The Consultant’s Companion: Actionable Frameworks from The Drug Development Playbook

A Field Guide for Life Science Consultants & R&D Leads

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How to Use This Document

This guide is designed for the "consultant mindset." It moves beyond scientific mechanisms to focus on **decisions, risk, and value preservation**. Use these frameworks to:

1. **Audit client programs** for common failure modes.
2. **Facilitate Go/No-Go meetings** with objective criteria.
3. **Draft strategic roadmaps** that align science, regulation, and business.

Part 1: The Master Strategy (The "Why" & "When")

Context: Most value is destroyed in Phase II. Your job is to reduce uncertainty per dollar spent.

The "Value-at-Risk" Audit

Before advising on a specific study, ask these three questions to frame the engagement:

- [ ] **The Single Question Test:** What is the *one* decision this next study must enable? (If the client lists three distinct goals, the study is likely underpowered or unfocused).
- [ ] **The "Kill" Threshold:** Have we defined the specific data point that would cause us to stop this program today? (If there is no kill criteria, it is a zombie program).

- [ ] **The Next-Stage Capacity:** Do we have the capital and capabilities to run the *subsequent* stage if this one succeeds? (Don't generate an asset you cannot afford to develop).

The Consultant's Funnel View

- **Phase I:** Buying information on safety/PK.
- **Phase II:** The "Valley of Death." Must prove concept *and* dose.
- **Phase III:** Generating evidence for regulators *and* payers.

Part 2: Target Selection (The "What")

Context: Biology is the hardest thing to fix later. If the target is wrong, the best chemistry won't save it.

The 5-Point Target Scorecard

Rate the client's target (1–5) on these dimensions. A score <3 on "Human Evidence" is a red flag.

1. **Human Evidence:** Is there genetic causal data (GWAS, protective mutations) linking this target to the disease phenotype in humans?
2. **Mechanistic Plausibility:** Do we understand *how* modulating this target affects the pathway?
3. **Druggability:** Is the pocket accessible? Can we get a modality (small molecule, antibody, RNA) to the tissue?
4. **Safety Plausibility:** What happens when this gene is knocked out in nature? (Check human loss-of-function variants).
5. **Strategic Fit:** Does this solve a problem payers care about?

The "Genetic Reality Check"

- **Action:** Before approving a target, run a search for human natural variants.
- **Decision Rule:** If human genetics show *no effect* or *opposite effect* on the disease, recommend a pivot immediately.

Part 3: Hit-to-Lead & Optimization (The "How")

Context: Potency is vanity; exposure is sanity. Don't let chemists optimize for binding affinity alone.

The "Dead End" Detector

Flag a chemistry series if you see:

- [ ] **Potency > Exposure:** Nanomolar potency but poor solubility/permeability.
- [ ] **The "Beautiful" Assay:** Great results in an artificial buffer, but fails in the presence of plasma protein.
- [ ] **Missing ADME:** No data on metabolic stability or clearance by the time hits are selected.

The Early DMPK Dashboard

Ensure the client is tracking these levers *during* design cycles, not after:

- **Oral Bioavailability:** (Solubility + Permeability + Metabolic Stability).
- **Clearance:** Identifying metabolic soft spots early.
- **Safety Signals:** hERG liability and CYP inhibition/induction.

Part 4: Preclinical & IND Readiness (The Regulatory Gate)

Context: Regulators want a safety margin and a manufacturing story, not just a cool mechanism.

The IND Readiness Checklist

Do not request a pre-IND meeting until you have visibility on:

- [ ] **Dose Rationale:** A quantitative MABEL (Minimum Anticipated Biological Effect Level) or MRSD (Max Recommended Starting Dose) derived from animal data + safety factors.
- [ ] **The 4 Pillars:**
    1. Pharmacology (PoC in relevant model).
    2. Toxicology (GLP repeat-dose in 2 species).

3. DMPK (Exposure margins).
4. CMC (Comparability of Tox batch vs. Clinical batch).

- [ ] **The CMC Bridge:** If the manufacturing process changed between Tox and Clinical, is there analytical data proving they are the same product?

The "Smart Sequencing" Strategy

- **Action:** Front-load non-GLP exploratory tox and key CMC stability studies.
- **Why:** To de-risk the expensive GLP slots and ensure clinical material is released on time.

Part 5: Clinical Development (The Evidence Engine)

Context: Phase II is where programs go to die. Design specifically to prevent ambiguous failures.

The Phase II "Truth Serum"

Force the client to answer these before starting Phase II:

- [ ] **Enrichment:** Are we treating "all comers" or selecting patients most likely to respond (biomarkers)?
- [ ] **The Dose-Response:** Will this trial output a clear dose-response curve, or just a "pass/fail" at one dose? (Pass/fail is dangerous).
- [ ] **The Endpoint:** Does the primary endpoint measure the *mechanism* (biomarker) or the *clinical benefit* (feeling/function)? (Regulators need benefit; early Phase II can use surrogates *if* validated).

Quality by Design (QbD) Audit

- Identify **Critical to Quality (CtQ)** factors: What specifically *must* go right for this trial to be valid? (e.g., sample handling for a labile biomarker).
- **Action:** Write these into the monitoring plan.

Part 6: Filing & Approval (The Narrative)

Context: A submission is a story (Module 2) backed by a data vault (Modules 3–5).

The "Filing Heatmap"

Do not press "Submit" on the eCTD until these gates are GREEN:

- [ ] **Clinical:** Primary endpoint met per SAP; safety narrative consistent.
- [ ] **CMC:** Commercial process validated; comparability to clinical batches proven.
- [ ] **Regulatory:** Pre-NDA/MAA meeting minutes align with the dossier strategy.
- [ ] **Inspection Readiness:** Mock inspections completed at manufacturing and key clinical sites; CAPAs closed.
- [ ] **Label:** Proposed label claims are supported by the data *and* commercially viable.

The "Module 2" Test

- **Action:** Read *only* the Module 2 Clinical Overview.
- **Test:** Does it proactively answer the regulator's top 3 fears (e.g., "Is that liver signal real?", "Is the dose too high?")? If it hides them, rewrite it.

Part 7: Post-Approval (The System)

Context: Approval is not the finish line; it's the start of the "Real World" phase.

The Post-Launch Evidence Map

Create a one-page map containing:

- **Regulatory Commitments:** PMRs/PMCs (Required safety studies).
- **Payer Needs:** Real World Evidence (RWE) studies to prove cost-effectiveness/value.

- **Safety Nets:** REMS/RMP operations and signal detection thresholds.

The "First 90 Days" Standup

- **Action:** Recommend a weekly cross-functional standup (PV, Medical Affairs, Regulatory, Quality) for the first 3 months post-launch.
- **Goal:** Rapidly triage spontaneous reports and manufacturing hiccups before they become regulatory "fires."

This document is a companion to the Aryan Kenia "Drug Development Playbook" series. For deep dives on each section, refer to the specific articles at aryankenia.com.