

Welcome to today's **FDA/CDRH Webinar**

*Thank you for your patience while we register all
of today's participants.*

If you have not connected to the audio portion of the
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Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

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Christopher Leptak, MD, PhD
Office of New Drugs
Center for Drug Evaluation and Research

Pamela Bradley, PhD
Personalized Medicine Staff
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

- The FDA published draft guidance on July 15, 2016
- Tri-center guidance from CBER, CDER and CDRH
- Open comment period through Oct. 13, 2016
- Purpose of today's webinar is to facilitate public feedback
- Public comments submitted to the docket will be considered in finalization of the guidance

Overview of Webinar

- **Presentation of draft guidance ~40 min**
 - Christopher Leptak, CDER
 - Pamela Bradley, CDRH
- **Q&A ~20 min**
 - Sheryl Kochman, CBER
 - Elizabeth Mansfield, CDRH
 - Michael Pacanowski, CDER

Companion Diagnostics

- The FDA issued final guidance “In Vitro Companion Diagnostic Devices” Aug. 2014
- Defined companion diagnostic (CoDx) as IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product
- Described CoDx uses:
 - Identify population most likely to benefit or most at risk of adverse reaction.
 - Monitor response to adjust treatment.
 - Identify population for whom product is known to be safe and effective.
- Clarified that, in general, the FDA expects contemporaneous regulatory approvals of the CoDx and therapeutic product
- Described other regulatory requirements (labeling, etc.)
- Did not provide a “how-to”

Draft Guidance: Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

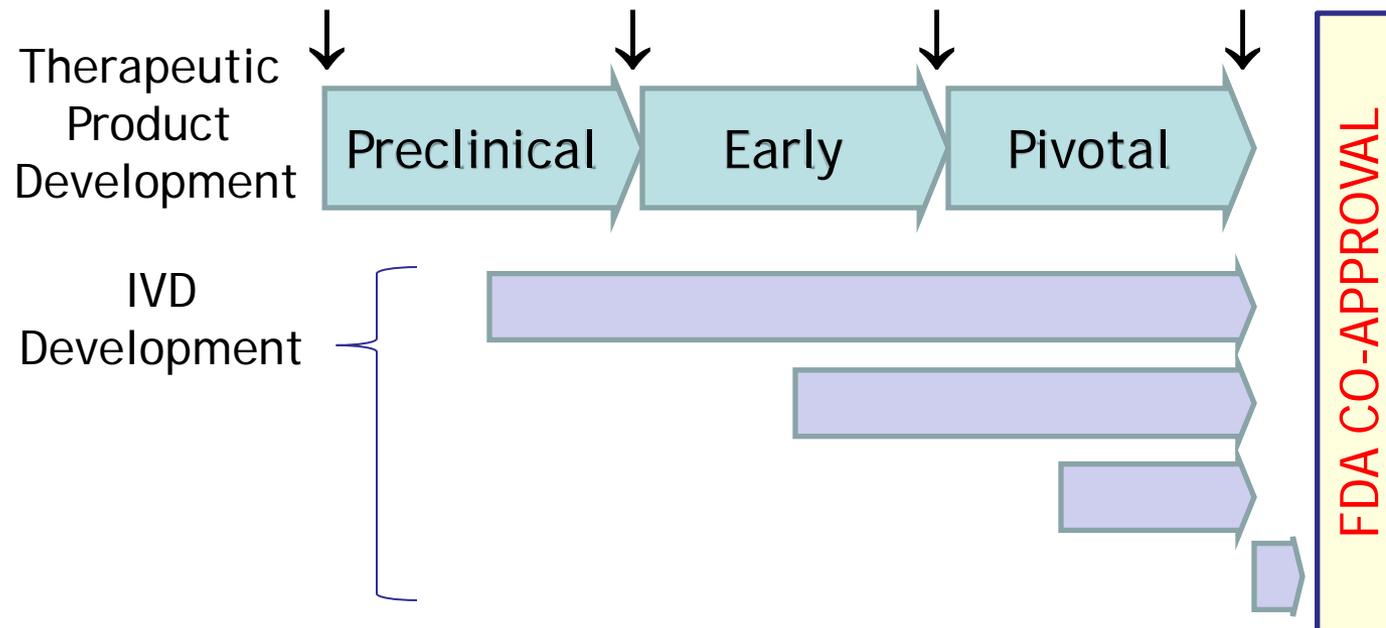
- Intended to provide the “how to” -- the practical aspects of codevelopment to support the design and implementation of successful codevelopment programs.
- The guidance describes:
 - General principles to guide codevelopment to support obtaining contemporaneous marketing authorization
 - Certain regulatory requirements
 - Considerations for therapeutic product clinical trial that includes investigation of an IVD CoDx
 - Submission process for the therapeutic product and CoDx

