolved primarily through strong device knowledge and one fit-for-purpose evidence stream. Others may require several complementary streams. A missing stream is not automatically a deficiency, and a populated stream is not automatically useful.

Why competent teams still get it wrong

The report sequence is mistaken for integration

Placing six summaries in adjacent chapters does not show how they interact. Integration requires cross-references at the claim level: the analytical finding that created the toxicological question, the device comparison that limits the biological study, or the complaint definition used to examine a possible clinical signal.

The decision to be made

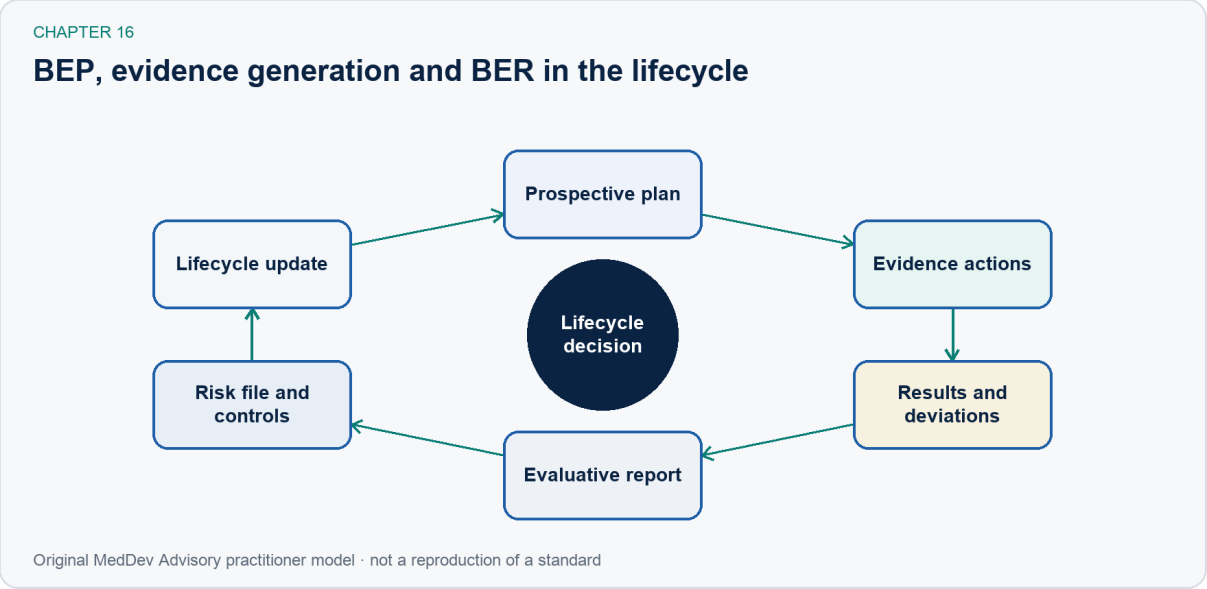

Figure 16. BEP, evidence generation and BER in the lifecycle

The documentation architecture must answer:

> **PRACTICE NOTE**
> How should the biological-evaluation strategy be planned, executed, evaluated and maintained so that every material BER conclusion can be traced to an approved question, the actual evidence and test article, any change or deviation, a competent interpretation, and the associated risk-management decision?

A sound architecture should make it possible to move in both directions:

- forward from an identified biological question to the planned evidence, actual activity, result, appraisal and decision; and
- backward from a BER conclusion to the evidence, article, protocol or source, approved plan, device boundary and risk question that justify it.

The architecture should also reveal discontinuity. If the marketed device changed after the BEP, the laboratory used a different article, a planned study was replaced by another evidence route, or a BER claim exceeds the plan's scope, the difference must be visible and assessed.

In this chapter, *approved* means accepted under the manufacturer's own controlled document and decision process. It does not mean approval by a regulator, notified body, standards body or laboratory.

The two documents have different jobs

The following comparison describes functions, not a complete table of contents.

Decision function	BEP: prospective control	BER: evaluative record
Device boundary	Defines the device, family, use and lifecycle state the strategy is intended to cover	Confirms the device and state actually represented and states any divergence
Biological questions	States what must be resolved and why	Shows how each question was resolved, narrowed, deferred or left open

Appendix A — The independent-review challenge

Use this appendix after a draft evaluation has been assembled but before it is treated as ready for approval or external use. It is an unscored review aid, not a compliance checklist. The value lies in the reviewer's reasons, evidence references, and unresolved questions.

Scope and identity

1. Can a reader identify the legal manufacturer, device, model or family, configurations, accessories, variants, and document versions actually covered?
2. Does the scope distinguish marketed, development, investigational, and legacy configurations?
3. Are intended purpose, indications, contraindications, users, patient populations, use environment, and reasonably foreseeable use conditions described consistently with controlled device records?
4. Are direct and indirect contacts explained as exposure pathways rather than reduced to a label?
5. Are contact route, anatomical site, frequency, episode duration, total or repeated exposure, and relevant population factors supported by evidence?
6. Could an apparently non-contacting component affect the patient-facing article or contacting medium through transfer, migration, processing, or failure?

Final finished device knowledge

7. Does the evaluation describe the final finished device rather than relying on generic raw-material identities?
8. Can every patient-relevant material, formulation, additive, processing aid, adhesive, ink, coating, colorant, residue, and degradation source be traced to a controlled version?
9. Are manufacturing, cleaning, packaging, sterilization, aging, storage, transport, and reprocessing states linked to the configurations evaluated?
10. Are supplier declarations used only for the claims and time period they can support?
11. Are unknowns distinguished from known absences?
12. Does the file explain which knowledge gaps can affect biological safety and which are administrative only?

Evidence provenance and fitness

13. Can every material claim be traced to its source, version, article tested, method, date, and decision use?
14. Does the evidence describe the same formulation, manufacturing process, surface, sterilization state, aging state, geometry, and use-relevant exposure—or is a bridge required?
15. Are favorable and unfavorable findings both visible?
16. Are method limitations, deviations, detection or reporting limits, sample preparation, and test-article condition considered in interpretation?
17. Is each bridge explicit about the changed and unchanged attributes?
18. Does family or worst-case reasoning address the specific question, rather than declaring one configuration worst for every purpose?

About the author

Arvind Rathore is the founder of MedDev Advisory and works with medical-device teams on biological-evaluation strategy and documentation, including Biological Evaluation Plans, Biological Evaluation Reports, toxicological-risk-assessment interfaces, EU MDR technical documentation, and FDA submission support.

Before establishing the practice, he was a Marie Skłodowska-Curie Early Stage Researcher at INSERM U1026 Biotis within the ImplantSens network. His work covered implantable electrochemical biosensors, cytotoxicity, oxidative-stress response, sterilization effects, and biomaterial–cell interactions, with research placements in France, Germany, and Sweden.

He holds an MTech in Biological Sciences and Bioengineering from the Indian Institute of Technology Kanpur and has peer-reviewed publications in Bioelectrochemistry, Advanced Sensor Research, and Biochimie. His research experience informs this handbook; it does not replace device-specific assessment or specialist review.

His work at MedDev Advisory combines device knowledge, biological evidence, risk-based reasoning, and reviewer-facing documentation. The practice is independent and is not a regulator, notified body, test laboratory, or standards organization.

For current professional information, visit About Arvind Rathore or contact arvind.rathore@meddevadvisory.com.

Closing principle

A biological evaluation is credible when another competent person can see what was known, what was uncertain, what was decided, why the evidence was sufficient for that decision, who exercised the required judgment, and what would cause the conclusion to be revisited.

That is the standard of reasoning this book is designed to support.