

BIF Analysis Protocol

General Decision Rules

Version 1.0 · Hydra Chronic Analytical Series

1. Purpose and Scope

This document defines the general decision rules governing analytical assessments conducted under the Barrier Integrity Framework (BIF).

The Barrier Integrity Framework defines what is assessed. This protocol defines how analytical determinations are made.

It establishes:

- the permitted status values for individual BIF dimensions
- the evidentiary structure supporting those determinations
- the treatment of insufficient evidence
- the use of analytical and scope reservations
- the non-compensability rules
- the aggregation of dimension findings into an overall verdict
- the documentation requirements applicable to each assessment

This protocol applies to all four BIF dimensions:

- Barrier Architecture
- pH Coherence
- Membrane Compatibility
- Delivery Logic

Dimension-specific operational criteria are defined separately and must be applied together with these General Decision Rules.

2. Dimension Status

Each BIF dimension receives exactly one status: Fulfilled, Not Fulfilled, or Not Assessable.

These status values are mutually exclusive and collectively exhaustive. No dimension may receive more than one status.

2.1 Fulfilled

A dimension is classified as Fulfilled when the applicable requirements are met; no defined exclusion criterion is demonstrated; and the available evidence is sufficient to support a positive determination under the applicable operational criteria.

Fulfilled is a positive analytical determination. It must not be assigned merely because no negative finding has been identified. Absence of evidence for failure is not sufficient evidence of fulfilment.

2.2 Not Fulfilled

A dimension is classified as Not Fulfilled when at least one defined exclusion criterion is demonstrably met, and the available evidence is sufficient to support that negative determination.

Not Fulfilled is an analytical finding. It must not be assigned solely because relevant product information is absent.

Where the evidence supports a defined exclusion criterion, the dimension is Not Fulfilled even if additional information concerning other aspects of that dimension remains unavailable.

2.3 Not Assessable

A dimension is classified as Not Assessable when the available evidence is insufficient to support either a reliable positive or a reliable negative determination.

Not Assessable is a data condition, not a negative analytical judgment. It does not mean that the formulation is structurally incoherent. It means that the evidence required to determine coherence within that dimension is unavailable or insufficient.

A Not Assessable finding in one dimension cannot be resolved by inference from another dimension.

3. Evidence Structure

BIF assessments distinguish three evidence levels.

Evidence Level A — Direct Product Data

Evidence specific to the formulation under assessment. This may include manufacturer declarations, technical documentation, quantitative formulation data, material specifications, measured physicochemical values, manufacturing or formulation parameters, or other product-specific evidence relevant to the applicable criterion.

Level A evidence has the highest product specificity. Its presence does not automatically establish fulfilment; the evidence must still satisfy the applicable operational criterion.

Evidence Level B — Primary Literature

Published scientific evidence relevant to a component, a defined concentration or concentration range, a formulation system, a physicochemical mechanism, a structural interaction, or another criterion relevant to the dimension under assessment.

Level B evidence supports mechanistic or empirical interpretation but is not, by itself, product-specific. Its applicability to the formulation must therefore be explicitly established.

Evidence Level C — Structural Derivation

An analytical inference derived from information such as INCI composition, known component properties, formulation structure, component relationships, or established physicochemical principles.

Level C evidence may support structural observations and Analytical Reservations. Level C evidence alone is insufficient to establish Fulfilled or Not Fulfilled where the determination depends on an empirically verifiable product property.

The minimum evidence required for each determination is specified by the operational criteria of the relevant BIF dimension.

4. Evidence Sufficiency

Evidence quantity and evidence sufficiency are not equivalent. Multiple weak or indirect sources do not necessarily constitute sufficient evidence.

Evidence is sufficient only where it permits the applicable criterion to be evaluated at the level of certainty required by the relevant operational rule.

Where a criterion depends on a product-specific property — for example concentration, final formulation pH, material specification, or demonstrated formulation architecture — that property must not be assumed from ingredient presence alone.

Where the minimum evidentiary requirement is not met, the dimension is Not Assessable, unless an independently demonstrable exclusion criterion is sufficient to establish Not Fulfilled.

