FRIENDS of CANCER RESEARCH

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Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications

Introduction

Drug and diagnostic co-development has traditionally occurred in a manner by which one drug is accompanied by one diagnostic test to sufficiently characterize the safety and efficacy of the drug, while contemporaneously demonstrating the analytical and clinical validity of the diagnostic test assessing the biomarker status and of the responding patients in a clinical trial. For rare biomarkers or indications, this approach may not sufficiently leverage opportunities to expedite development for therapies and balance the need for efficient development of a companion diagnostic (CDx). The field of oncology has progressed substantially with an improved understanding of the biology of cancer, which has coincided with the availability of next generation sequencing (NGS) technologies that can query many biomarkers in one test. In cancers where NGS can be employed to assess biomarker status, these advances make the traditional one drug-one test approach to development of targeted therapies less ideal and poorly aligned with clinical and laboratory practice and patient needs.

New drug development follows the typical investigational new drug (IND) processes for clinical development, and Study Risk Determination (SRD) is typically conducted to determine whether FDA investigational device exemption (IDE) approval is required for the use of an unapproved diagnostic test in the clinical study. Although local testing (e.g., tests performed at a lab affiliated with the patient's treatment facility using a laboratory

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developed test (LDT) or commercial test kit/platform if one exists) may be used to identify patients for studies of drug activity and biomarker assessment, one central lab test prototype is generally used for enrolling patients into the pivotal study.

Challenges with the traditional development and regulatory review of drugs and CDx range from concerns about homogenous clinical trial populations, delayed patient access to clinical trials, and pre-/post-market requirements. Drug sponsors seek to balance enrollment speed with trial integrity, i.e., ensuring that the trial is enrolling a well-defined patient population that reflects the intent-to-treat (ITT) population. There may be delayed access to clinical trials because patients may be first screened using local lab testing and then are only enrolled in the trial following confirmation that patients meet trial eligibility criteria with central lab testing. This process presents challenges to drug and diagnostic co-development and can result in undue patient burden and potential medical harm since it may entail re-biopsy. It can also lead to delayed enrollment and accrual, increased wait time for patients to be in study, and delayed development (resulting in delayed post-market access) of the diagnostic and therapeutic. Where biomarker positive samples are very rare and regulatory requirements are not adjusted to account for this rarity, pre-/post-marketing requirements for diagnostic developers may dis-incentivize or slow the development of an approvable CDx for rare diseases or rare variants.

The type and extent of information required by FDA to support approval of diagnostic tests may need to vary based on the benefit/risk balance for the individual device and its intended use. FDA has generally not applied differing requirements for levels of evidence or certainty when a CDx addresses rare biomarkers. This is likely because of a lack of guidance on what flexibility can be applied, a lack of well-developed alternate methodologies, and a lack of designated pathways where flexibilities can be applied. However, the Humanitarian Device Exemption seeks to address issues that exist in developing CDx for rare diseases including limited availability of positive samples, limited information about potential alterations that could be treatable, and requirements to screen large numbers of samples to find a reasonable number of useful samples. To address these issues, flexibility in development expectations would benefit both patients and product developers to overcome some of the challenges to bringing therapies and CDx to market for rare diseases/biomarkers.

A more balanced approach to patient selection and diagnostics development in oncology clinical trials is needed, particularly for patients with rare diseases. Our goal is to propose a framework that would facilitate enrollment of patients in an efficient manner while maintaining clinical trial integrity and approval of a CDx based on requirements that consider the benefit-risk profile and feasibility of obtaining samples. Furthermore, to ensure timely availability of a diagnostic at or near the time of drug approval, we propose refining validation requirements for CDx approval. This document explores recommendations to 1) improve patient access to clinical trials for rare disease/biomarker therapies via expanded use of local tests, and 2) de-risk and streamline the development of a CDx for rare cancers to align with drug development.

