A framework for indication or asset prioritization

Importance and complexities of pipeline and portfolio decision making

Pipeline and portfolio choices are among the highest-impact decisions a drug-developing biotech makes, and for an early-stage company they can be the difference between survival and failure. The principles are the same whether you are choosing one indication over others for a single asset, or choosing one asset over another. The choice requires weighing many factors, most of which carry real uncertainty. In an ideal world the best indication or asset would carry the lowest scientific risk, the strongest commercial opportunity, the shortest development timeline and the lowest cost. Trying to optimize for all of this will most likely leave you with nothing to develop.

Choosing well, therefore, is not about finding the indication or asset that scores highest on every single dimension. It is about knowing which dimensions matter most to this company, given its strategy and constraints, and then finding the indication whose actual profile best fits those priorities. A clear picture of the opportunities and risks associated with each potential asset or indication, and of how each affects the company, is what allows a team to minimize risk where the company is most vulnerable and hence improve its chances of long-term success. Common problems that get in the way of good decision making are confirmation- and/or authority-bias, information overload and a lack of analyzing the information in a structured way.

A three-step framework

My research surfaced surprisingly few well-described frameworks for pipeline and portfolio decision making and the few frameworks that I found, the 5R framework by AstraZeneca or Simon-Kucher's framework are more suitable for larger companies, where capital and time requirements are less of a concern than they are for early-stage biotech companies. This leaves early-stage companies having to develop their own frameworks, as I've witnessed first hand with AbCellera.

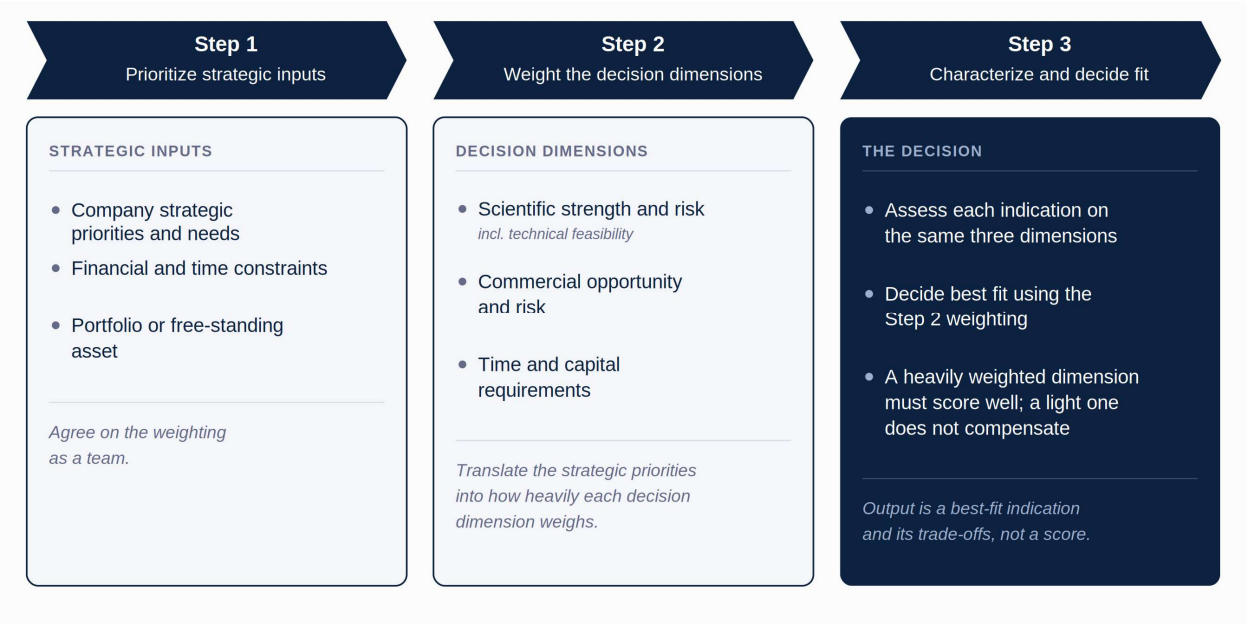
My framework lays out the decision dimensions to consider and how to strategically think about how to prioritize which decision dimensions to optimize for. While doing this properly is a time intensive task, it's too important a decision to make without understanding the full picture. And while the framework supports structured thinking, the real challenge lies in the assumptions, the weighting, and synthesizing the information.

