Overview of FDA regulations for Companion Diagnostics

National Cancer Policy Forum Workshop
Policy issues in the development and adoption of molecularly Targeted therapies for cancer

Session 2A: Evidentiary standards: Regulatory Science

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Disclaimer

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Organization of this presentation

- Who does what at FDA: CDER vs CDRH
- What is a IVD companion diagnostic
- What is Rx/Dx Co-development
- Examples of approved drugs based on co-development

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Basics Regulations Companion Dx

- Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)
  - Responsible for approval for drugs and biologics (including cell therapy, vaccines and gene therapy)
  - IND and NDA/BLA
- Center for Devices and Radiological Health (CDRH)
  - Responsible for approval of medical devices
  - IDE and PMA/510K

Regulatory Differences: CDRH & CDER

	CDER/CBER	CDRH
Initial interaction with	Pre-IND	Presub
Initial approval allowing testing in humans	Investigational New Drug (IND)	Investigational Device Exemption (IDE)
Approval for marketing	New Drug Application (NDA) Biological Licensure Application (BLA)	Premarket approval (PMA) Premarket Notification (PMN) or 501K

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In vitro diagnostic product (IVD)

In vitro diagnostic products (IVD's) are:

- reagents, instruments, and systems used in diagnosis of disease or other conditions
- in order to cure, mitigate, treat, or prevent disease
- intended for use in the collection, preparation, and examination of specimens taken from the human body.

[21 CFR 809.3]

IVD Companion Diagnostics (IVDCD)

- Companion diagnostics (IVDCD) are a special class of IVDs
- Provides information that is essential for the safe and effective use of a corresponding therapeutic product.
- Drugs and their companion tests refer to each other in their labels.
- Guidance. In vitro companion diagnostic devices. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm

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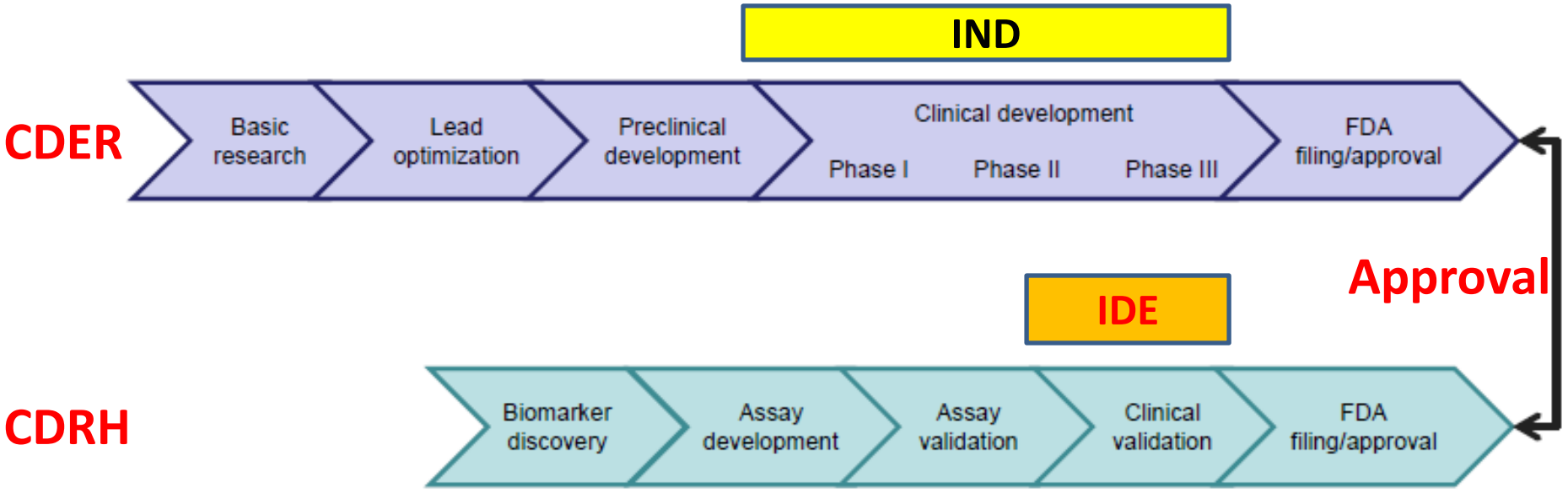
Codevelopment

