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Bridging Pharma's $200 million commercial gap

Robust contingency plans to capture full asset potential

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Dr. Christian Wieber advises international PharmaCos and Biotechs in the intersection of R&D and commercial topics where he focuses mainly on asset, TA and overarching portfolio strategies and related activities and strategies which are required from the development until launch. Based in Frankfurt he is a director with Strategy& Germany.

Dr. Sebastian Kwisda globally advises PharmaCos and Biotechs with an emphasis on R&D topics and the R&D interface to commercial. He mainly focuses on TA- and asset strategies as well as scenario planning during clinical development. Based in Zurich, he is a Manager with Strategy& Switzerland.

EXECUTIVE SUMMARY

With the ever-increasing complexity of clinical development and market dynamics, more pharma companies are under-achieving against commercialization timelines and commercial expectations, leaving significant value on the table.

Our analysis of new molecular entity (NME) launches over the past two decades shows that 75 percent failed to meet launch expectations. They missed the targeted launch dates by an average of 19 months per asset and underperformed at a rate of around $200 million per asset versus market expectations. This suggests significant room for improvement.

One major contributor to underperformance is companies' restricted ability to react in a timely manner to change, both internal and external. The need to balance multiple launch programs simultaneously – each with increased development and commercial complexity – is leaving R&D, franchise, and therapeutic area leaders with limited bandwidth for contingency planning.

Too often companies have little in the way of alternatives to Plan A for their pipeline assets. Despite having identified different scenarios and associated forecasts, current models of contingency planning are typically insufficient to enable companies to switch gear easily when needed.

To minimize delays and maximize revenue potential, companies mustneed to allocate time and dedicated budgets to mapping out alternative development routes and implementing well-structured contingency plans, affording them vital agility.

This means:

- Starting the planning process early (ideally ahead of clinical development or during Phase I) with a strong commercial and market lens
- Strategically defining and anticipating all relevant external (and internal) challenges with matching evaluation periods and planning potential mitigation options
- Linking contingency plans to key governance, financial, and resource-planning processes.

Neglecting these crucial steps puts companies at risk of significant time setbacks and missed revenue opportunities. The importance is magnified when dealing with assets with first-in-class (FIC) or best-in-class (BIC) potential, making efficient preparation and streamlined development timelines even more critical.

I. Assessing the growing complexity of clinical development

For a long time, the pharmaceutical market and therefore clinical development was almost exclusively driven by large multinational pharma companies (PharmaCos) focusing on large and lucrative therapeutic areas.

The ability to demonstrate a benefit in a particular therapeutic or disease area (TA or DA) was relatively easy, as Standards of Care (SoCs) – or standardized treatment plans – typically had not been established. In this context, clinical development required less focus on external events, execution being the biggest lever of success.

Accordingly, any assessment of assets' target product profiles (TPPs) during clinical development focused primarily on fairly static goals, such as hitting primary or secondary endpoints in trials. A TPP sets out the intended use, target populations, and other desired attributes of a particular drug or therapy, including its safety and efficacy-related characteristics. These identify minimal requirements for a positive business case (the downside); what is expected or hoped for (the base case); and what would be considered to outperform expectations (the upside).

However, the market environment has changed, with the result that optimal planning during clinical development has become significantly more important as a lever for success. Now, large disease areas have established SoCs, challenging pharma R&D teams to demonstrate more than an incremental benefit for each new product seeking authorization.

