Personalized Medicine: What's New and Interesting at FDA

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How is FDA addressing Personalized Medicine?

- Personalized Medicine
  - Companion Diagnostics
    - Policy and practice
    - Internal and external
  - Novel Technologies
    - UHTP (next-gen) sequencing
    - Array-based CNV
    - Proteomics
  - Policy Issues
    - LDTs
    - RUOs
    - various
  - Scientific Questions

FDA's View of Personalized Medicine

- Commissioner Hamburg
  - Committed to Personalized Medicine program
- Dr. Spielberg
  - Assigned to manage three medical product centers
  - Personal interest in personalized medicine
  - Initiating OC coordination of personalized medicine in product centers
- CDRD/CDER/CBER
  - Working together to identify issues, create solutions
    - Internal practices
    - External guidance

CDRH Role in Personalized Medicine

- In CDRH
  - Personalized Medicine Staff
    - 4 dedicated staff in PM
    - ~10 review staff in review divisions
    - CMO
  - Current scope is IVDs, with other device issues as needed
  - Priority for CDRH, but requires careful approach within current laws/regulations

Current PM Activities

- Draft Companion Dx guidance
  - published July 2011
  - plan to finalize 2Q2012
- Preparing “Codevelopment Guidance”
  - Many interesting issues
  - Not a “how to” but a general guide
- Other guidances, e.g. Trial Enrichment
- Internal policy building
  - Centers’ roles in decision-making
  - Cross-center communications
  - Timing/coordination

Recent Approvals and What We've Learned

- Vemurafinib
  - Approved prior to PDUFA and MDUFMA dates
  - Marker positive trials
  - CDER and CDRH worked in coordinated manner with sponsors, internally
  - Issues:
    - Differing review timelines
    - Differing times of availability for drug/diagnostic
    - Some unexpected issues in Dx (resolved)

Outcome: Successful codevelopment

Recent Approvals and What We've Learned (2)

- Crizotinib
  - Approved prior to PDUFA and MDUFMA dates
  - Marker positive trials, very small population
  - CDRH and CDER worked in coordinated manner with sponsors, internally
  - Issues:
    - Review timelines very compressed
    - Issues in clinical trial testing (resolved but with lessons learned)
    - Postmarket studies
  - Outcome: Successful codevelopment

Lessons as Result of Two Approvals

- Accelerated drug approval does not significantly change when companion Dx needed
- Intercenter communication was highly effective and review staff worked well together
  - Co-attendance at meetings
  - Questions transmitted in timely manner
  - Approvals and press well-coordinated
  - *Generalize the model*
- Drug and Dx sponsors should carefully define expectations for each other
- Modular PMA process for Dx highly preferred over traditional
- Codevelopment works!

Intercenter Policies and Communications

- Different Centers have different laws, regulations, cultures, and needs
- Positive developments:
  - Working in close proximity with each other
  - Inviting each center to others' meetings
    - See the big picture, warts and all
  - Identifying issues together and creating draft policy
  - Regular internal interactions on broader scope
  - One internal SOP nearly finalized

Other Intercenter Advances

- Creating agreed-to ways of working together
- Recognizing each Center's role in process
  - Including limitations
- Creating streamlined regulatory communication methods
  - Different centers use different systems to archive, track submissions
- Recognition of status of tests in INDs

Prognosis and Predictions

- Progress is rapid, but still has its unpredictable moments
- Everyone playing well together
  - Each center learning a lot from the other
- Sense that system will work
  - New lessons from every new model
- Greater internal uniformity already in place
- Guidance lagging submissions as we learn
- System operational but still needs some refinement
- Sponsors “getting it”
- THIS WILL WORK

Other Issues

- Companion Dx will *usually* be PMA submissions, due to risk of misclassification + therapy
  - Count on PMA unless you hear otherwise
- LDTs are acceptable as Companion Dx
  - If supporting drug approval, must be approved (cleared) by FDA
  - Require compliance with quality system and all other device regulations
  - LDT model does not change regulatory pathway

Common Pitfalls

- Late decision to include companion Dx
  - Sometimes unavoidable
  - FDA has *some* ways to help, but can't fix a fundamental timing issue
- Tests used to enroll pts in trials can't be compared
  - Manage this from the beginning
  - Write specific testing protocols where possible
- Samples are limiting/unavailable
  - Plan to save samples (extra if possible)
  - Try to assure that test neg pt samples are saved

Presubmission Advice

- For codevelopment, use early interactions with FDA to plan
- CDRH: preIDE process
  - Both Dx and therapeutic sponsor ought to participate
  - Informal—ask questions!!!
- CDER/CBER: preIND
  - Both therapeutic and Dx sponsor can benefit
  - Ask for CDRH attendance
  - ASK QUESTIONS
  - EXPLAIN POSSIBLE ISSUES

Final Words

- Process of learning by doing
  - We have not encountered every possible situation
  - We do our best, but can't answer questions that aren't asked
  - Processes can be more time-consuming than "standard" submissions
  - Many mechanisms can be adjusted to accommodate PM issues

- Thanks!
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