Improve Patient Access

Ensure that policy does not inadvertently create roadblocks or reduce patient access

As development of targeted therapies directed at rare biomarkers and rare variants of more prevalent biomarkers becomes more common, reliable testing and screening capabilities to recruit patients for studies will be increasingly important. Using a single diagnostic assay intended to support assessment of clinical trial eligibility can slow patient accrual when patients are initially screened by a local, non-FDA approved testing platform. On the other hand, enrollment based on multiple tests with potentially variable performance and varying design (e.g., DNA vs. RNA) may not optimally select patients for enrollment and may complicate later efforts to obtain CDx approval. Establishing minimum performance standards could help address and alleviate these challenges.

Recommendations

Detection of rare biomarkers and rare variants to support the development of targeted therapies poses unique challenges, particularly as it pertains to the analytical comparability of the test(s) used to enroll patients into pivotal clinical trials. However, the benefits of identifying and accruing patients using multiple local tests, particularly when identifying rare variants, may outweigh the risk of variability in the clinical trial population. To support this paradigm, alignment of minimum performance standards and variants/variant classes can help standardize biomarker measurement which in turn could reduce barriers to patient enrollment and ensure homogeneity in the trial population. Per current FDA guidance,[1] enrollment using multiple local tests is allowed (including for pivotal trials), and FDA recommends that the sponsor evaluate comparability of test results among potential sites prior to initiating trial testing at those sites. Clinical trial sponsors (drug developers) could articulate, prior to patient enrollment, the minimum performance standards needed to accrue patients based on the particular study needs.[2] Local labs with individual tests could then provide evidence of minimum performance data if they intend to enroll patients into trials. In keeping with FDA guidance, these data would include information regarding accuracy, precision, analytical sensitivity, and analytical specificity, which the sponsor could share with FDA and enroll patients in the pivotal study using the local test results (as already occurs) but more efficiently and potentially with less variability. While exploratory, the NCI-MATCH Designated Laboratory Network[3] approach could be used as a model to qualify labs and find alignment between central/local testing through prerequisite validation standards.

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[1] Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product - Draft Guidance for Industry and Food and Drug Administration Staff (fda.gov)

[2] Recommendations for proposed minimum performance standards available in Friends of Cancer Research White Paper—Blueprint for Breakthrough Forum: Research and Reimbursement in the Age of Precision Medicine. https://www.focr.org/sites/default/files/pdf/Friends%20Alexandria%20Blueprint%20White%20Paper_October.pdf

[3] James V. Tricoli, et al. Design and development of the molecular analysis for Therapy Choice (NCI-MATCH) Designated Laboratory Network. JCO 2019 37:15_suppl, 3016-3016

Diagnostic tests have varying underlying designs and methodologies, and laboratories use different analyses, which can lead to discordance across tests. To account for potential variance, patient samples that are positive for the rare biomarker are typically used to standardize test performance and support test validation. While accepted practice, it is nonetheless a poor use of precious biomarker positive clinical samples that is costly and time consuming. FDA could consider issuing guidance recommending the use of a combination of contrived samples, representative variant validation, variant class-based validation for certain variant types, and, where available, prior data that demonstrate analytical validation of the assay (e.g., previous FDA approval of an NGS-based test) to ascertain test performance while expediting test development and patient accrual **(Table 1)**. In instances where clinical samples are particularly hard to obtain, whether for a local test or a CDx in development, FDA could consider allowing substitution with similar tumor types (e.g., perform analytical validation on non-small cell lung cancer (NCSLC) samples where small cell lung cancer samples are unavailable) or a "DNA is DNA" approach allowing use of any sample with the biomarker in question, regardless of its tissue of origin. Use of a representative approach for simple genomic alterations such as single nucleotide variants (SNVs) should be considered as appropriate surrogates. The extent that these alternative approaches could be used will depend on the complexity and prevalence of the biomarker being detected.