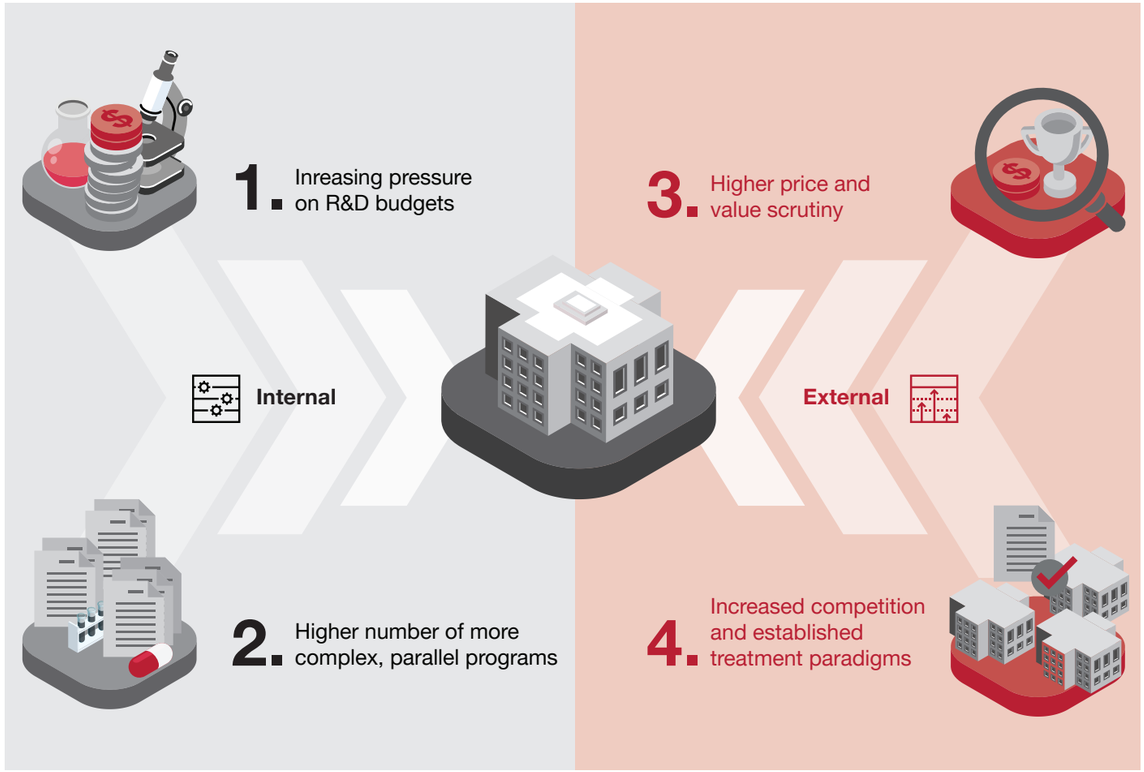
This in turn has demanded more significant innovation.

Many companies have moved to rarer, or even orphan diseases, with less competition, where it is easier to differentiate and justify the need for new products. In the meantime, regulatory changes and increasing market access complexity have made successful clinical development and therefore successful commercialization a more challenging and costly endeavor.

Simultaneously, the pressure on healthcare expenditure has created new challenges around price negotiations.

In this increasingly dynamic environment, with a plethora of additional internal and external influences on success, planning beyond the base-case scenario is becoming paramount to maximize an asset's TPP.

EXHIBIT 1
Up to now, many companies have struggled to achieve this for a number of reasons



Source: Strategy& analyisis

Growing pressure on R&D budgets

To address the increasing need for innovation and to sustain growth in an evolving environment, many PharmaCos have shifted their focus away from mature brands toward R&D. At the same time, the return on investment (ROI) of pharmaceutical innovation has decreased in recent years.

The increasing pressure to improve returns while reducing cost has produced two main outcomes:

- An increased focus on hitting or outperforming the base-case TPP.
  - With limited resources, very few companies consistently plan to mitigate against the downside TPPs, a scenario that is particularly prevalent for assets with less strategic importance. Additionally, focusing on stakeholder interests (with an inherent expectation of positive news) may have created a bias toward the upside.
- A shift in focus to smaller-population, less familiar TAs/DAs that "promise" a higher chance of becoming or outperforming the established SoC, due to growing difficulty in demonstrating significant innovation in larger disease areas.
  - Moving into unfamiliar territory makes preparation beyond the immediate line of sight harder. As a result, building optimal plans beyond the base case is time and resource intensive, conflicting with increased budgetary pressures.

More programs with higher complexity

Over recent decades there has been an observable surge in new molecular entities (NMEs) making it to market, as well as a steady rise in the expansion of existing products into new indications. Yet the average number of companies responsible for these new launches has not changed.