5. Analytical Reservation

An Analytical Reservation may be attached only to a dimension classified as Fulfilled. It is used where a plausible structural risk factor or unresolved analytical issue exists; the available evidence does not support a defined exclusion criterion; and the remaining evidence is independently sufficient to support the positive determination.

An Analytical Reservation does not lower the evidentiary threshold for Fulfilled. If the unresolved factor prevents a reliable positive determination, the dimension must be classified as Not Assessable instead.

An unknown concentration, unspecified formulation parameter, or other missing information is not in itself evidence of incompatibility. Missing evidence must not be converted into negative evidence.

An Analytical Reservation must identify:

- the unresolved factor
- the evidence supporting its relevance
- why it does not meet an exclusion criterion
- why the remaining evidence is nevertheless sufficient for a positive determination

6. Scope Reservation

A Scope Reservation applies only to the overall verdict. It is used where either Barrier Architecture or Delivery Logic is Not Assessable and the conditions for a Limited-Scope Verdict are otherwise satisfied.

The Scope Reservation identifies the dimension excluded from the overall determination. It does not convert that dimension to Fulfilled. It does not imply a negative finding. It defines the boundary of the issued verdict.

7. Functional Classification of Dimensions

For verdict aggregation, the four BIF dimensions are divided into two functional categories.

7.1 Non-compensable Dimensions

- pH Coherence

- Membrane Compatibility

These dimensions must be assessable and Fulfilled for an overall positive coherence determination to be issued.

Where either non-compensable dimension is Not Assessable, and no independent Not Fulfilled finding determines the outcome, the overall result is: No Verdict Issued.

A positive finding in another dimension cannot compensate for insufficient evidence in a non-compensable dimension.

7.2 Scope-limiting Dimensions

- Barrier Architecture
- Delivery Logic

Where either scope-limiting dimension is Not Assessable, a positive verdict may still be issued within a restricted analytical scope, provided no dimension is Not Fulfilled; both non-compensable dimensions are Fulfilled; and all other assessable dimensions are Fulfilled.

The resulting verdict must explicitly exclude the unassessed dimension.

This functional classification concerns the consequences of insufficient evidence. It does not establish a hierarchy of physiological importance among the four BIF dimensions.

8. Non-Compensability

BIF dimensions are evaluated independently. A positive finding in one dimension cannot:

- compensate for a Not Fulfilled finding in another dimension
- convert a Not Assessable dimension into Fulfilled
- reduce the evidence required by another dimension
- or neutralize an exclusion criterion established elsewhere in the assessment

The BIF does not use a cumulative scoring model. Overall coherence is determined by the logical relationship among the four dimension findings.

9. Overall Verdict

The overall verdict is derived from the dimension findings according to the following strict priority order.

Priority 1 — Not Coherent

If at least one dimension is Not Fulfilled, the overall verdict is: Not Coherent.

This rule takes precedence over all Not Assessable findings. The presence of insufficient evidence in another dimension does not prevent issuance of Not Coherent where a defined exclusion criterion has already been established with sufficient evidence.

Priority 2 — No Verdict Issued

If no dimension is Not Fulfilled, and at least one non-compensable dimension is Not Assessable, the result is: No Verdict Issued.

This outcome indicates insufficient evidence for an overall coherence determination. It is not a negative verdict.

Priority 3 — Limited-Scope Verdict

If no dimension is Not Fulfilled; both non-compensable dimensions are Fulfilled; at least one scope-limiting dimension is Not Assessable; and all remaining assessable dimensions are Fulfilled, the result is: Coherent within the assessable scope.

A Scope Reservation is mandatory. The verdict must identify every dimension excluded from the assessment scope.

Priority 4 — Coherent with Reservation(s)

If all four dimensions are assessable; all four dimensions are Fulfilled; and at least one dimension carries an Analytical Reservation, the overall verdict is: Coherent with Reservation(s).

Each reservation must be explicitly documented.

Priority 5 — Coherent

If all four dimensions are assessable; all four dimensions are Fulfilled; and no Analytical Reservation applies, the overall verdict is: Coherent.

No alternative positive verdict terminology may be substituted.