Codevelopment Guidance Topics

- General
- Codevelopment Clinical Trials
- Requirements for Investigational Products
- IVD Development - Planning Ahead
- IVD Development in Later Stages of TP Development
- Coordinating Review
- Labeling Considerations
- Postmarket Considerations

Codevelopment

- Codevelopment does not require simultaneous development of CoDx and therapeutic product from beginning to end.
- Biomarker discovery (↓) and test development can occur at any point during the therapeutic product development process.



- Whether initiated at the outset of development or at a later point, codevelopment should generally be conducted in a way that will facilitate obtaining contemporaneous marketing authorizations for the therapeutic product and the associated IVD companion diagnostic.

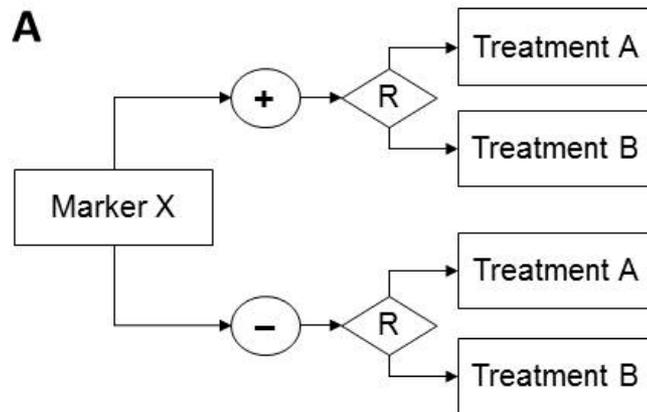
Codevelopment Guidance

- General
- **Codevelopment Clinical Trials**
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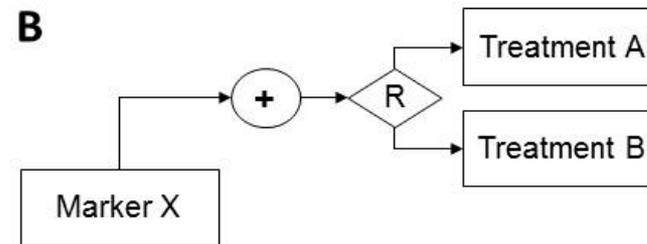
Clinical Trial Design

- When a clinical trial is properly designed to establish the safety and effectiveness of a therapeutic product in a population based on measurement or detection of a marker, the results of the clinical trial can also be used to establish the clinical validity of the IVD companion diagnostic
- Considerations:
 - Mechanistic rationale for selecting the marker
 - The nature of the disease
 - Level of characterization in the test-negative population
 - Prospective-retrospective analyses

Biomarker Based Clinical Trial Designs



- + Obtain information from all subjects
- + Assess predictive vs. prognostic
- + May include futility analysis
- + May stack enrollment toward biomarker positive (e.g., 80/20)
- Large trial



- + More efficient (if biomarker is predictive or prognostic)
- + Potentially exposes fewer patients to ineffective therapy
- May hinder enrollment
- No information about marker-negative

Enrichment Strategies

- Draft guidance Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products
 - Published December 2012
 - Guidance:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf>
 - Webinar:
<http://www.fda.gov/Drugs/ucm343578.htm>

Prospective-Retrospective Approaches

- A prospectively-defined retrospective analysis of trial outcomes according to the test result
- Requires a pre-specified plan to collect specimens and analyze patient outcomes based on the IVD result
- Discuss acceptability of approaches with the FDA

Considerations for Identifying Intended Populations

- Ensure adequate representation of markers in study population
- Pre-specified cutoff values are essential for the analysis of use of the IVD in a clinical trial