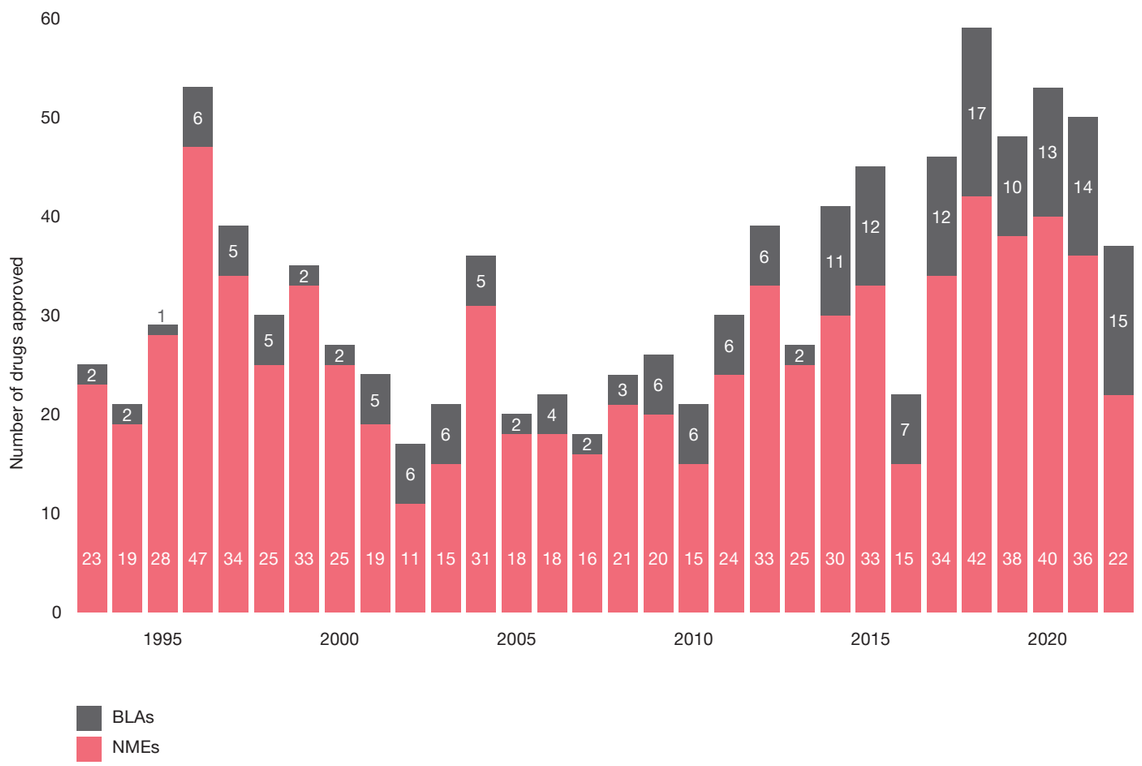
To sustain growth many PharmaCos have increased the number of clinical development programs, with the result that pharma leaders are balancing more decisions and resources across more parallel programs than previously. While a typical company had an average of 41 programs in clinical development (Phase I to III) in 2005, this number had risen to 49 in 2022[1] (a 19.2 percent increase) (*see Exhibit 2, next page*).

While the increasing number of programs alone is difficult to handle, the even more acute challenge in clinical development is the rising complexity of those programs.

There are two main drivers for this: First, larger TA/DAs are increasingly competitive, requiring more elaborate ways to differentiate against an often generic SoC to demonstrate value beyond incremental innovation. Examples of approaches here include head-to-head comparison, devices, new routes of administration, biomarkers, novel (composite) endpoints, and proving the impact on general outcome parameters (for example, a reduction in all-cause mortality).

Second, many PharmaCos are venturing into new areas (diseases and modalities, for example cell and gene therapies (CGTs)) without a previous footprint in, or prior knowledge of, the field. While these new ventures offer potentially significant returns, many unknowns and risks are associated with clinical development. These include trial recruitment, regulatory acceptance of data from smaller trials, post-market authorization evidence generation, and pricing models. Next to mitigation of these associated risks of clinical development, preparation of markets ahead of launch is a pre-requisite for success – especially for CGTs.

EXHIBIT 2
Novel FDA approvals since 1993



Source: Strategy& analysis

Higher value scrutiny

While internal changes have contributed to increasing complexity, most of the new drivers for modifications to clinical development planning are external.

Between 2008 and 2021, prescription drug launch prices grew by 20 percent annually; in the year from 2020 to 2021, 47 percent of newly launched drugs in the U.S. hit market prices of more than $150,000 per year[2].

