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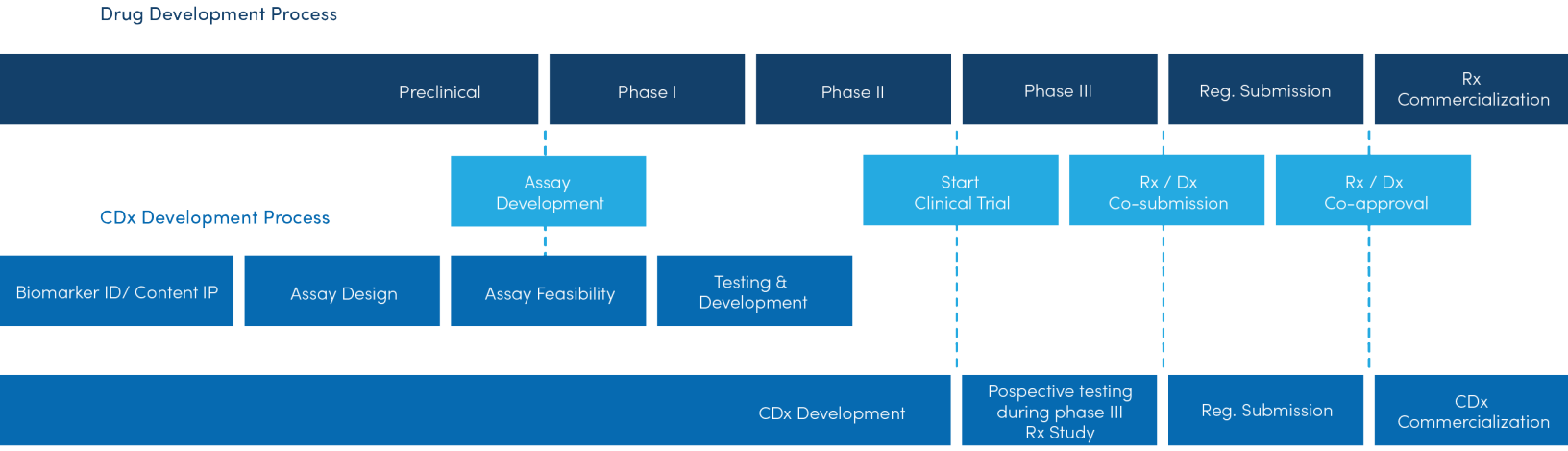
Plan for a Successful International Drug Approval with Early Development of the Accompanying CDx

Companion diagnostic testing has revolutionized Oncology Precision Medicine by providing detailed roadmaps for optimal treatment regimens and patient outcomes based on the underlying genetics of each patient. For drug approvals tied to a CDx, drug development costs are decreased through the targeting of patient subsets for clinical trial enrollment, patient stratification, and clinical trial endpoint; all of which ultimately focus the drug approval path with a narrowed intent-to-treat population, resulting in increased drug efficacy as well as reduced rate of adverse events. Accordingly, the successful approval of a targeted therapy is highly dependent on the performance of the companion diagnostic along with timeline and goal alignment of the diagnostic company with the drug developer.

Thoroughly Vet the Partnership

With early planning and execution, the benefits of partnering with the right pharmaceutical company and diagnostic test developer can be tremendous. This starts with the opportunity to tailor the drug development program and clinical trial design much earlier in the process. Choosing a diagnostics partner too late in the pharmaceutical company's clinical development project, runs the risk that the companion diagnostic assay won't be developed, validated, and approved by the time of drug approval. This can lead to potential inefficiencies during development and launch planning. More importantly, poor uptake and failure to realize the full commercial potential of the therapeutic could be the consequence of poor planning.

When intending to apply for global drug approvals it is important to consider your companion diagnostics partner's international presence, as the process will be more tenuous to navigate due to the constraints specific to the regulatory authorities in your targeted regions of interest (such as USA, EU, Japan, or China). Therefore, it is valuable to find a partner with experience in the regions you wish to submit for approval. An ideal partner should further have quality management system accreditations for manufacturing IVDs along with a mature global distribution network and marketing engine. It is recommended to incorporate CDx commercialization needs into the budget and timeline.



Clinical Trial Assay (CTA) Versus CDx

When designing a clinical trial, it is common to consider the use of a CTA (over a CDx) the seemingly faster, less expensive path. However, in the long run, CTAs can complicate the process, resulting in risk to both timeline and budget. Developing and validating a CDx during Phase 1/Phase 2 (Ph1/Ph2) such that it may be utilized for Phase 3 (Ph3) subject enrollment will typically streamline the process, saving the drug company time and money. Thorough validation of a CDx also ensures the correct intent-to-treat population is enrolled for a Ph3 trial, and the CDx and drug pathways are better synced for regulatory submission, approval, and commercialization.