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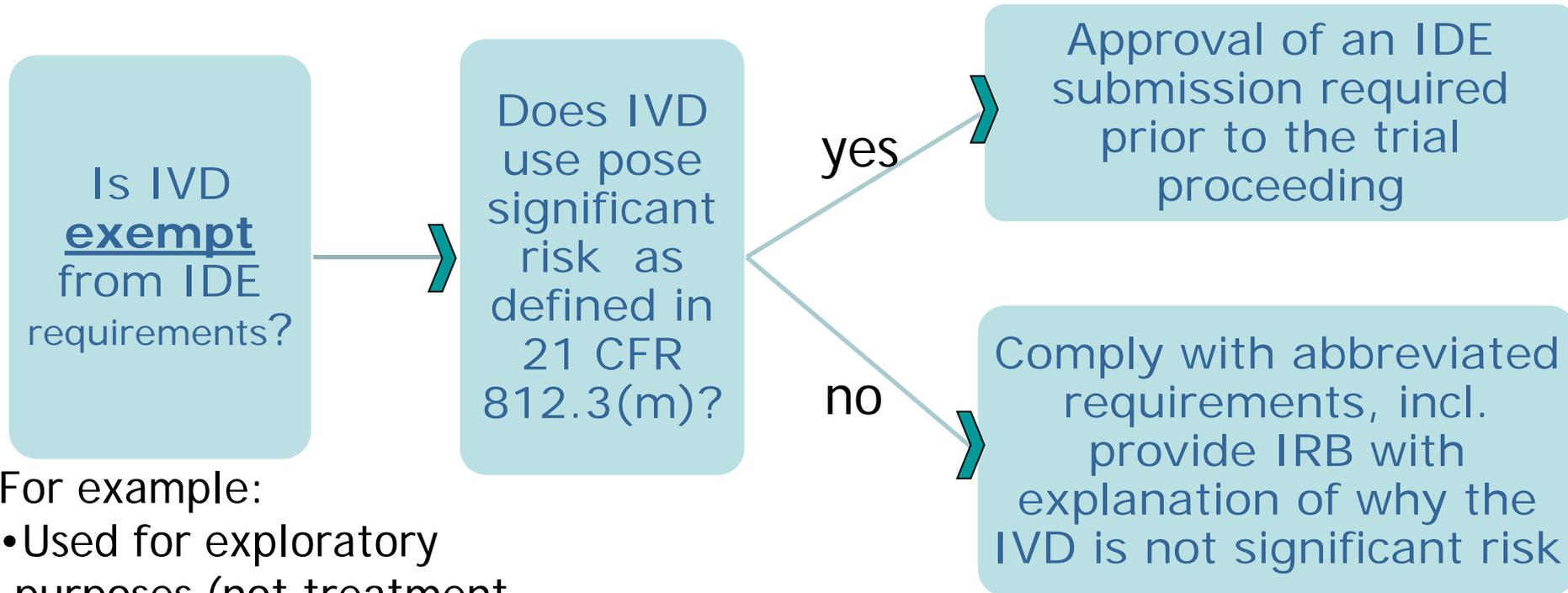
Requirements for Investigational Products

- Both the therapeutic product and the IVD may be investigational
- Both have own regulatory requirements
 - Therapeutic Product: Investigational New Drug, 21 CFR 312
 - IVD: Investigational Device Exemption (IDE) Regulation, 21 CFR 812
- Compliance with one set of requirements doesn't fulfill compliance with the other

Investigational IVDs

- An IVD is investigational if used for a purpose that has not already received marketing authorization for that specific intended use
- IDE regulatory requirements depends on the level of risk that its use presents to study subjects
 - Exempt
 - SR or NSR

Investigational IVD Risk Determination



For example:

- Used for exploratory purposes (not treatment decisions) or retrospective analyses
- AND uses non-invasive sampling

Submission of Information about the test

- **Significant risk**
 - IVD information in IDE submission
 - IDE can cross-reference other submissions to streamline

- **Nonsignificant risk**
 - IDE submission not required
 - If adequate test performance is necessary to interpret trial results, some IVD information may need to be included in IND

IDE submissions

- IVD cutoff value(s)
- Preamerical and analytical studies designed to demonstrate the reliability of the assay, particularly around the cutoff value(s)
- Other analytical studies that support the conclusion that use of the IVD does not expose subjects to unreasonable risk of harm
- Clinical trial protocol

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The test is important

- **Problems with the test could:**
 - Compromise the ability of the trial to demonstrate an effect of treatment.
 - Compromise the ability to determine whether the test can appropriately identify the subjects for whom the therapeutic product is intended to provide benefit.

Problems

- Test not adequately analytically validated prior to use in trial
- Multiple tests with different performance used in trials
- Tests changed during trials
- Bias from prescreening

Some suggested solutions

- The FDA recommends making sure the IVD is analytically validated prior to use in clinical trials
 - Sufficiently analytically robust, particularly around the test's clinical decision point(s).
 - You should complete analytical validation studies that evaluate critical performance parameters prior to using the test in a trial that is intended to provide the clinical validation.
 - You should use test with "market-ready" performance in pivotal trials.