The surge in prices, as well as the growing availability of effective, high-priced drugs for previously untreated patients, has created novel challenges for healthcare budgets, with an impact on regulatory and market access environments. The changing environments across key stakeholder groups are intensifying the pressure on commercially optimized clinical development, not helped by growing differences between target regions.

Recent examples of policy changes include:

- The European Medicines Agency's (EMA) recent introduction of EUnetHTA. The EU-wide regulation tool aims at supportings collaboration between European health-technology assessment (HTA) organizations that brings added value to healthcare systems at a European and national level.[3]
- The creation of stronger regulations in Germany around the negotiation of reimbursed prices and reduction of spending caps (for example, for orphan drugs), by the GKV-Finanzstabilisierungsgesetz (FinStG)[4].
- The introduction of U.S. legislation in 2021 to close the orphan drug loophole, which has seen drugmakers "piggybacking" on the orphan status of an older drug. The Closing Loopholes for Orphan Drugs Act seeks to stop this by limiting the orphan drug exclusion to only apply in instances where the drug is used for the rare condition or disease for which it was designated.[5]
- The Inflation Reduction Act (IRA) of 2022, also in the U.S. This allows the Centers for Medicare and Medicaid Services authority to negotiate the prices of certain high-cost drugs for the Medicare program.[6]

Regulators

To promote sustained innovation while ensuring treatment affordability, regulators across the world are continuously reviewing and adapting their policies, processes, and requirements.

In this dynamic market, ensuring sustained success as a PharmaCo is no easy feat. **In the context of asset development, particular challenges include:**

- Higher evidence requirements, including real-world evidence (RWE)
- Timeline challenges and delays in clinical assessments with regulatory authorities
- Limited scientific consultation capacity with regulatory authorities in advance of the approval process.

Additional complexity for PharmaCos surrounds the need to anticipate key changes in relevant markets across the globe, and to assess how ongoing programs will need to be adapted to accommodate those changes.

Market access

Market access environments are also becoming increasingly challenging, requiring PharmaCos to develop multiple scenarios per asset per target market based on the possible outcomes of:

1. HTA and/or benefit assessments
2. Pricing negotiations
3. Reimbursement
4. Access along the product lifecycle.

Understanding the relative challenges of individual target markets, and how the respective scenarios are likely to evolve in each, can have an influence on clinical development, as well as evidence generation plans.

Established treatment paradigms and increasing competition

Existing treatment paradigms are becoming increasingly entrenched in modern healthcare practice, and new drugs must break through these deeply ingrained ways of thinking. Developing a successful asset that is unlikely to be first-in-class (FIC) or best-in-class (BIC) needs careful positioning; incrementally improving the SoC is no longer sufficient. Rather, PharmaCos should seek to shape markets from the earliest opportunity, and medically engage and educate the ecosystem, so that stakeholders are primed about the coming benefits.

Competition has increased significantly across most therapeutic areas too, making it increasingly difficult for PharmaCos to differentiate their offerings. For this reason, development teams need to continuously monitor the market for evolving threats and opportunities; for factors that could influence the required level of differentiation; and the anticipated impact of a new treatment on the different stakeholder groups.

Factors to monitor include:

- Current and future unmet needs across treatment lines
- Anticipated primary and secondary efficacy of own assets
- Competitors' timelines
- Competitors' pivotal trial design and (interim) results (for example, patients included, endpoints used, precision medicine approaches, return on asset)
- Options to differentiate beyond the asset (e.g., digital health solutions, programs "beyond the pill").

The growing number of market variables, and options to differentiate new products, reinforces the need for careful planning, prioritization, and scenario-based preparation.