Here's the three-step framework:

1. **Weight the company's key strategic priorities and needs relevant for the pipeline or portfolio decision.**Align as a team and either categorize the strategic inputs into "mission-critical", "important", "nice-to-have" and "not important", or weight them according to their importance. The strategic inputs come from the corporate strategy and may include specific strategic needs. For early-stage companies in particular, financial and time constraints deserve careful attention. When making pipeline decisions, it needs

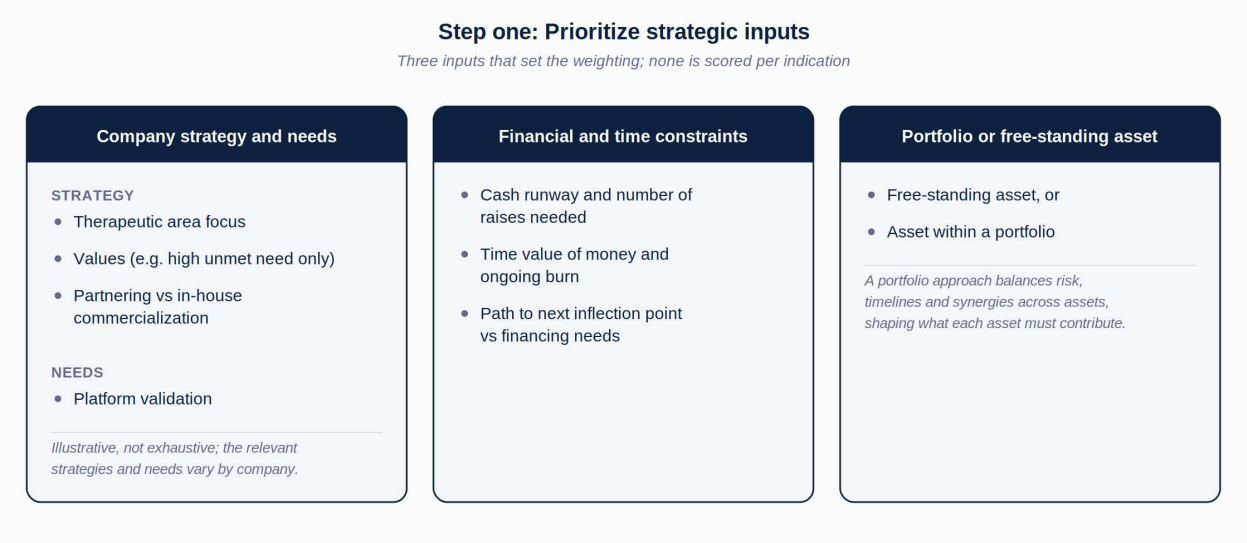
to be clear whether the prioritization is for the asset alone or to strategically optimize a portfolio.

2. **Translate those strategic priorities and needs into a weighting of each decision subdimension.** The three higher-level dimensions I optimize for are scientific strength and risk, commercial opportunity and risk, and time and capital requirements. The strategic priorities determine how important it is to optimize each dimension, and it is critical to score that importance, by weighting or categorization as above, separately for each subdimension.
3. **Characterize each indication on the decision dimensions and decide on best fit.** Evaluating every indication on the same three dimensions, with the same parameters at the same depth, supports comparability. In practice, though, the right depth and the parameters that matter vary by indication, so some deviation from applying an identical template to every indication is often warranted. The goal is to find the indication that best matches the strategic needs.