Table 1: Proposed Minimum Requirements to Support Use of Tests Detecting Rare Variants

Performance Characteristic	Minimum Requirement*
Concordance (Sensitivity, specificity, accuracy)	30 biomarker negative samples A range up to 30 biomarker positive[#] samples If possible 6 known positives (confirmed using an orthogonal method)
Limit of Detection	1 known positive* sample in a serial dilution series with at least 3 replicates at each dilution step
Precision	Repeatability across operators, reagent lots, days, instruments using 2 positive samples per variant type, with one at 1.5x LOD and one at 2x LOD
Limit of Blank	5-10 replicates across 2-3 healthy donor samples using the same sample type
**Requirements and number of samples should be guided by the complexity and prevalence of the biomarker being detected* *[#]Can be a contrived sample*	

De-risk and Streamline the Development and Review of CDx to Align with Drug Development

Review drugs for rare indications and companion diagnostics in tandem via benefit-risk assessment

Regulatory processes associated with the co-development of a targeted therapy and CDx should also be aligned if concurrent approval of the drug and diagnostic is required. As with the development and regulatory pathways for targeted therapies, the regulatory pathways for the associated CDx should be reflective of the unmet need for rare indications, which may require additional flexibilities by FDA review divisions. The goal would be to create a mechanism to identify diagnostic tests for a rare tumor type that would lead to an intensive, interactive, and collaborative development and review process. Similar to what is done for drugs used in rare diseases, this approach could include the use and publication of a formal benefit-risk assessment for the diagnostic and the level of pre- and post-market evidence could be calibrated relative to considerations in the benefit-risk assessment. Drug and diagnostic review divisions should make a concerted effort to align review processes such that the drug and diagnostic are given contemporaneous approvals.

Expedite development and regulatory pathways for companion diagnostics for rare biomarkers

In order to achieve more rapid availability of an approved diagnostic, it may be appropriate to rethink the application of FDA's benefit/risk framework. It is important to balance timely patient access with analytical and clinical validation, bridging studies, and potential post-market study requirements for PMA approval that are required of the CDx test developer. A risk-based approach to identify which data elements are essential prior to approval (minimum core data set) and which data elements could be shifted to the post-market space as a requirement for maintained approval could support expedited development of a CDx for a rare biomarker or variant and allow a sponsor the opportunity to de-risk CDx investment prior to full proof of concept on a therapy. This could serve as a means to expedite the development of high-risk tests and facilitate contemporaneous regulatory review. Likewise, and perhaps more applicable for rare biomarker CDx, FDA could reconsider the extent of required evidence based on the benefit-risk assessment for the diagnostic, the rarity of the biomarker, availability of tissue samples, and the unmet need. Although post-market studies as a condition of approval are appealing, the ability to access rare samples after approval is generally not improved and may be worse than in the pre-market setting.

Recommendations

Sponsors are afforded flexibilities to facilitate drug development for rare indications. In a similar vein, the Center for Device and Radiological Health (CDRH) and CDx developer could engage in dialogue earlier in the development process to explore flexibilities that could be applied to the CDx development for a rare biomarker. Further, CDRH should commit to an expedited review timeline of 75 days for CDx for rare indications to ensure contemporaneous approval of the CDx and the drug, as drugs for rare indications are typically reviewed in a compressed timeline.

A core set of validation data should be submitted pre-approval for all diagnostic tests, including validation of analytical performance characteristics such as sensitivity, specificity, accuracy, precision, reproducibility, and limit of detection; but FDA should have the flexibility to consider the necessity of other data requirements in the context of a rare variant. In determining when to apply such flexibilities in development requirements, FDA should consider:

- Prevalence of disease/cancer type (e.g., whether orphan disease or low prevalence cancer type)
- Prevalence of mutation/biomarker/variant within that cancer
- Tissue type and availability
- Test type and prior analytical validation generated in similar cancer types or sample types

To qualify for the rare disease/biomarker flexibilities, FDA should use a threshold of 10,000 patients likely to have the disease or condition (not be tested for it). Examples of rare variants and tissues, where it would be appropriate for FDA to apply development flexibilities due to these considerations, are included in **Table 2**.