- Development of paired therapeutic products and diagnostic devices with interdependent uses (e.g., a drug and a companion diagnostic).
- Biomarker discovery and test development can occur anytime during the drug development process.
- Safety and efficacy of the new drug ("clinical utility") and new Dx is typically demonstrated in the same clinical trial.
- Goal is **simultaneous** approval of the drug and diagnostic.



IDE Regulation (21 CFR 812)

- Regulatory submission that permits clinical investigation of devices/IVDs
- An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution.
- Focused on risk
- Delegated responsibilities

Labeling features Important for IVDCD

- Analytical validity
  - Does the test measure the correct analyte?
  - Does the test measure the analyte reliably?
  - Precision, reproducibility, sensitivity, specificity, etc.
  - Cutoff/reference range
- Risk dependent:
  - The extent of analytical validation required for a pivotal trial exceeds what is required for feasibility studies.
- The context in which the device is used
  - clinical laboratory, point-of-care setting
- Intended use/Indications for use:
  - Clinical purpose (diagnosis, prognosis, monitoring)
  - Target population for whom the test is intended

A Risk-Based Approach to IVD Regulation

- Need to think about the benefits and risks of a test
- For an IVD tests, it is important to think about the risks associated with false positives or false negatives. What would happen if the test results are wrong? Are the benefits greater than the risks of inaccurate results?
  - False positive: the patient would receive unneeded treatment, be exposed to treatment risk without benefit
  - False negative: the patient would not receive needed treatment.
- For companion diagnostics, this will depend on the disease, the risks of treatment with the drug, and other treatment options (e.g., standard of care)

FDA Policy for CDx Trials

- Significant risk (SR IVD): An IDE is required for an investigation even if there is an IND for use of the drug, or if the drug is IND exempt.
- Non-significant risk (NSR IVD): An IDE is not required, and cannot be accepted for review.
  - The trial still has to comply with the abbreviated requirements.
  - Some information on the test may be requested in the IND.
  - A presub with CDRH is recommended.

Significant Risk (SR)

Significant risk device (812.3(m)) means an investigational device that:

Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

- Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

In other words, does the use of the IVD guide patient care? Eg, patient selection

Laboratory Developed Tests (LDTs)

- LDTs is a type of IVD test that is designed, manufactured and used within a single laboratory.
- LDTs can measure a wide variety of analytes (substances such as proteins, chemical compounds like glucose, or DNA), in a sample taken from humans.
- While the uses of an LDT are often the same as the uses of FDA-cleared or approved in IVD, some labs may choose to offer their own test.
- The FDA does not consider diagnostic devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them.

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm

Laboratory Developed Tests (LDTs) (cont'd)

- FDA has not enforced premarket review because LDTs were relatively simple lab tests and generally available on a limited basis. But, due to advances in technology and business models, LDTs have evolved significantly since initial in vitro diagnostics regulations in 1976.
- LDTs are now more complex, and present higher risks, which are similar to those of other IVDs with premarket review.
- FDA has identified problems with several high-risk LDTs including: claims not adequately supported with evidence; lack of appropriate controls yielding erroneous results; and falsification of data.
  - Faulty LDTs that could have led to: patients being over- or undertreated for heart disease;
  - cancer patients being exposed to inappropriate Rx or not getting effective Rx;
  - incorrect diagnosis of autism; etc.