Step one: Prioritize strategic inputs relevant to pipeline/portfolio decision making

I cluster the strategic input relevant for pipeline and portfolio decision making into three categories: the company's strategy and needs, its financial and time constraints, and whether it is optimizing for a portfolio or a free-standing asset. Having clarity around the company's strategic priorities and needs relevant to the indication/asset decision making and their relative importance will inform which decision dimensions are most critical to optimize for.



Company strategy and needs

Some aspects of the corporate strategy map directly onto portfolio prioritization, like a certain therapeutic area focus or certain values, such as pursuing only areas of high unmet need, that naturally constrain the candidate set. A decision to commercialize in-house rather than partner makes time and capital requirements to commercialization more important, while a partnering approach would shift the lens more to time to significant de-risking. A platform that can reach targets others cannot might create a competitive advantage for specific indications and argues for weighting those. And the need to validate a platform to become more attractive for potential partners would call for low scientific risk and ideally capital-efficient time to relevant inflection points. The art is to agree (ideally as a team) on which of the company strategy and needs are most relevant and potentially mission-critical and to translate how this in turn impacts which decision dimensions become most important to optimize.

Financial and time constraints

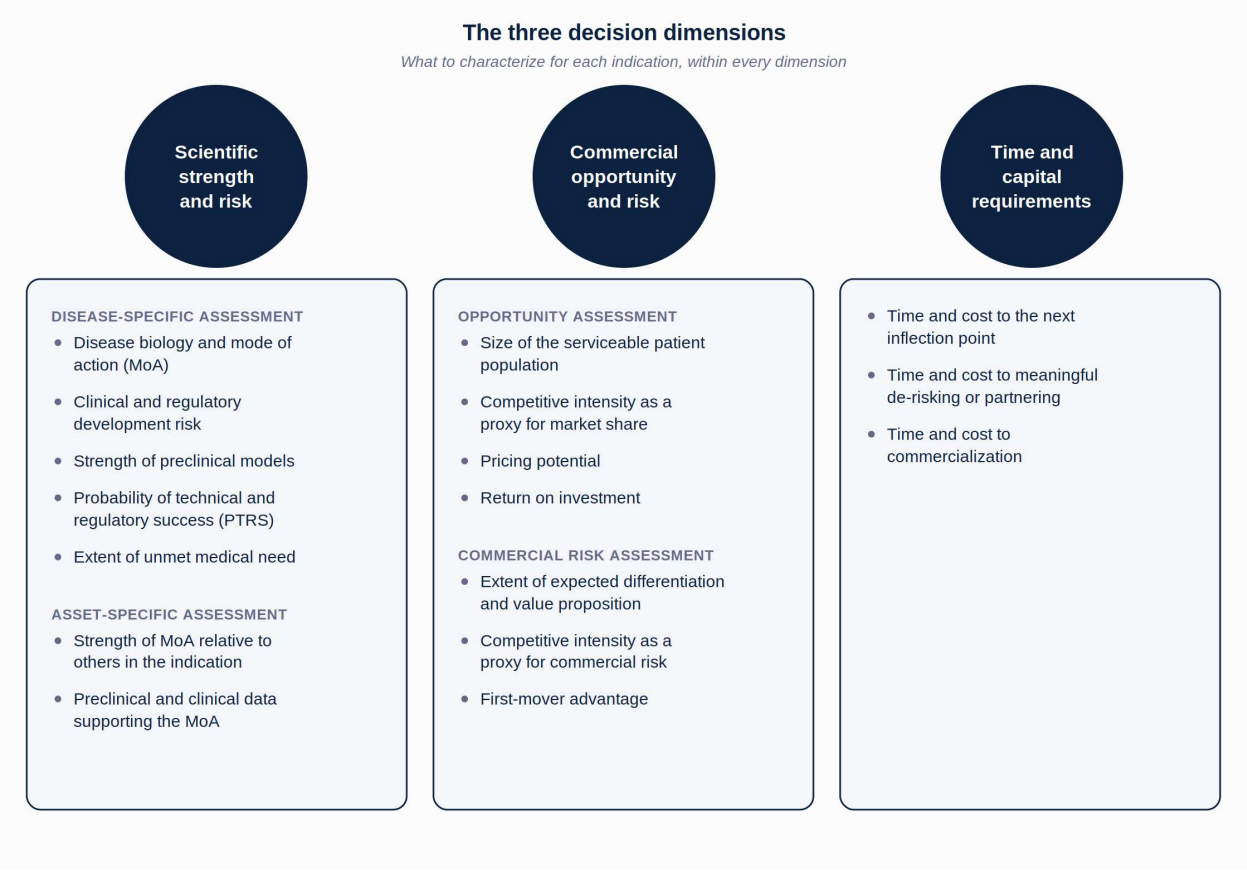
The financial pressure to reach certain milestones within a certain budget is often critical for small companies. Time and capital are linked: every day a company operates it burns cash, and the time value of money makes a shorter development path worth more even when cost and profit are otherwise identical. Requirements vary enormously across indications, so how the cost and timeline to the next minor or major inflection point fit a company’s financing needs can be the decisive factor. An indication with a short or low-capital path to the next inflection point may take priority because it lets the company generate the data needed to raise on reasonable terms, or to partner the asset within its existing runway. Where this is the binding constraint, it weights time and capital to inflection above maximizing the commercial potential.

