FDA Regulation of Companion Diagnostics
Disclosure

+ Slideset drawn from Part I of presentation made by Janice Hogan, Hogan Lovells, October 2016
+ Updated where appropriate
Outline

+ Background
+ FDA’s Final Companion Diagnostic (CDx) Guidance (2014)
+ Pathways to Market
+ Clinical Study Issues
Expanding knowledge in the areas of genomics and proteomics provides opportunities for:

- Development of novel therapies
- Designing and managing more effectively the clinical evaluation of therapeutic products (drugs and biologics)
- Improving the use of existing therapeutics
- Targeting treatment, taking into consideration a patient’s genomic profile or their specific molecular characteristics related to a disease

In vitro diagnostics (IVDs) will play a key role in assessing a patient’s specific state or disease condition, and in developing “essential information” in drug/biologic use.

“Personalized [Precision] Medicine,” using diagnostics and drugs together, is intended to optimize patient care and provide the best medical outcome (“right treatment to the right patient at the right time”)

Expectations for Personalized/Precision Medicine
The development of assays to assist in personalized/precision medicine presents obvious opportunities for IVD manufacturers, drug manufacturers and clinical laboratories alike, including:

– Opportunities to identify uses for existing or new drugs or uses in therapeutic “sub-populations” not otherwise considered, or possible, without the use of a diagnostic for patient selection
– To predict drug candidates that may warrant further development due to identification of responders
– To assist with clinical study design to expedite successful efficacy studies
– The potential to avoid the perception that adverse toxicity occurs for all patients using effective drugs through the identification of subpopulations at risk for toxicity based on biomarkers
– The potential for the diagnostic assay market to grow as the number of identified biomarkers increases
FDA’s CDx FINAL GUIDANCE 2014
Jointly released by CDRH, CDER, CBER

Definition of IVD Companion Diagnostic:
- An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product (Emphasis added).

An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:
- Identify patients who are most likely to benefit from a particular therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

FDA does not include in vitro diagnostic tests that are not essential to the safe and effective use of a therapeutic product, so understanding what is essential (versus helpful) is important
Regulatory Pathways

- Follow current applicable regulatory requirements:
  - Medical device regulations for the IVD companion diagnostic
  - Drug and biologic regulations for the therapeutic product application, as applicable
- Reinforced risk-based approach to determine the need for 510(k) or PMA
- Collaborative review of the assay and the therapeutic product by relevant FDA offices

Both IVDs and laboratory developed tests (LDTs) will be subject to FDA review if the test is a companion diagnostic product

*Most companion diagnostic devices will be Class III devices.*
Generally, approval or clearance of the diagnostic device will be required at the same time as the therapeutic product approval. Exceptions:

- A therapeutic product that is intended to treat a serious or life-threatening condition for which no alternative treatment exists
- The benefits of the use of the therapeutic product far exceed the risks that may be presented with use of that product without an approved or cleared companion IVD

**FDA Safety and Effectiveness Concerns**

- Analytical accuracy: measure of expression level of marker of interest
- Clinical accuracy: identification of appropriate patients
- Errors create a risk for withholding appropriate therapy or administering inappropriate therapy
Investigational Use

- Tests used to make treatment decisions in a clinical trial of a therapeutic product are investigational devices (unless already approved or cleared for the specific use under study)
  - Clinical treatment decision tests are significant risk devices under 21 CFR 812.3(m)(3), requiring compliance with full investigational device exemption (IDE) regulations
- If test and therapeutic product are studied together to support their respective approvals (or clearance as appropriate for the diagnostic device), investigational study may be conducted under an investigational new drug application (IND)
  - Study must be designed also to meet the requirements of the IDE regulations
  - Depending on details of study plan and participants, a sponsor may submit an IND alone, or both an IND and an IDE. Sponsors should consult with the therapeutic product center and the relevant device center as to which approach is best or necessary for a particular study
Labeling

- Use of IVD companion diagnostic will be stipulated in both the assay and the therapeutic labeling (and generic equivalents of the therapeutic product).
- FDA’s preference is that the therapeutic labeling (indications for use) should identify a type of FDA approved or cleared diagnostic device rather than the specific manufacturer of the assay.
Some drugs involve a diagnostic test but the test is not considered a true “companion”

Genetic tests that are part of the standard of care for evaluation of a disorder or condition are not regarded as “companions”

These tests can be cleared in some cases via pathways other than a PMA

Examples include cystic fibrosis related genetic tests

Similarly, recent approval of EXONDYS 51 for DMD:

“EXONDYS 51 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping”
There were 27 PMA companion diagnostic approvals and one clearance via the de novo process between 2007 and 2015.
PATHWAYS TO MARKET
Alternative Pathways

+ De Novo Pathway
  – In 2012, FDA cleared a de novo submission for the FerriScan R2-MRI Analysis System, which is a companion diagnostic for deferasirox (but not an IVD)
  – Compared to most other CDx, the system may present lower risks because it was 510(k) cleared and marketed prior to the de novo submission
  – The de novo submission was supported by data from a prospective study of deferasirox with 166 subjects.