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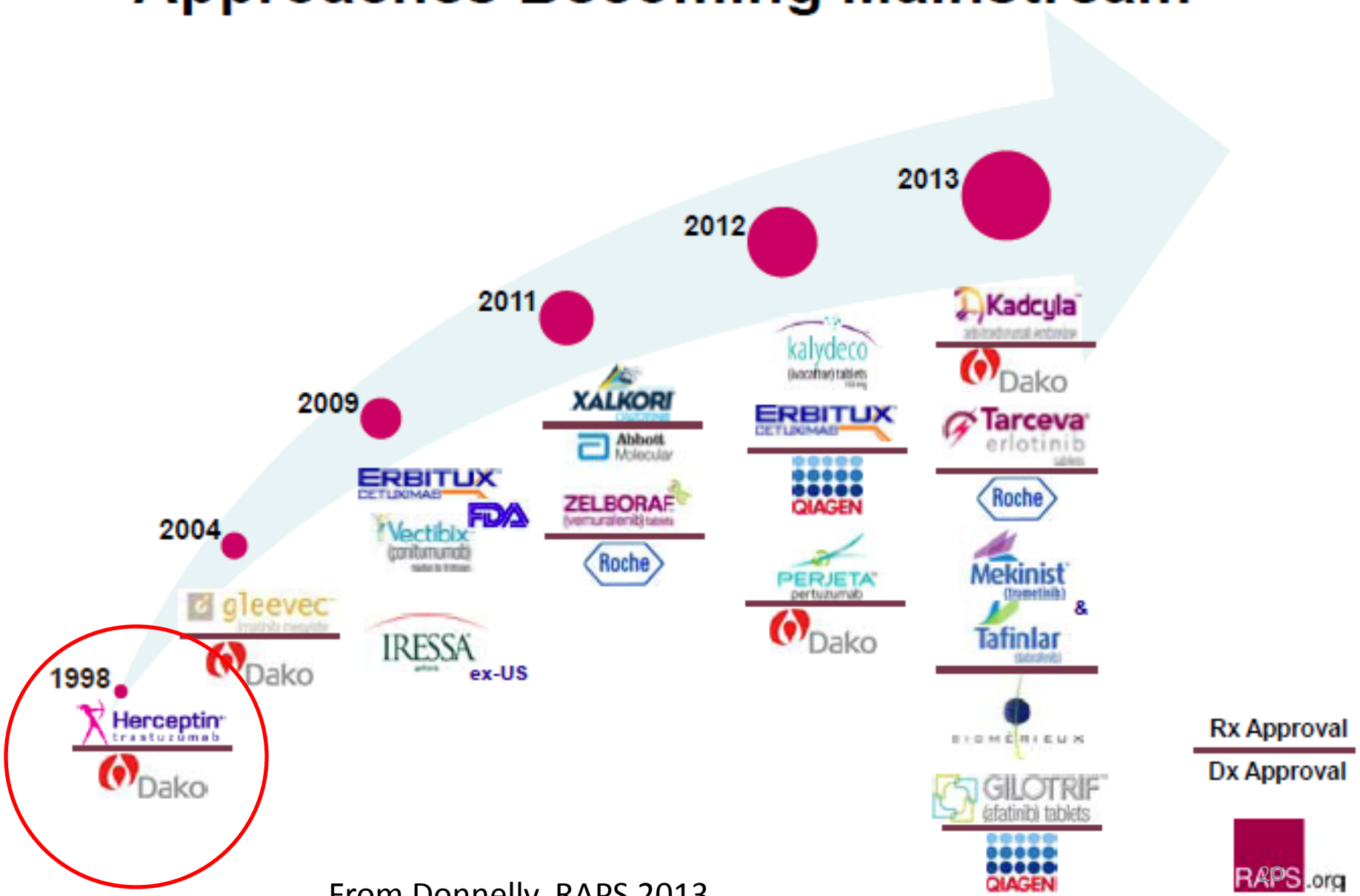
Targeted Rx/Dx Co-Development Approaches Becoming Mainstream