Some more recommendations

- **Clinical Trials Assays (CTAs) should be fully specified**
 - All components, protocols, instrumentation
- **Use a single testing protocol at all sites**
 - Evaluate comparability of test results among potential sites prior to initiating testing at those sites
- **Consider preanalytic reagents and instrumentation to be part of the test system and validate with the IVD**
 - Tools and reagents for DNA extraction, processing, etc.
 - Have SOPs for all steps
- **You should not make changes to the test/SOP during the trial**

Prescreening Recommendations

- Avoid enrolling subjects into a trial based on confirmation of a local test result.
- Ask participating clinical sites to send forward specimens from all potential enrollees for testing with the trial test, not just positive prescreening.
- When unavoidable, be aware of the potential for bias, evaluate whether the expected prevalence of the marker is being skewed by prescreening, and develop approaches to adequately address potential selection bias.

Recommendations for Analytical Validation Studies to Support Submission

- Know what studies are relevant and plan ahead
 - e.g., analyte stability studies
- Collect and bank adequate samples
- Not all AV studies need clinical trial specimens
 - But should be same target population
 - Validation studies with contrived samples are appropriate in some cases

Recommendations for Banking Samples

- Bank specimens for future AV studies, bridging studies
- Bank intent-to-diagnose population, not just enrolled
- Consider accessibility to samples in foreign countries
- Consider informed consent policies for all uses of samples (e.g., retesting)
- Thorough specimen annotation is needed
- Consider lability issues when storing specimens; may need to store purified/extracted analyte

Training vs. Validation

- The set of clinical samples used to design an IVD and establish the clinical decision point(s) and assay cutoff(s) is referred to as the “training set.”
- Testing should be conducted with a second set of independent clinical samples and with the final IVD to validate (i.e., the “validation set”).
- If changes are made to the IVD based on results from the validation set, then this dataset effectively becomes a new training set for the modified IVD, which should then be validated with an additional set of samples.

Recommendations for IVD Bridging Studies

- Statistical Plan to assess concordance and discordance between 2 tests using the same samples from trial subjects.
- Takes into account discordance, missing samples and effect on drug efficacy.
- Retest population should be representative of the intended use population for the device and adequately reflect the characteristics that affect test performance.
- Re-analysis of the trial for effectiveness of device is potentially biased if subset not representative.
- Plan to analyze worst case scenario for missing data with sensitivity analysis.

The Pre-Submission Program

- As soon as you know there is codevelopment intent, we recommend using the Pre-submission Program for feedback about IVD issues
- Pre-sub program
 - An opportunity to ask questions and conduct discussions
 - Clinical or analytical study protocol review
 - Appropriate regulatory pathway
 - A formal written request from a sponsor for FDA feedback

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- Labeling
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Coordinating Review Timelines

- **Submissions**
 - Drugs - New Drug Application (NDA)
 - Biologics - Biologics License Application (BLA)
 - CoDx will likely be Class III and require a Premarket Application (PMA)
- **Statutory timelines differ for therapeutic products and IVDs**
- **In practice, IVD review keeps to therapeutic product timelines**
 - Therapeutic product expedited review/accelerated approval shorten timelines

What Helps Expedite IVD Review

- IVD priority review
- Modular PMA
 - Allows issues to be identified & addressed along the way
 - Manufacturing inspection - submit this module early
 - BIMO inspection - organize information in the PMA
- Master Files
- Letters of Authorization

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Labeling

- Product labels should be consistent with each other
- IVD claims based on the trial design
 - Prediction: supported by evidence that clinical benefit accrues only to, or primarily to, a population defined by the IVD result or that serious adverse reactions are confined to a population defined by the IVD result
 - Selection: trial designs in which only test-positive (or test-negative) subjects are selected for enrollment in a trial typically support IVD companion diagnostic claims for patient selection
 - Monitoring: beyond guidance scope