Lack of consistent planning, which remains all too common, can have a detrimental impact on both a PharmaCo's top and bottom lines, for example in:

a. Delayed reaction to external events

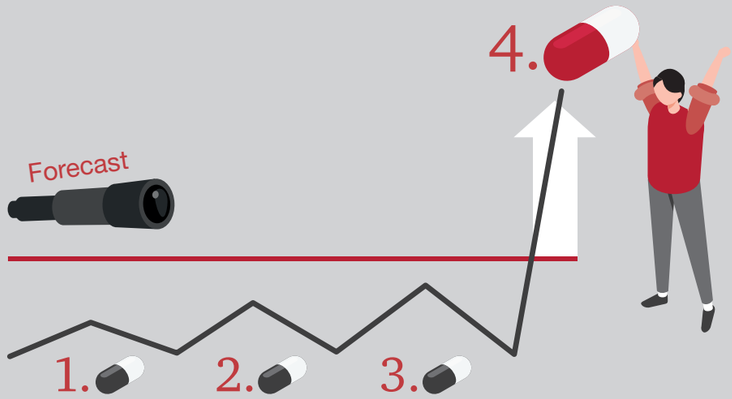
b. Sub-optimal mitigation measures, due to a lack of resources and insufficient preparation

c. A lack of understanding of "no regret moves" (actions that have no downside, which can produce substantial value) and/or "quick wins".

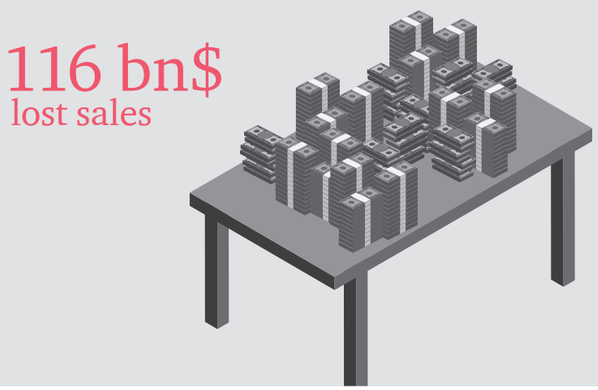
II. Analysis of launch success

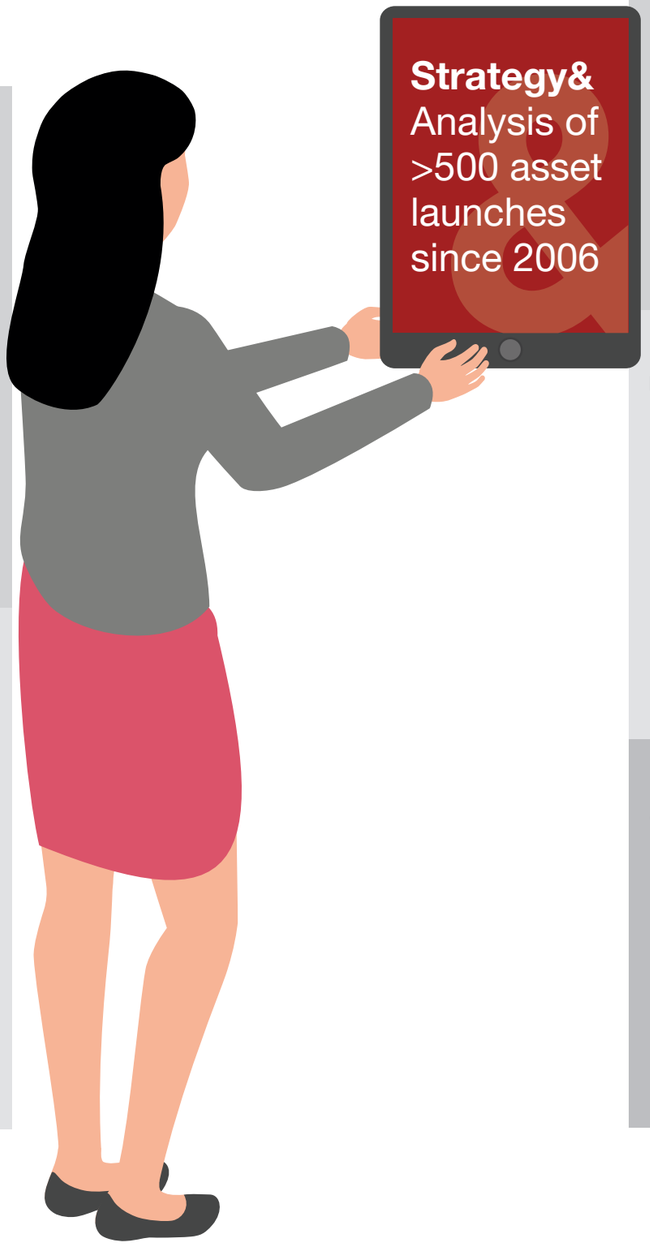
To scope the challenge facing PharmaCos, we conducted a deeper quantitative analysis of launch activity over the past two to three decades. This has revealed that:

1. **Three out of four do not meet or outperform forecasts**



2. **116 bn$ Pharma companies left on the table in the last 15 years in terms of overall lost sales until launch estimated launch versus actual launch**





3. **940 years of accumulated asset launch delay versus estimations**

4. **On average each asset accumulates lost sales of ~200 mln$**

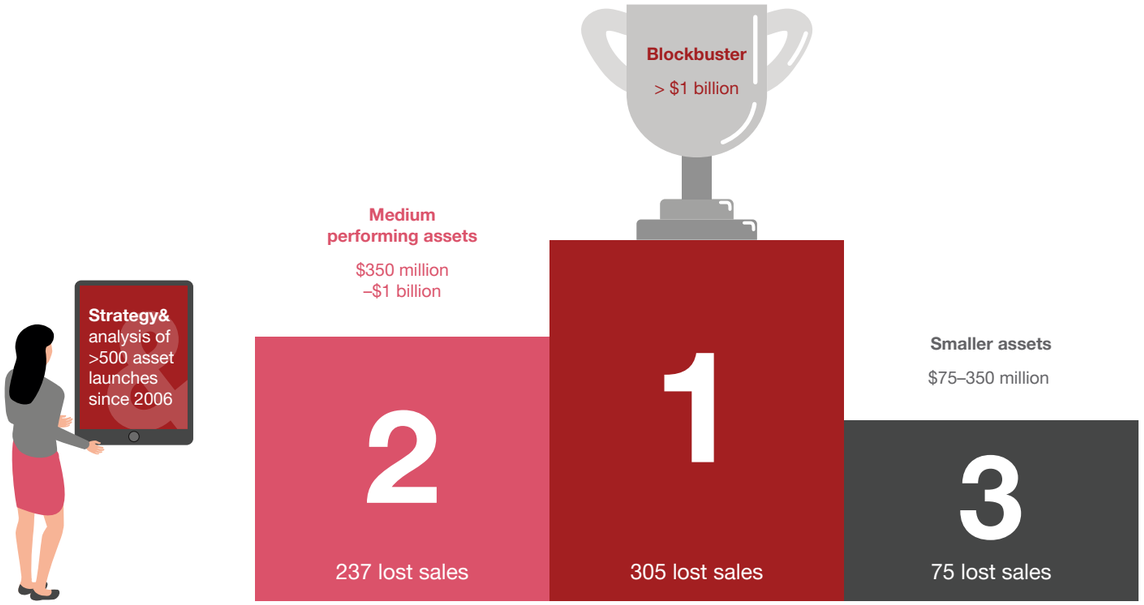
5. **On average each asset has average delayed time of ~19 months**

Across the therapeutic areas, six in 10 assets failed to reach their expected peak sales within three years of launch, before falling behind significantly against initial expectations. This trend applied across all assets, irrespective of whether they were launched on time.

The worst recorded performance in terms of lost sales saw around $305 million in average lost sales from what were initially envisioned as blockbuster assets; compared with $237 million for medium performing assets ($350 million-$1 billion peak sales per year); and only $75 million for smaller assets with yearly sales worth less than $350 million.

$305

million in average lost sales is the worst recorded performance



In terms of launch delays, an opposite pattern can be seen, where a potential blockbuster had the smallest launch delay at an average of 16 months, ranging up to 22 months for medium assets, and 19 months for smaller ones. It would seem that priorities are generally being set appropriately, as the assets with the highest impact are facing the shortest delays. However, more than a year's delay still implies significant losses for those type of drugs.

16

month smallest average launch delay for potential blockbuster

Therapeutic areas	#	Non realized sales	Month delayed
Dermatology	16	60	13
Sensory Organs	16	82	8
Endocrine	34	121	16
Gastro-Intestinal	28	128	17
Genito-Urinary	12	137	21
Various	28	138	24
Oncology	143	148	18
Blood	44	196	17
Musculoskeletal	24	212	21
Central Nervous System	68	263	23
Cardiovascular	29	267	12
Immunomodulators	24	268	33
Systemic Anti-infectives	94	292	21
Respiratory	21	336	28
Grand Total	**581**	**201**	**19**

Looking across the therapeutic areas, there is quite a significant difference by category. While on average the worst performing assets are located in the areas of Respiratory (1), Systemic Anti-infectives (2), and Immunomodulators (3), other big therapeutic areas such as the Central Nervous System (5) or Oncology (8) seem to perform slightly better, especially considering the much larger number of assets involved.