Portfolio or free-standing asset

Finally, it has to be clear whether the company is optimizing the indication within a portfolio or as a free-standing asset. A portfolio approach adds a layer: balancing risk, timelines and synergies across assets shapes what each individual asset most needs to contribute, which in turn changes how its indications should be weighted.

Step two: Weighting decision dimensions

I assess three decision dimensions: scientific strength and risk, commercial opportunity and risk, and time and capital requirements. The ideal indication would score high on all three, but in reality none is perfect and each has a unique profile of strengths and weaknesses. This is where clarity on the company's strategic priorities shows which dimensions matter most and whether any are "must-win" (e.g. under hard financial constraints). Deciding this deliberately lets a company absorb the risks it can compensate for and avoid the ones that would do the most damage.



Scientific strength and risk

Drug development is inherently risky and unpredictable, and without the science working there is no product to commercialize, however attractive the commercial opportunity. I assess scientific strength in two categories: the science specific to the disease, and the science specific to the asset. The distinction matters because an asset that genuinely works can still fail clinically for disease-specific reasons, for example a heterogeneous patient population that contains a non-responsive subgroup, or a surrogate endpoint that is not sufficiently responsive to change. Knowing whether you are dealing with indication-inherent risk or mainly asset-based risk is itself an important decision factor. For example, where platform validation is the priority, an indication

with low disease-specific risk is preferable, because it reduces the risk of a negative trial that has nothing to do with the asset's performance.

Disease-specific assessment

For the disease side I think in three questions: how well can we predict the outcome of an intervention from our understanding of the mode of action and disease biology; how good are our tools to demonstrate improvement in patients; and how good are our preclinical tools to de-risk assumptions early? The probability of technical and regulatory success (PTRS) reflects all three, and in some cases PTRS alone is enough for an early portfolio decision. Depending on the strategic priorities, though, it can be worth examining the components individually.

Disease biology and mode of action (MoA): The ability to predict an intervention's outcome from its MoA depends on the complexity of the disease biology and how well it is understood. Confidence falls sharply as pathophysiology grows more complex, where blocking one pathway may be compensated by upregulation of a redundant one, or where the biology is simply unclear. Poorly understood biology also tends to hide patient heterogeneity. Unknowingly recruiting a heterogeneous population, with only a subset responding, dilutes the responder pool, potentially to the point where the asset cannot demonstrate efficacy. Oncology has advanced as far as it has in part because we understand what drives cancers well enough to recruit selectively on molecular profile.