From Donnelly, RAPS 2013

FDA Approved IVD test for Herceptin

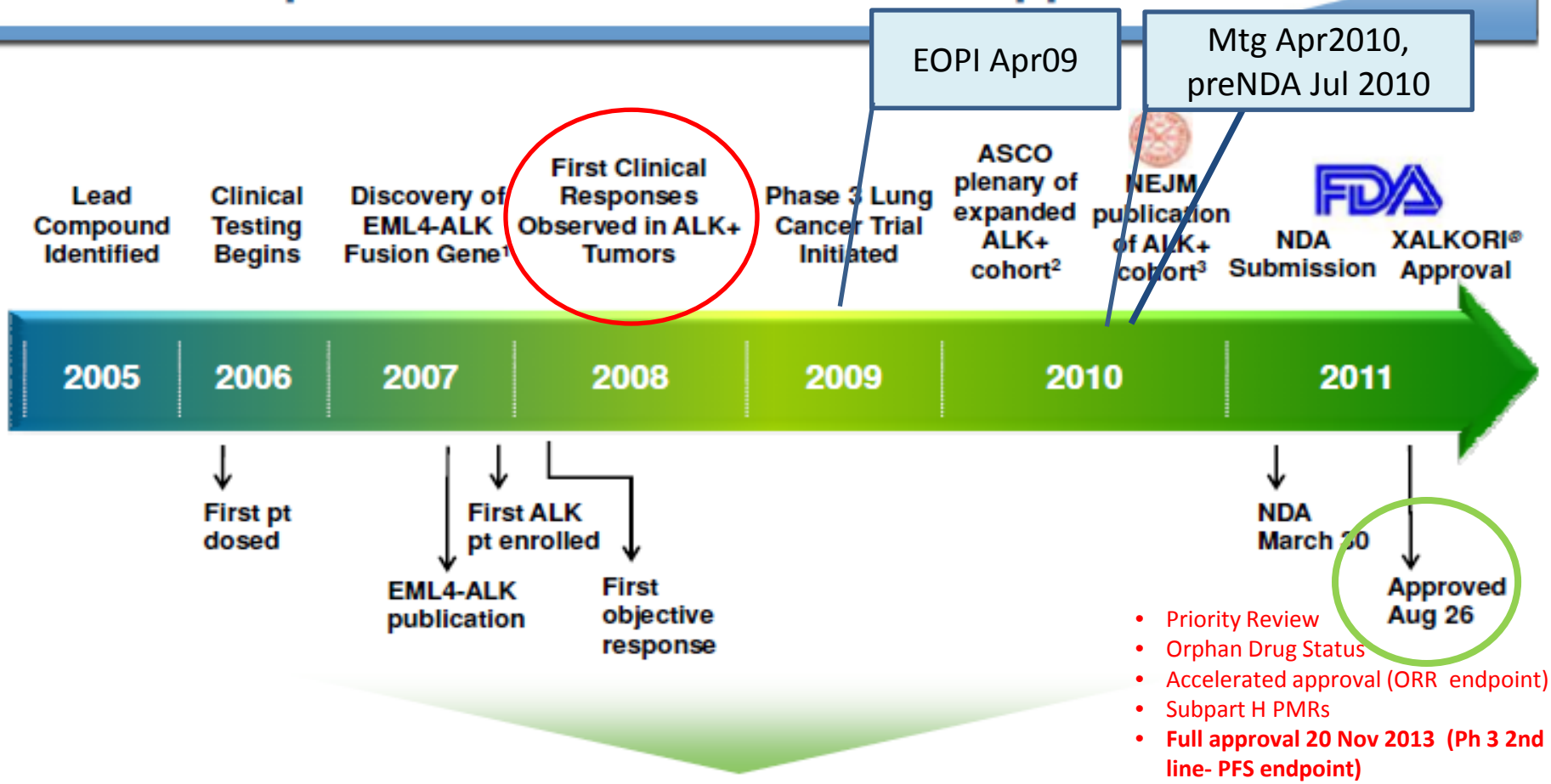
Name of test	analyte
Inform her2/neu	FISH qualitative gene amplification
Pathyvysion her-2 dna probe kit	FISH qualitative gene amplification
Pathway anti-her 2/neu ventana	IHC Semiquantitative c-erb-2 protein
Insite her2/neu kit	IHC Semiquantitative c-erb-2 protein
Spot-light Her2 CISH Kit	Cish Semiquantitative c-erb-2 protein
Bond oracle her2 ihc system	IHC Semiquantitative c-erb-2 protein
HER2 CISH pharmaDX kit	Cish Semiquantitative c-erb-2 protein
INFORM HER2 DUAL ISH DNA Probe Cocktail	ISH enumeration of ratio her2 gene and chromosome 17
HERCEPTEST	IHC Semiquantitative c-erb-2 protein
HER2 FISH PharmDx Kit	FISH quantitative gene amplification

