TRUEGATE BIO

IND-Enabling CMC Gap Assessment Framework

A structured approach to identifying what a program has, what it needs, and in what order, before committing to an IND timeline.

Purpose

A CMC gap assessment is often treated as a checklist against 21 CFR 312 and the relevant ICH guidances. That produces a list, not a strategy. This framework is built around a different question: **which gaps, if left unaddressed, change the regulatory pathway, the timeline, or the risk posture of the filing** — and which are routine execution that can proceed in parallel without senior attention.

The output is a risk-stratified assessment, not an inventory.

Structure

1. Product and Process Definition

Before gaps can be identified, the target state has to be defined precisely enough to compare against.

- Drug substance and drug product description, including any novel excipients, delivery mechanism, or formulation attributes that lack direct precedent
- Manufacturing process outline: unit operations, critical process parameters as currently understood, and points where process knowledge is thin
- Intended clinical use, dosing, and route of administration, since these drive specification and stability requirements downstream

Output: a one-page process and product summary that becomes the reference point for every subsequent gap.

2. Current-State Inventory

What exists today, organized by CMC section rather than by department:

Category	What is captured
Drug Substance	Characterization data, manufacturing process description, in-process controls, batch history
Drug Product	Formulation development data, manufacturing process, container-closure system, fill-finish considerations

Category	What is captured
Analytical	Method inventory, validation status of each method, reference standard status
Stability	Existing stability data, storage conditions studied, protocol design if in progress
Facilities	Manufacturing site status, GMP readiness, any tech transfer already completed or planned

Output: a current-state table, not a narrative. Each row gets a status: established, in progress, or not started.

3. Gap Identification and Risk Stratification

Each gap identified in Section 2 is stratified into one of three tiers:

Tier 1 — Pathway-defining. Gaps that affect what regulatory pathway is available or what the FDA will expect at filing. Example: absence of a stability-indicating analytical method, which affects whether a meaningful stability program can even begin.

Tier 2 — Timeline-defining. Gaps that don't change the pathway but sit on the critical path to filing. Example: a specification that hasn't been set because the reference standard isn't yet characterized.

Tier 3 — Execution. Gaps that are real but routine, and can proceed without senior strategic input once flagged. Example: formal method validation protocols not yet written for an already-qualified method.

Why this matters: Tier 1 gaps get resolved or explicitly risk-accepted before anything else proceeds, because they can invalidate downstream work. Tier 3 gaps get delegated and tracked, not escalated repeatedly. Most gap assessments treat all gaps as equally urgent, which either paralyzes a small team or causes real risks to get lost in a long list.

4. Sequencing and Dependencies

Gaps are rarely independent. A dependency map shows which Tier 1 and Tier 2 items block others:

- Which analytical methods must be validated before specifications can be finalized
- Which process characterization work must complete before a stability protocol can be locked
- Which decisions require a regulatory interaction (e.g., a Pre-IND question) before internal work can proceed efficiently

Output: a simple sequencing diagram or table showing what can run in parallel and what is strictly sequential.

5. Recommended Next Steps and Estimated Timeline

For each Tier 1 and Tier 2 gap: the specific activity required to close it, who is best positioned to lead it, and a realistic time estimate. Tier 3 items are consolidated into a tracked punch list rather than individually estimated.

What This Produces

A document that tells a founder or a program lead three things clearly: **what has to happen before anything else can proceed, what determines the realistic filing timeline, and what can simply be assigned and tracked.**

That distinction is usually the actual value of a gap assessment, more than the inventory itself.

This framework reflects a general approach developed through CMC and regulatory work in FDA-regulated biologics programs, including IND and BLA submission support for cell therapy products. Applied here as a demonstration of methodology; no proprietary or client-specific information is represented.

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