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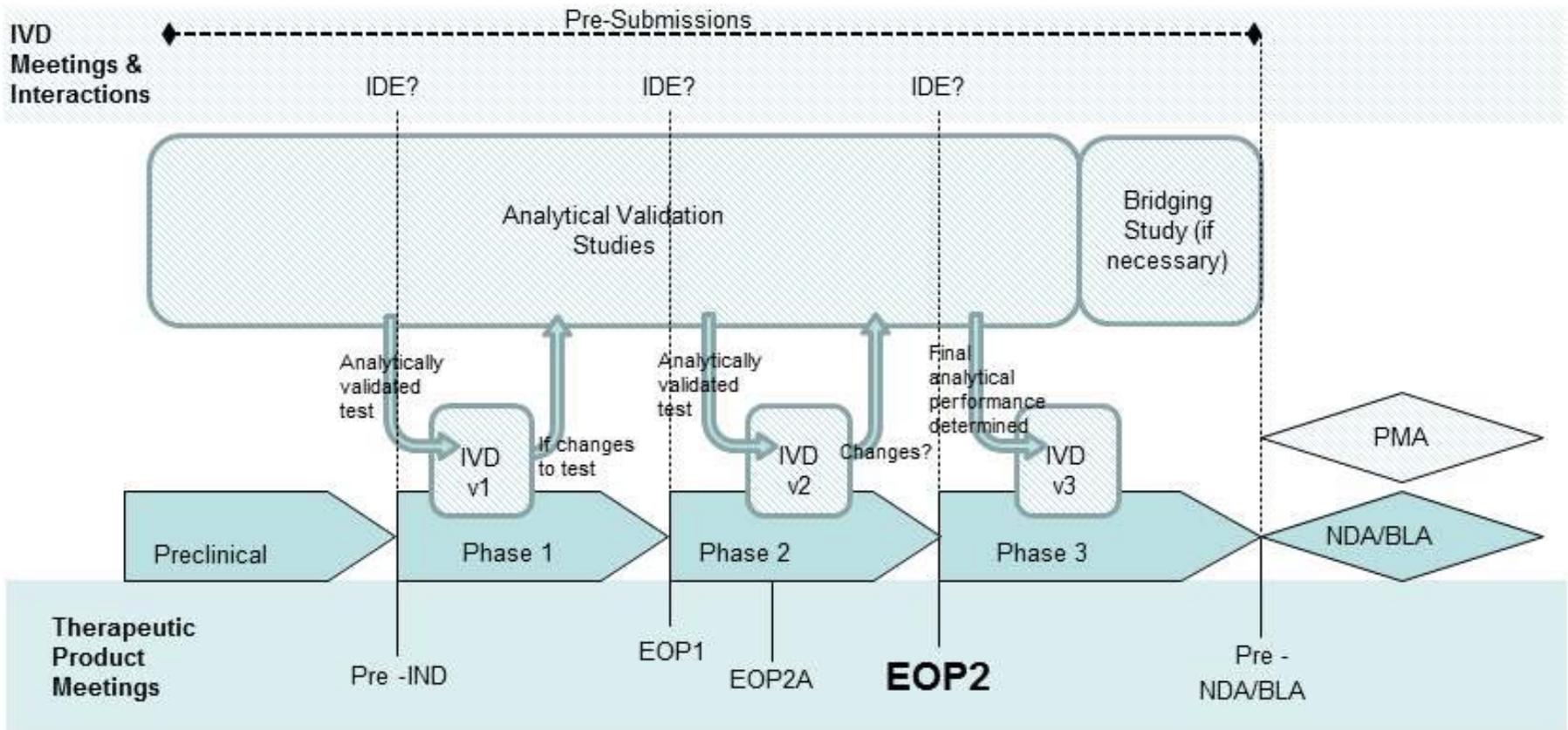
Postmarketing Considerations

- Consult the FDA when designing postmarketing studies that involve codx.
- For adverse events, report IVD problems to IVD center; therapeutic product problems to TP center. If not clear, or if both products could have contributed, report to both centers.

Key Points

- Use clinical trials strategy that provides evidence for TP and IVD; Read enrichment guidance
- Interact with the FDA early and often
- Plan ahead - collect specimens (annotate and store well) for AV studies, bridging studies
- Engage IVD partner as soon as possible
- Determine what IDE requirements apply to the investigational IVD
- Complete analytical validation studies before using IVD in trial
- Use test with “market-ready” performance in pivotal trials

Critical Points of the Codevelopment Process



We Want Your Input

- Comments due October 13, 2016
- Docket # FDA-2016-D-1703
- Submit electronically at <http://www.regulations.gov>
- Submit written comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Q&A

- Pamela Bradley, CDRH
- Sheryl Kochman, CBER
- Christopher Leptak, CDER
- Elizabeth Mansfield, CDRH
- Michael Pacanowski, CDER

Questions?

Division of Industry and Consumer Education:

DICE@fda.hhs.gov

Slide presentation, transcript and webinar recording
will be available at:

<http://www.fda.gov/training/cdrhlearn>

Under the heading-“In Vitro Diagnostics”