+ Humanitarian Device Exemption (HDE)
  – In 2015, ARUP Laboratories received two FDA approvals for companion diagnostics for Gleevec through the HDE pathway.
  – The HDE program is intended to benefit patients by treating or diagnosing a condition that affects a very small patient population (8,000 individuals).
  – Data requirements for HDE approvals are generally less, reflecting the rare nature of the genetic targets
Expedited Access Premarket Approval (EAP)

- FDA devoted significant attention to companion diagnostic products in the 2015 EAP Guidance document
  - CDx may qualify for the EAP program if their use is in the best interest of patients (e.g., to minimize serious side effects or target important therapies)

- The types of evidence that might support approval of CDx under EAP would include intermediate and surrogate endpoints as well as clinical endpoints
  - For example, if a drug is reviewed via the accelerated drug approval pathway based on a surrogate endpoint, the companion diagnostic may be considered for the EAP pathway
### Examples of CDx Approvals

<table>
<thead>
<tr>
<th>Company/Device (Submission Number)</th>
<th>Submission Type</th>
<th>Summary of Clinical Studies</th>
<th>Prospective vs. Retrospective Studies?</th>
<th>Simultaneous Drug/Biologic Approval?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Molecular, Inc., VYSIS CLL FISH Probe Kit - P150041</td>
<td>PMA</td>
<td>Device was tested as part of a Phase II study for the approval of venetoclax. Study required that a 17p deletion must have been documented using the device for enrollment in the study. The overall response rate data from this study was used to support approval of venetoclax. (N=261)</td>
<td>Prospective</td>
<td>Yes</td>
</tr>
<tr>
<td>Roche Molecular Systems, Inc., cobas® EGFR Mutation Test v2– P150047</td>
<td>PMA</td>
<td>Device was tested via a bridging study to support the safety and effectiveness of the test to select patients for treatment with erlotinib by detecting the presence of specific EGFR mutations. Patients’ available plasma samples were evaluated using the cobas® EGFR Plasma Test v2. The results were bridged to the cobas® EGFR Tissue Test v1 results from a multicenter Phase III study for erlotinib. (N=180 for the bridging study)</td>
<td>Retrospective</td>
<td>No</td>
</tr>
</tbody>
</table>

* Bridging study: a study linking the results of a diagnostic test kit to earlier laboratory assessments or device versions used during the clinical study of the therapeutic.
Next Generation Sequencing (NGS) allows rapid sequencing of large segments of an individual’s DNA, potentially even the entire genome.

FDA believes that NGS technology can accelerate personalized medicine.

In 2016, FDA hosted a public workshop on NGS-based CDx for cancer.

- Goal was to seek feedback on preanalytical, analytical, and clinical validity characteristics that FDA should consider in regulating such tests when used to guide treatment decisions.
- No consensus on validity metrics among experts at the meeting.

FDA has approved 3 NGS-based CDx

- Praxis Extended RAS Panel (Illumina)
- Oncomine DX Target Test (Life Technologies)
- FoundationFocus CDx BRCA (Foundation Medicine)
CLINICAL STUDY
ISSUES
CDx Study Issues - Pathways for Study Approval

+ Two general pathways exist for FDA to regulate a CDx during drug development:
  – Solely under the drug’s IND
  – Through a separate IDE

+ Two ways to qualify to proceed solely under IND
  – Non-significant risk (no real risk), or
  – IDE-exempt:
    • Non-invasive (does not require tissue biopsy or unique, separate blood draw)
    • Does not require an invasive sampling procedure that presents a significant risk
    • Does not introduce energy into a subject
    • Is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established method
  – Must include full description of the diagnostic in the IND

- Under either pathway, the sponsor is still expected to have a written protocol and IRB review
Phase I CDx trials typically qualify for IND-only approach; phases II and III generally do not
  – In most later phase trials, the CDx is used to select the study population or adjust dose, without confirmation of the CDx result by an accepted, alternate method.

Description of CDx in the IND needs to include:
  – What is the marker
  – Method (chemically, physically, immunologically, PCR (nucleic acid), mass spec (molecular weight), etc.)
  – Sample type (tissue, blood, other body fluid, etc.)
  – Quantification
    • Qualitative (yes/no)
    • Quantitative (specific value)
    • Semi-quantitative (a lot, a little, etc.)
  – How the results are used (e.g., treatment selection)

Whether or not the CDx qualifies for regulation under an IND, FDA encourages sponsors to have an on-going dialogues with CDRH on:
  – The performance characteristics of the CDx, and
  – Its potential utility with respect to the drug
CDx Study Issues - IND for Drug and IDE for CDx

+ Information within an IDE is confidential and proprietary
+ Unless a drug sponsor has a right of reference, FDA may not rely on information in the diagnostic’s IDE to determine that the drug’s protocol has a satisfactory risk/benefit balance
+ Similarly, information in an IND is confidential and proprietary
+ Unless the diagnostic sponsor has a right of reference, FDA may not rely on information in the IND to determine that the IDE application proposes a protocol that has a satisfactory risk/benefit balance
If the diagnostic will be used to narrow the indicated population for use of the drug or as the sole basis for adjusting drug therapy, FDA usually will require a separate device approval or clearance (generally PMA).

FDA guidance recommends coordination among sponsors and FDA Centers to aim for simultaneous approval of drug and diagnostic.

Where safety or effectiveness of the drug depends on use of the diagnostic, FDA rarely allows approval of one without the other.

In some circumstances FDA will permit or expect a single product approval, under an NDA or BLA, for both products together.
General Regulatory Considerations for CDx

+ Complexity of submissions requires close interaction with FDA
+ Presubmission interactions are important, often essential
+ PMA regulatory pathway is likely at present, although other options are possible
+ PMA structure and timeline should be considered as part of overall timetable and development plan
+ Alternative pathways should be considered as early as possible and, if applicable, discussed with FDA, including 510(k), de novo, HDE
+ If a PMA is required, availability of expedited access should be considered
+ Strategy for future modifications to test, if anticipated, should also be considered early in regulatory/clinical planning
Thank You!

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