That said, if a CDx is not developed in time to meet enrollment needs a CTA can be used with a bridging study. At first it may appear that the timeline can be shortened with a CTA, but this is not necessarily true as the CDx may require further validation which can take upwards of a year or two impacting bridging study timelines. Further, any methodology or technical differences between the CTA and CDx increases the risk of discordant results during the bridging study and thus, the most successful CTA will be reflective of the eventual CDx design.

In some trials, multiple CTAs are used for selection of subjects. For instance, local sites may run CTAs in the regions targeted for drug submission to increase likelihood for specific population enrollment. But, this scenario should be avoided if possible, as the use of multiple CTAs when selecting subjects increases the likelihood of bridging study failures due to variability in the sensitivity and variant calling between clinical trial assays. If CTAs must be utilized, mitigate risk by using a limited number of CTAs, each of which is vetted for performance claims including specimen type, sample handling, sample storage, sensitivity, selectivity, variant calling, and clinical cut-off. It is wise to qualify the CTA through tests against contrived proficiency panels including variants of interest, variants not of interest, and dilutions around the expected clinical cut-off. However, when planning for clinical trials the time to CDx development and validation is ideally accounted for such that the CDx is used for patient enrollment mitigating risk to the drug development program.

Sample Collection Needs Differ Between Partners

Unfortunately, the CDx is not always considered in early clinical plans. Specimen processing and storage is often considered difficult and expensive, resulting in limiting specimen collection protocols focused on drug clinical planning alone. For example, it is not uncommon to discover that the drug developer didn't store screening samples appropriately including issues with not storing negatives, not storing consistently, not storing in a manner that ensures stability, and/or not collecting appropriate demographics on screen failures for the Phase 3 subjects. If appropriate subject specimens/samples and associated demographics are not considered upfront there is large risk that a new clinical protocol specific to collect positives and negatives for CDx clinical accuracy validation will be required, resulting in possible delays and increasing costs. Upfront bridging studies will become increasingly complex as the additional clinical specimens will have to be tested with the CTAs (multiple, if necessary), the CDx, and the reference method (an additional method representing "truth" which is required for CDx clinical accuracy validations).

Stringent Protocols are Recommended for Sample Collection and Storage

To mitigate risk to the timeline, stringent specimen collection and processing protocols should be defined early, keeping the CDx validation needs under consideration. Protocols should specify CDx appropriate demographics necessary to characterize the samples including the negatives (e.g. specimen type collected, specimen processing, specimen/sample storage conditions, when collected (age of specimen), patient age, gender, region, and diagnosis).

Next thoroughly consider sample storage and sample processing protocols. For example, frozen DNA from the specimen of interest may be acceptable for storage, but frozen cells would be expected to impact assay results. Thus, frozen cells would be an additional specimen type resulting in studies evaluating 2 sample types rather than 1 sample type. If a gene expression assay is being developed, remember that RNA is highly likely to change and/or degrade over time. Finally, ensure whatever sample type you choose is processed correctly via stringent protocols that are shared across collection sites (*e.g.* extractions, dilutions, storage conditions, etc.).

Regional Considerations

Before finalizing CTAs, CDx, or commercialization strategies consider requirements and timelines specific to the regions being targeted for drug approval.

- Determine whether the assay configuration and technology chosen for the CTA or CDx are fit for clinical trials and global commercialization.
- If targeting Japan, reimbursement requirements must be incorporated into the commercialization timeline and budget as this reimbursement must be set prior to marketing of either the drug or CDx.
- Certain regions require co-submissions of drug and associated CDx. It is advised to research regions to plan for any co-submission time line requirements.
- Anticipate lengthy submission review periods, which may take 6 to 12 months.

Conclusion

These common oversights can be avoided and/or resolved by early engagement with a CDx partner and careful planning of the P1/P2/P3 studies. Moreover, in summary, it is recommended that CDx validation be completed prior to the pivotal trial initiation thereby increasing the likelihood of a simultaneous CDx and drug launch.

Regardless of the precise path followed for subject enrollment, it is critical to choose an experienced IVD partner to effectively navigate international regulatory pathways and fluctuations, and optimize market access. It is also wise to co-develop companion diagnostics in conjunction with your drug to expedite approvals and commercialization. Ultimately, a pharma company and their partnering diagnostics company may have different expectations, and it is important to bridge the gap of coordinating their specific goals, needs and requirements to align project milestones. With so much to consider it is prudent to approach CDx partners early to mitigate risk to clinical and drug submission timelines.