As of June 2014

Crizotinib Development

- 2005: Lead compound identified: oral multi TKI with potent inhibitor for c-met and alk TK
- 2006: Phase I started in solid tumors. At RP2D, enriched for c-met tumors: c-met amplification, c-met kinase activation mutant, chromosomal translocations/fusion c-met or HGF
  - Initial clinical data demonstrate minimal activity in the phase I trial
- 2007: Discovery of EML4-ALK gene in NSCLC pts
- 2008: First pt with EML4-ALK gene demonstrated significant antitumor activity
- 2009: change enrichment to NSCLC EML4-ALK positive pts
- 2011: subpart H “accelerated approval/conditional approval
- 2013: converted to full approval

Crizotinib Development: From Compound Identification to FDA Approval



Rapid Timeline from Compound Identification, Target Discovery and Clinical Results

1. Soda et al. *Nature* 2007, 448: 561.
2. Bang JY *et al*. Oral presentation at ASCO, 2010
3. Kwak et al. *New Engl J Med*. 2010;363:1693–03

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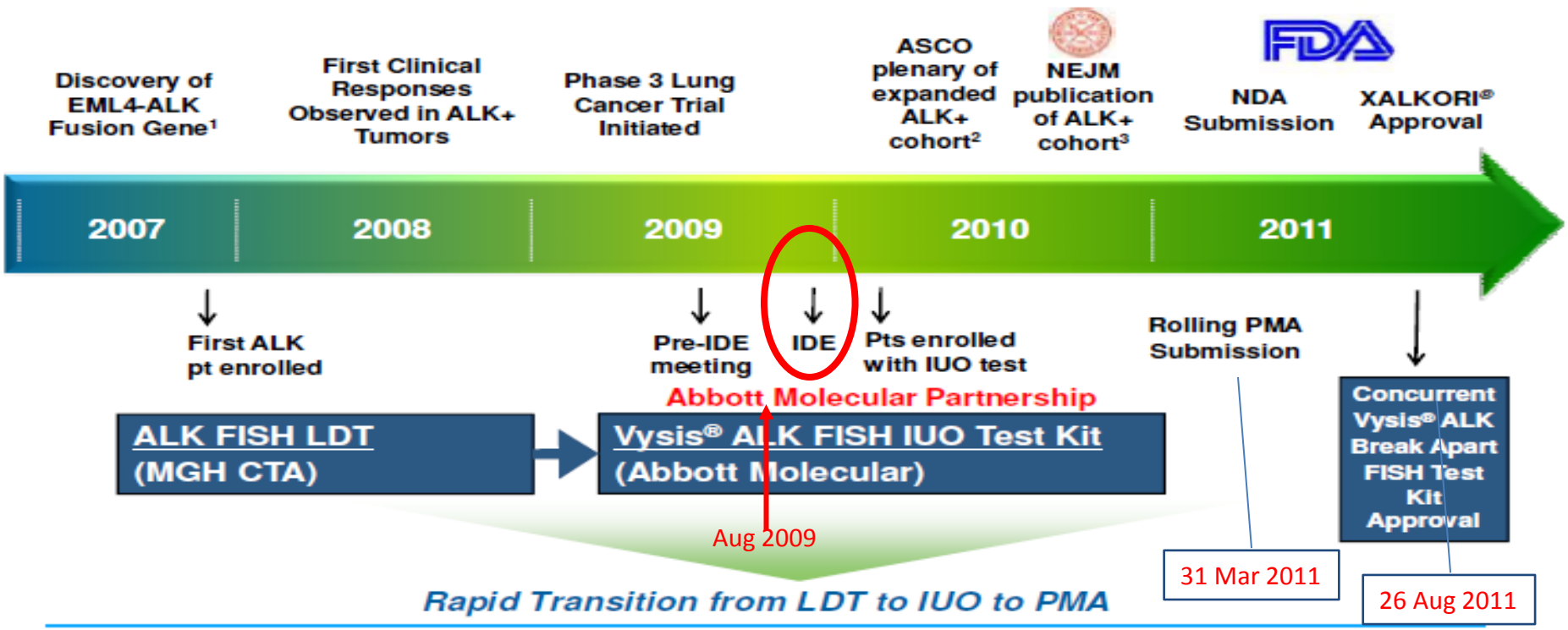
Adapted from S.Ho, IOM 2012 workshop