10. Verdict Matrix

Dimension findings	Overall result
≥1 Not Fulfilled	Not Coherent
No Not Fulfilled + ≥1 non-compensable dimension Not Assessable	No Verdict Issued
No Not Fulfilled + both non-compensable dimensions Fulfilled + ≥1 scope-limiting dimension Not Assessable	Coherent within the assessable scope
All four Fulfilled + ≥1 Analytical Reservation	Coherent with Reservation(s)
All four Fulfilled + no reservation	Coherent

The matrix is applied in the stated priority order.

11. Required Limited-Scope Formulation

A Limited-Scope Verdict must not be abbreviated to Coherent. The required formulation is:

“Coherent within the assessable scope. [Dimension name] could not be assessed due to [specific data condition]. This verdict does not extend to [dimension name].”

Where more than one scope-limiting dimension is Not Assessable, each excluded dimension must be identified.

The Scope Reservation must remain visible wherever the overall verdict is reported.

12. Treatment of Missing Information

Missing information must be recorded explicitly. The assessor must determine:

- what information is unavailable
- which criterion depends on that information
- whether the missing information prevents a positive determination
- whether an independent exclusion criterion can nevertheless be established
- and what effect the information gap has on dimension status and overall verdict

Missing information must not be replaced by assumptions about likely formulation behaviour.

An INCI list alone does not establish concentration, pH, material specification, formulation architecture, delivery behaviour, or concentration-dependent compatibility. Where those properties are required by an operational criterion, their absence has to remain analytically visible.

13. Decision Log

Every BIF assessment must contain a Decision Log. For each dimension, the Decision Log records:

- the operational rule or criterion determining the status
- the evidence used
- the evidence level
- relevant missing information
- the effect of missing information on the determination
- the analytical interpretation
- the basis for the assigned status
- any Analytical Reservation
- any rule clarification required during assessment
- any unexpected result or methodological issue

The Decision Log forms part of the analytical record. Its purpose is to make the reasoning underlying each determination traceable and to identify rules that require further methodological refinement.

14. Protocol Development and Rule Clarification

If application of an operational rule reveals that the rule is ambiguous, incomplete, internally inconsistent, or unworkable, the assessor must not alter the rule during the assessment in order to obtain a preferred result.

The issue must be recorded in the Decision Log. The assessment is completed under the protocol version in force at the time the assessment begins, insofar as a determination remains possible.

Any methodological correction or clarification is introduced through a subsequent protocol version before the next assessment to which the revised rule applies.

Completed assessments are not retrospectively rewritten as though the revised rule had existed at the time of the original assessment.

Where comparison across protocol versions is required, the applicable version must be stated.

15. Relationship to Dimension-Specific Operational Criteria

These General Decision Rules do not independently determine whether a particular formulation fulfils Barrier Architecture, pH Coherence, Membrane Compatibility, or Delivery Logic.

Each dimension requires its own operational criteria defining, where applicable:

- required inputs
- assessment criteria
- minimum evidence
- relevant thresholds
- exclusion criteria
- permissible Analytical Reservations
- decision sequence
- and documentation requirements

The General Decision Rules govern how the resulting findings are classified and aggregated.

Where a dimension-specific rule conflicts with these General Decision Rules, the conflict must be recorded and resolved through protocol revision. It must not be resolved ad hoc within an individual assessment.

16. Analytical Boundaries

A BIF verdict is an analytical determination within the defined Barrier Integrity Framework. It:

- does not constitute a claim regarding clinical performance
- does not establish therapeutic efficacy
- does not constitute a product safety assessment
- does not replace regulatory evaluation
- does not predict individual response
- does not establish superiority over formulations not assessed under the BIF

Not Coherent identifies a demonstrated inconsistency within the defined analytical model.

No Verdict Issued identifies insufficient evidence for an overall determination.

Coherent within the assessable scope applies only to the dimensions explicitly included in that verdict.

Coherent with Reservation(s) identifies a positive determination accompanied by one or more documented analytical limitations.

Coherent indicates that all four dimensions fulfil the applicable criteria on the basis of sufficient evidence under the protocol version used.

None of these classifications should be extended beyond the defined scope of the BIF.

17. Document Status

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