III. Opportunities for improvement

Each product is unique, so the reasons for delays in commercialization or for launches underperforming will vary from case to case. Some delays are the result of conscious, strategic decisions, for instance. In other cases, disappointing commercial results may be down to poor planning or execution.

That said, our own observations reveal that most PharmaCos lack institutionalized contingency-planning processes during clinical development and commercialization preparation, and that this is contributing significantly to their outcomes.

Typically, companies are so preoccupied with Plan A that they do not devote sufficient time and resources to anticipating and planning for alternative scenarios.

To improve their results, companies need to redress this balance.

This means:

- Starting the planning process sufficiently early (ideally ahead of clinical development or during Phase I)
- Viewing product potential through the commercial and market lens much earlier in the life cycle, specifically during clinical development (i.e., at the start of the planning process)
- Strategically defining and anticipating all relevant external (and internal) factors that could influence the new treatment's market impact and performance
- Planning additional evaluation periods during clinical development, based on the most critical factors identified
- Defining potential mitigation options for those factors
- Linking contingency plans to key governance, financial, and resource planning processes.

To navigate the complexity of future asset development, PharmaCos need to rethink contingency planning during clinical development – and include a new and more structured approach to developing differentiated assets within the anticipated timelines, on a consistent basis.

IV. Contingency Planning 2.0

Contingency Planning 2.0 is the next generation of contingency planning, designed to holistically de-risk development and optimize choices beyond clinical development. It differs from current practices in five main ways.

Specifically, it:

1. Involves rethinking clinical development entirely, with an assessment of potential organizational biases toward upside or base case TPPs (for example, shareholder considerations) before moving to the asset level.

2. Starts with initial planning of the asset development before or at the latest during Phase I, when the initial clinical development plan is outlined.

3. Is strongly connected to key resource, governance, and financial planning processes.

4. Requires organizations to move into continuous monitoring of internal and external influences, enabling a stronger and earlier commercial presence to be leveraged, as well as differentiated competitive intelligence (CI) capabilities.

5. Demands that asset teams set up new roles and responsibilities, so people are included early in the development process to reduce the gap between the scientific and commercial perspective of a new asset's potential.

Organizational assessment

We hypothesize that many PharmaCos currently have significant organizational bias toward upside- and base-case target profiles. In other words, they are not planning for alternative scenarios, which is leaving them exposed. Most standardized processes are being directed to either fulfilling the base case or considering how to realize the asset's upside potential.

Increasing the upside of any asset chiefly requires organizations to increase the risk of the development plan (for example, accelerating development, or head-to-head comparison).

Contingency Planning 2.0 can brings that risk down and looks to protect the base-case target profile, i.e., by mitigating the downside. Understanding potential biases and addressing them is crucial to increase organizational buy-in before modifying processes at the asset level itself.

> We are not yet proficient at failing fast. The attitude of planning for the best, while ignoring the worst, creates significant blind-spots during development."
>
> **Anonymized: Executive commercialization of pipeline products top 20 PharmaCo**

Start planning at the development outline stage

Contingency planning should start before or, at the very latest, during the early parts of Phase I when the development plan is outlined.

Contingency Planning 2.0 should ideally involve the following steps:

- Strategic assessment of the relevance of the therapeutic/disease area (TA/DA) and asset as part of the overall portfolio and company strategy.
- Ecosystem assessment, including the definition of external influences – i.e., company TA/DA footprint, established SoC, unmet need per relevant ecosystem stakeholder, competitive pipeline, and anticipated trial read-out dates. That's in addition to anticipated initiatives "beyond the drug", the mechanism of action (MoA), plus scientific validation (reason to believe), key markets, and anticipated regulatory and market access events/concerns.
- Assigning the asset to archetypes based on market assessment:
  a. **Speed** – either one key competitor (for example, the same new MoA – race to be FIC), underdeveloped disease area (orphan) or "winner takes all" market (e.g., prevalence-driven gene therapy market)
  b. **Differentiation** – typically in well-developed TAs/DAs with clearly established SoC and strong competition (relevant if achieving BIC is unlikely).
- Prioritizing the most relevant internal and external influences based on an assessment of the ecosystem, as well as the market archetype.
- Definition of scenarios for the most relevant outcomes per influencing factor.
- Definition of high-level mitigation strategies with clear initial steps if the posed scenario develops.
- Definition of "no regret moves" and/or "quick wins".