Table 2: Example Considerations for Benefit-Risk Assessment for Rare Diseases and Rare Variants

Rare Disease/Variant/Required Tissue for Validation	Characteristic Qualifying as Rare
NTRK	• Prevalence of variant (0.32% across solid cancers)
ROS-1	• Prevalence of variant (1.0% of lung non-small cell lung cancer)
Triple negative breast cancer patients after progression on primary therapy that metastasizes to the bone	• Tissue type and availability
Fine Needle Aspirate (FNA) in NSCLC	• Paired biopsy and FNAs from the same patient needed for validation

In the case of a rare variant or rare disease where development flexibilities may be appropriate, FDA should consider a variety of options for aligning the development expectations with the risk/benefit of the test and the unmet need for the drug. FDA reviewers should have license in these rare biomarker and rare disease scenarios to modify the requisite number of samples for an analytical study, the sample types, or waive requirements for certain analytical studies if these studies are recapitulating existing data or merely being done to "check the box" rather than generating new and meaningful information. Flexibilities that could be applied are included in **Table 3**.

Table 3: Regulatory Flexibilities that Could be Applied for CDx for Rare Variants/Biomarkers.

Analytical Validation

- For biomarkers that have already been analytically validated on NGS tests that have previously received FDA approval, FDA should leverage this validation in order to expedite review and approval for a rare indication.
- To demonstrate analytical validity of rare variants/biomarkers, FDA should allow sponsors to provide some combination of the following instead of requiring use of clinical samples:
    - contrived samples
    - similar tumor types/sample types
    - representative variant validation for certain variant types
    - if available, prior data that demonstrate adequate analytical validity for their assay
- FDA should not require revalidation of variants if they are in the exact same location or within the same base pair as a previously validated variant, and the primers are the same.
- Repeat validation should not be required for every mutation/biomarker on a test platform when adding a new variant or to enroll a trial using a previously approved test, when the variant of interest was included in the first release of the approved test. Even if a small number of samples was used to validate that specific mutation for the first release, the test should be considered validated or, if anything, additional validation should be minimal with a small number of additional samples.
- FDA should not require that a variant be validated across all different types of cancers.

Clinical Validation

- FDA should rely on the clinical performance (based on clinical outcome data) of an assay, rather than requiring concordance studies to LDTs used in enrollment using rare or limited clinical samples if different from the proposed CDx. Often these LDTs are tests of varying design, that have not gone through FDA pre-market review and are of unknown performance.
- If FDA requires bridging studies between a candidate clinical trial assay (CTA) and the to-be-marketed CDx, the agency should consider whether such studies could be conducted as a post-market commitment.

Other Regulatory Flexibilities

- Allow use of a prespecified modification plan for already approved CDx seeking additional indications:
    - A prespecified modification plan would allow a test developer to submit a validation plan for future modifications that FDA could approve for post-market use in lieu of reviewing additional post-market analytical validation data to support a modification.
    - For example, where a new mutation of clinical significance is in the same class (i.e., SNV) and same locus as a previously validated variant.
- Waive or, if necessary, shift into post-market certain studies (e.g., interfering substances, reproducibility, bridging studies).
- Allow for post-market collection of real-world evidence.

The alignment of review programs for drugs and CDx could be further facilitated by creating a risk-based pathway for a CDx for rare biomarkers. FDA could publish a benefit-risk assessment at CDx approval for both PMAs and supplemental PMAs, akin to what is included in the summary basis of approval published for drugs, to enable greater regulatory flexibility for tests for rare biomarkers.

Conclusion

Current CDx guidance aims to enable co-development of a diagnostic and targeted therapy, which in turns allows for demonstration of analytical and clinical validity of the diagnostic test.[4] However, this will become more challenging as narrower subpopulations are identified (both in oncology and in rare disease spaces). The traditional pathway for drug and diagnostic test co-development may not represent the most efficient method for development of targeted drugs and their CDx for rare tumors. Policies should address how to speed CDx development and review while limiting disruption to the current framework, including leveraging current flexibilities available for rare indications and unmet medical need. Modifications to the development process can maximize patient access by not restricting the screening requirements to a single test, provide for rapid access to clinical trials by alleviating the need for repeat biopsy and test analysis, expedite clinical drug development by identifying additional eligible patients, and ensure consistency between different tests with the same intended use. Ultimately, identification of patients who would benefit from therapies can be performed more efficiently, and greater patient access can be achieved.

[4] Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product - Draft Guidance for Industry and Food and Drug Administration Staff (fda.gov)