An Introduction to pre-IDEs

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The Basics -

- What, why, when, how, where, who

What is a pre-IDE?

- “Pre-submission” process [510(k), PMA, IDE]
- Not necessarily a prelude to an IDE
- Allows you to ask complicated questions in a non-review forum
  - Protocol review
  - Regulatory pathway
- Free, confidential advice on regulatory process and feedback on proposed studies
- Non-binding - not an agreement meeting

Why would I need a pre-IDE?

- Allows FDA opportunity to become familiar with new technology or intended uses
- Interactive and flexible process (can send in supplements)
- Especially useful for
  - New Intended Uses
  - Novel devices
  - Companion diagnostics
- May prevent costly delays or errors
- Goal - improve the quality of future submission

When to submit a pre-IDE

- Intended use defined
- Patient population defined
- Ready to discuss protocols and regulatory pathway

Types of submissions where pre-IDE recommended:

- Waiver studies (January 2008 guidance)
  Waivers are not 510(k)s
- PMA or deNovo 510(k) anticipated
- New technologies
- Multiplex panels (e.g. genotyping; pathogens)
- Multivariate assays with composite score (IVDMIAs)
- Drug-device companion diagnostics
- Submissions where an IDE may be required

Is this your first submission? A pre-IDE may be useful.

How do I get the process started?

- Submit written request and materials to the Document Mail Center*
- Format of interaction can be:
  - Written comments
  - Meetings:
    - teleconference, videoconference, in-person

*** Where =** U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

What do I include in my pre-IDE?

- Content depends on the questions you're asking:
  - Clinical questions = clinical protocol review
  - Analytical questions = validation protocol review
  - Regulatory questions = regulatory pathway review
- Specific questions are helpful!
- Cover letter with:
  - Name of Division Director
  - Contact information
  - Cover letter briefly describing device, intended use, proposed outcome, predicate if known
  - Request for written comments, conference call, in-person meeting

Making the most of Pre-IDE discussions – written or meeting[1]

- Know your:
  - Intended use !!!
  - Study population (for clinical study)
  - Protocols
  - Plans for analytical and clinical testing
  - Statistical analysis Plan
    - Sample size justification
    - Statistical methodology
  - Suggest a regulatory pathway, justify

[1]adapted from Gen Engineering & Biotechnology News March 1, 2009 (J. Gibbs)

Making the most of pre-IDE meetings

- To make the most efficient use of time and resources, submit :
  - A brief statement of the purpose of the meeting
  - Specific questions to be addressed by FDA
  - A preliminary proposed agenda
  - A list of all individuals who will participate from your company
  - A list of FDA personnel who you believe should participate (medical officers, statisticians, management, etc.)
  - An information package, the content of which is dependent upon the objectives of the discussion or meeting

What outcome should I expect from the pre-IDE process?

- FDA's most current thinking and advice on your proposal

Examples of not so useful pre-IDE questions

- No specific questions asked!
- Does FDA agree with all the proposed analytically performance study designs?
- Is the sample size of 500 subjects adequate (without providing a statistical analysis proposal)?

Examples of useful pre-IDE questions

- Does FDA agree with the proposed negative, mutant, and internal control strategy for the X mutation test?
- Does FDA agree that the existing medical and scientific literature referenced in the pre-IDE have established the clinical utility of X testing, and therefore X company will not be required to perform a separate clinical study for the approval of the test?
- In light of a proposed parallel PMA application for a companion diagnostic, can the Agency please confirm that a cross-referral to the PMA in the sNDA filing is sufficient?

Most Common 510(k): “Me, too”

- Use a pre-IDE when you want to change it up –
  - New intended use population
  - New and different technology

- Intended use population
- Method comparison study - split sample design
- ***Predicate selection (are we choosing an appropriate predicate wisely?)*** *is there a predicate?*

Recommended readings

- Predicate decision summaries
- CLSI document EP-9 Quantitative
- CLSI document EP-12 Qualitative
- Statistical Guidance for Reporting diagnostic tests (www.fda.gov/cdrh/osb/guidance/1620.html)
- CLSI Guidances for analytical studies
  (e.g. EP5, EP6,EP17)