> Often, asset teams present to governing bodies just to secure resources or funding, or to update them on forecasts, which is too 'ritualized'. We should learn to use governance entities, as well as peers in other asset teams, as sounding boards to broaden our viewpoint."
>
> **Anonymized: Executive commercialization of pipeline products top 20 PharmaCo**

Connection to resources, governance, and financial planning

As soon as the development plan outline is drafted, it's vital that resources and budgeting are appropriately allocated.

Scenarios and their respective evaluation/inflection points, in turn, need to be reciprocally connected to key functions, for instance:

a. Financial forecasting. Changes within the ecosystem should automatically lead to updated assumptions and modified forecasts for optimized planning.

b. Evidence generation. Certain scenarios (e.g., regulatory or market access changes, as well as below-expectation efficacy read-outs) may require additional evidence to increase differentiation.

c. Launch preparation and go-to-market modeling due to ecosystem changes.

> While we are getting better at including commercial considerations earlier in the cycle, REAL scenario planning happens very late – typically between Phases II and III. What we often lack are stronger regional and real-world evidence considerations during this scenario planning."
>
> **Anonymized: Executive commercialization of pipeline products top 20 PharmaCo**

Continuous, tech-enabled monitoring

Faster reaction to external events requires continuous monitoring of the entire drug development and go-to-market ecosystem. Particularly in the early development phases, this will require a stronger commercial perspective, regional input, and associated functional presence.

Additionally, asset teams will need to highlight evolving competitive influences to CI teams and in turn be informed about changes in competitive development programs – ideally via automated, tech-enabled processes.

A strong collaboration between regional teams, CI, and the asset teams will allow for targeted adaptions to the primary development plan. Sufficient CI capabilities and resources will be necessary to ensure this level of interaction across multiple, simultaneous development programs.

> One significant problem is that when some teams work on an asset for years, they lose sight of the overarching market developments. Too often, competitive intelligence personnel have not been empowered to act as a regular challenger."
>
> **Anonymized: Executive commercialization of pipeline products top 20 PharmaCo**

New roles and responsibilities

Depending on existing CI and asset team capabilities, new functions and roles will be required to ensure that nothing is left to chance.

While not every asset will require a dedicated resource for Contingency Planning 2.0, highly strategic assets can benefit considerably from the allocation of a dedicated "contingency lead" who works continuously as part of or alongside the asset team.

Less strategically relevant assets, or those with lower market complexity, will still require a stronger commercial presence significantly earlier in the process, however. The commercial viewpoint, combined with upscaled CI capabilities, should ensure sufficient monitoring to enable rapid adaptation in line with ecosystem changes, without a loss of focus on primary clinical development.

> Competitive intelligence has been something of a sore point in our company since it was outsourced. Now, the assessment and integration of CI information during the various development steps depends entirely on the capabilities of the asset team leader."
>
> **Anonymized: Executive commercialization of pipeline products top 20 PharmaCo**

V. Conclusion

With the increasing pressure on R&D budgets, we believe that structured and optimally integrated contingency planning can systematically optimize protection against an asset's downside position, or at least help PharmaCos to understand which assets should fail fast due to market developments.

Even an improvement of up to six months leading to longer peak sales would have a significant impact on R&D productivity. Such an increase would relate to "saved" sales of up to $75 million depending on the asset size, and an accelerated launch per asset – typically up to five months earlier.

Based on these numbers and the long-term cumulative effect of such gains, we believe that Contingency Planning 2.0 is a must-have for PharmaCos looking to improve their R&D productivity in the future.

ENDNOTES

1. Strategy& analysis of Cowen and Company Pharmaceutical Industry Pulse (2000-2022)

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