ALK CDx Development: From Phase 1 LDT to PMA approval



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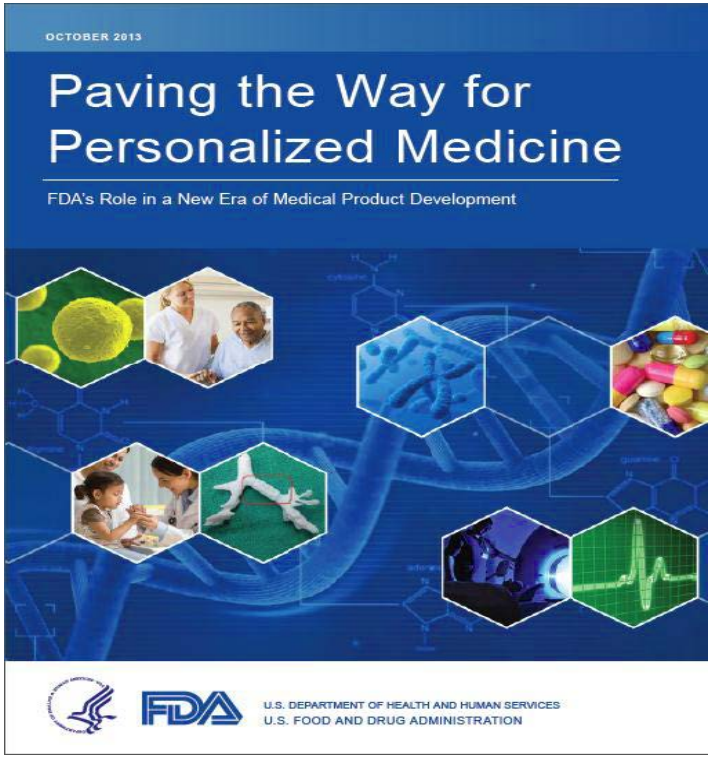
Summary

- Begin planning early when drug may require CDx.
- Submit IDE as soon as feasible, and get IDE approval before you start selecting pts based on IVDCD
- IDE submission depends on Risk
  - Only high risk IVD (e.g. treatment selection) needs IDE
- If plan for registration trial is based on IVD, then, locked IVD should be in place before starting trial.
- LDTs regulatory environment may change in the future, particularly for LDTs with commercially available IVDCD
- Safety and efficacy of the new drug ("clinical utility") and new Dx is typically demonstrated in the same clinical trial.
- Goal of Codevelopment is **simultaneous** approval of the drug and diagnostic

Recommended reading



29 Oct 2013 report at Personalized medicine website:
http://www.fda.gov/scienceresearch/specialtopics/personalizedmedicine/default.htm

FDA approved Companion diagnostics:

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

IVD regulatory assistance:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/default.htm

FDA CDRH Learn:
http://www.fda.gov/training/cdrhlearn/default.htm

Device Premarket Approvals database:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Similarities and differences in the Oncology Drug Approval Process. A Senderowicz and O Pfaff. CCR 2014

Thank you!!