- **Clinical and regulatory development risk:** The ability to demonstrate efficacy depends on suitable endpoints and feasible trials. Endpoints need to reliably measure change in disease severity with accepted thresholds for clinical relevance. There is a real risk of failing clinically not because the drug does not work but because the available endpoints do not adequately capture its effect, or because regulators do not agree on the clinical relevance of the change measured. Feasibility also requires enough patients, both in total and willing to enroll; where the population is too small for a conventional phase 3, it requires regulators to accept unconventional designs.
- **Strength of preclinical models:** The ability to de-risk efficacy and safety early depends on the availability and translatability of in-vitro assays, tissue- and animal models. Where no relevant models exist, de-risking has to happen in much more expensive clinical studies, and where animal outcomes translate poorly to humans, the extent of early de-risking is limited. This drives the cost and timeline to meaningful de-risking, which matters from both a partnering and a financing perspective.
- **Probability of technical and regulatory success (PTRS):** PTRS data give a good read on the likelihood of an asset advancing from one phase to the next in a given indication and reflect all of the risks above. They also show how risk is distributed across development, and therefore the timing and extent of de-risking. For an early assessment, PTRS is often enough on its own.
- **Extent of unmet medical need:** The extent of unmet need sets the efficacy bar a new drug has to clear. In psoriasis, for example, the bar has risen substantially: reaching PASI50 was a good outcome in the early 2000s, whereas drugs today need a substantial proportion of patients reaching PASI100. The higher the bar, the harder it is to deliver

meaningful value to patients, physicians, and payers, and the more likely that any added value reaches only a small subset of patients, which significantly weakens the commercial case.

Asset-specific assessment

On the asset side I weigh two things most heavily: the theoretical strength of the MoA relative to other MoAs in the same indication, and the strength of the data supporting the assumption that this MoA will have a clinical effect.

- **Strength of MoA relative to others in the indication:** This looks beyond the general reliability of theoretical predictions in the indication and asks whether there is scientific ground to believe this particular MoA can deliver real benefit to patients, physicians and payers over existing MoAs, ideally with differentiation over competitive pipeline products as well. That benefit may apply to the whole patient population or to a specific subpopulation where the asset is expected to be particularly valuable.
- **Preclinical and clinical data supporting the MoA:** Asset-specific de-risking comes from the availability and coherence of in-vitro, in-vivo and in-human data for the same or closely related targets and modalities. The closer the data is to the asset's MoA, the more relevant it is. In general, in-human data beats in-vivo, which beats in-vitro, but translatability still has to be factored in.

Commercial opportunity and risk

Commercial attractiveness is a combination of the commercial opportunity and the associated commercial risk. An indication might have a large commercial opportunity, but chances to succeed and unlock this potential could be slim due to high scientific and/or commercial risk. Shying away from scientific risk by developing drugs with only minor improvements over existing drugs often leads to increasing commercial risk, where the asset gets approval, but fails to compete for reimbursement and uptake.

Opportunity assessment

Before diving into the opportunity assessment, I want to stress the importance of being clear about the asset's value proposition, not just to patients and physicians but also to payers. Patient and physician values overlap substantially, though not entirely, but payers often value very different things: their lens is improving health across their whole population within a limited budget. Since a drug cannot succeed commercially without reimbursement, and reimbursement at a desirable price is increasingly hard to secure, the payer value proposition is decisive.

The commercial opportunity can be estimated from patient population, peak market share and price to produce a peak sales figure. Peak sales is a good first indicator of how attractive an indication might be, but the time and cost of developing the asset for that indication, which vary enormously, have a significant effect on the overall return and must be considered alongside it.

- **Size of the serviceable patient population:** A bottom-up estimate starts from incidence or prevalence at the top of the funnel, then applies assumptions on (future) diagnostic and

treatment rates, potentially relevant biomarker prevalence and/or failure rates of earlier lines of therapy to reach the serviceable population.

