"Play It As It Lies" – Decision making in early to mid-stage API development and manufacturing

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The term "play it as it lies" refers to the requirement in golf, per the rules, to play the ball where it lands on the fairway, or in the rough, without any change to the overall situation (https://www.golflink.com/list_1703_play-as-lies-golf-rule.html).

There is aptness in this concept, as applied to pharmaceutical development. In the current environment, API development is increasingly complex, compressed and tumultuous. This has resulted in the prevailing need for chemical development and manufacturing leaders and scientists to "play it as it lies," to deal with less than ideal circumstances by making hard decisions - prioritizing risk management and tolerating more risk in development programs. This contrasts with the theoretically preferred approach, which is to proactively manage most, if not all, foreseen risks.

A number of factors are responsible for this predicament:

Increasing time pressure on pharmaceutical development
At a default, timelines are being further compressed. This "baseline" compression is compounded by granting of fast track and breakthrough status to certain therapies by regulatory agencies. These designations blur delineations between stages of development, boundaries that would be present in more conventional approaches, and they make the term "phase appropriate" more nebulous than it had already been. With CMC activities on the critical path for most if not all of the development cycle, less time is available for creation of a plan, let alone reflection on and adjustment of strategy.

Small molecules continue to become more complex
The complexities come in multiple forms:

- Structural complexity – more density of functionality and more chiral, single isomer drug candidates;
- Challenging physicochemical properties – an increasing proportion of molecules selected for advancement into clinical development are in the biopharmaceutical classification system (BCS) Class II category (poorly soluble but permeable; reliable sources describe a 2-3-fold increase in the proportion of these molecules in recent years);
  - Therefore, significant additional work on the solid form of the API must often be done to render many candidates tractable for formulation development and manufacturing of dosage form, which consumes additional time and money

Technology transfer is more frequent within the development cycle of a drug
There are many reasons for multiple tech transfers:

- In-licensing or partnering of the drug candidate, where the work may have been done in-house at a big pharma, a biotech or at a CRO or CDMO that will not be continuing the work as development continues by the licensee;
- Unexpected increases in required scale and capability of a given process, due to success and expansion of clinical trials, making the current vendor ineligible to continue with manufacturing due to limits in capacity;
- The intentional initial strategy of working with a low-capacity CDMO, in the interest of moving forward as rapidly as possible, necessitating a later change to accommodate increased demand for API;

- The current API manufacturer, although it is meeting scale requirements, does not meet criteria of investors or partners for commercial manufacturing.

With multiple tech transfers, the risk of key information being "lost in translation" is increased. Vigilance and diligence of those responsible for the transfers is required. This further strains already limited development resources.

Despite the implementation of matrixed organizations and promotion of cross-functional interactions, formation of silos, within and outside of CMC, still occurs with significant frequency

Formation of silos prevents close, timely communication and collaboration between interdependent development functions, e.g., chemical development and formulation development, or formulation development and clinical development. The involvement (or lack thereof) of the end users of API and drug product supply (toxicology, PK/ADME, clinical development) in discussions and decisions with their CMC colleagues who supply the drug has a profound impact on the appropriateness of the material they receive to perform their studies. The type of interaction needed is dynamic and reciprocal - drug substance and drug product functions need to manage and meet the expectations of their end users, and the end users need to vet their expectations with their suppliers.

Increased technical complexity and time pressure can promote the insularity typical of formation of silos in the functional areas of drug development – leaders and individual team members become so consumed with accomplishing their immediate goals that they lose sight of the need for increased communication across functions to determine whether circumstances and needs have changed.

How to "Play It As It Lies" in a proactive, systematic manner – Liaisons and communication

The remedy for the phenomena described above, which are not completely avoidable, is to engage a liaison who understands integrated drug development, and is able to navigate fluidly between functional areas to prevent or mitigate the disconnects that tend to occur. Depending on sponsor resources, this liaison could be a technically savvy project leader. This person would keep all development stakeholders apprised of current issues in all areas that impact their function, and foster discussion and interaction across functions before a crisis forces a meeting that is likely to be less productive. These sorts of individuals are already in place, even at small organizations, but the criticality of and technical/managerial prerequisites for their roles are increasing, due to continually increasing challenges and less margin for error.

Decision making in CMC development is driven by input from the end users of API and drug product, in addition to the options presented by the properties of the candidate molecule. The decisions are made and implemented by pharmaceutical development experts, with the buy-in of the sponsor's management, but these decisions need to be as informed as possible. Synergy,in the form of communication and collaboration between the end users of the API and drug product and CMC experts is essential to the successful, timely development of drugs, especially in an environment where the trend is toward more complex molecules, developed with more aggressive, risk tolerant programs. ■