- **Competitive intensity as a proxy for market share:** Market share assumptions are highly speculative early on. For crowded pipelines it can help to count the distinct MoAs in development, apply the disease-specific PTRS to estimate how many will statistically be approved by your expected launch, and assume equal share across approved MoAs. For same-MoA competition, watch timelines and expected differentiation against each competitor closely.
- **Pricing potential:** The price payers will accept depends on the value added over existing options and the price of those options, as well as the serviceable population size and treatment duration. It's important to understand that publicly available list prices typically get heavily rebated.
- **Return on investment:** Return depends not only on the commercial opportunity but on the cost and time of development, the cost of commercialization, and how long the drug can hold premium pricing. A net present value analysis helps compare indications, ideally a risk-adjusted NPV (rNPV) to account for differing risk profiles. At early stages the inputs are coarse and an rNPV is most useful when given with a range of realistic outcomes, reflecting low, base and high case scenarios.

Commercial risk assessment

Not every approved product is profitable; some never recoup development cost, and in the worst case, commercialization cost exceeds revenue. The cost of failing commercially often exceeds the cost of failing scientifically, since most scientific failures occur early, before a full clinical program has consumed sums typically in the hundreds of millions. It is therefore important to weigh not just the risk of failing to reach approval (scientific risk) but the risk of failing to build a commercially viable product (commercial risk).

- **Extent of expected differentiation and value proposition:** The value proposition to payers determines the ability to secure reimbursement at a premium; the value proposition to patients and physicians determines uptake of a product that is accessible. The better the proposition can be defined and underpinned with data, even at the preclinical stage, the higher the asset's value at every inflection point.
- **Competitive intensity as a proxy for commercial risk:** Competitive intensity also has to be read as risk. It widens the error bars on commercial forecasts, can lengthen trial recruitment, undermines the ability to predict differentiation, and can drive market segmentation and pricing pressure.
- **First-mover advantage:** Being first within a MoA can be an advantage but does not guarantee a lasting lead. Entering many years behind same-MoA competitors demands very careful evaluation of differentiation, because a late entrant risks lacking the payer-valued differentiation needed to hold a premium over earlier competitors that may be losing exclusivity and dragging down price for the whole class.

Time and capital requirements

Time and capital are linked, through both the time value of money and ongoing burn, and they feed the return calculation while also being independent decision factors. What matters is the time and capital needed to reach the next inflection point, meaningful de-risking, and commercialization, seen from both an internal capital-management view and an investor and partnering view. Internally, reaching an inflection point that supports a strong financing round can be decisive. Externally, longer and costlier paths raise investment risk, and partners increasingly look for de-risked assets. Weighing these financial risks deliberately, alongside the scientific and commercial ones, is what minimizes risk at the company's most vulnerable point.

- **Time and cost to the next inflection point:** The ability to reach an inflection point on existing cash improves the chances of securing the next round on reasonable terms and reduces financial risk. For investors, the time and capital to a readout that meaningfully shifts the asset's risk profile is a major consideration, since reaching it within the money raised reduces both the risk and the dilution of their investment.
- **Time and cost to meaningful de-risking or partnering:** Meaningful de-risking, often after phase 2 data, materially increases the chance of partnering, and investors will scrutinize the time and money required to get there. A longer path raises investment risk and increases the risk-adjustment applied to the commercial opportunity.
- **Time and cost to commercialization:** Time and cost to commercialization, and the cost of commercialization itself, are further factors that investors and partners weigh, with longer and costlier indications raising the company's risk profile. They also reduce the company's optionality to carry the asset all the way to market without a partner.

Step three: Characterizing each indication on the decision dimensions and finding the best fit

To see what is at play for each indication, do a high-level assessment of the three dimensions from step 2. Then, using the subdimension weighting set in step 2, decide on the indication with the best strategic fit. Setting that weighting before diving into indication specifics helps reduce bias. The output is a chosen indication best suited to the company's strategic priorities and needs, together with a clear, ideally team-aligned, understanding of the trade-offs made. Implementing the framework can lead to better decisions that increase a company's probability of long-term success.