Intended Use

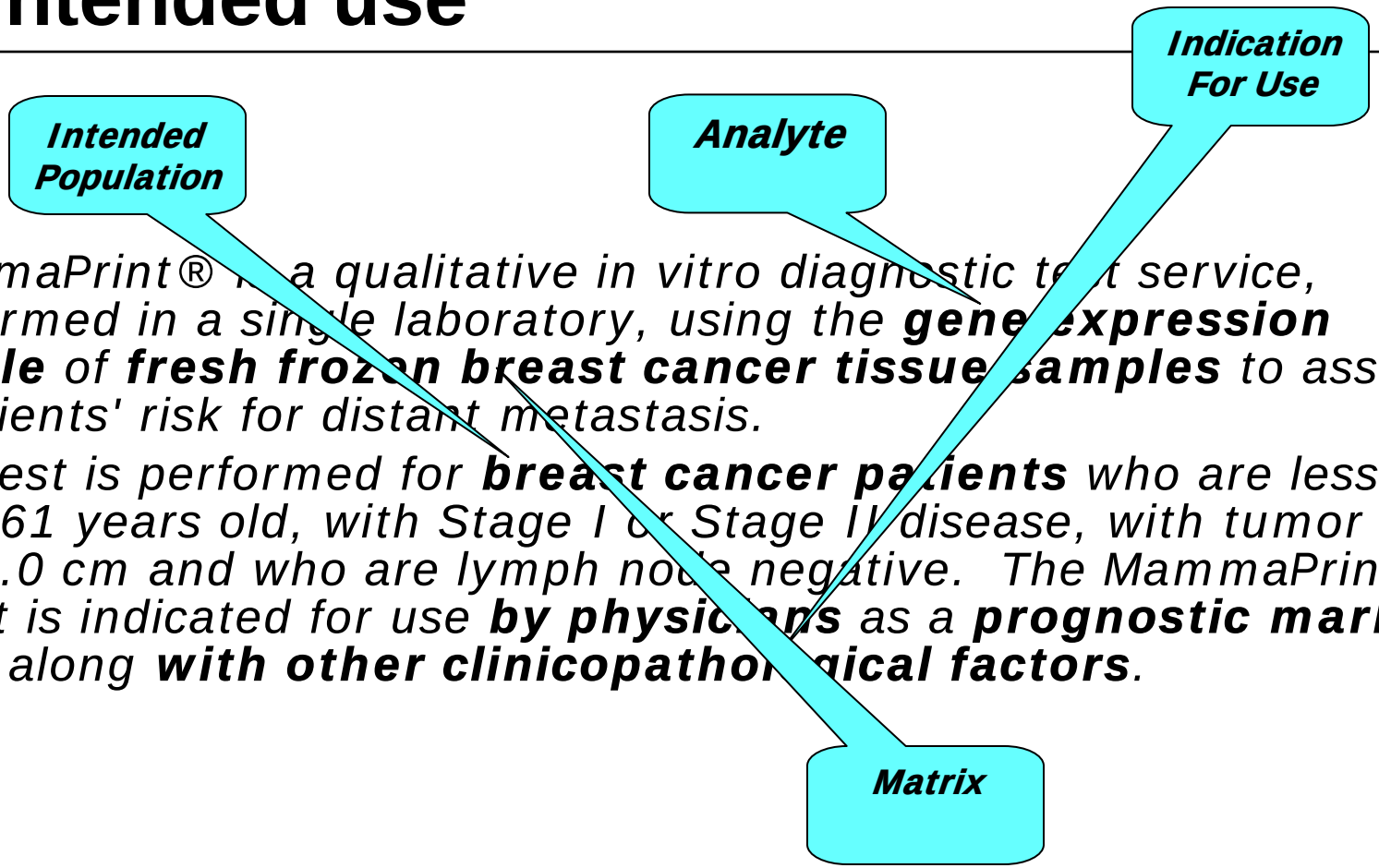
- Who, what, and when
  - Intended population, analyte, clinical usefulness
- Same device can have more than one use
- Study should match intended use
- Study should be consistent with US practice or if not, justification for why not

- Devices are regulated by their intended use:

  PSA: screening PMA

  PSA: monitoring already diagnosed patients 510(k)

Intended use



*MammaPrint® is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the **gene expression profile** of **fresh frozen breast cancer tissue samples** to assess a patients' risk for distant metastasis.*

*The test is performed for **breast cancer patients** who are less than 61 years old, with Stage I or Stage II disease, with tumor size <= 5.0 cm and who are lymph node negative. The MammaPrint® result is indicated for use **by physicians** as a **prognostic marker** only, along **with other clinicopathological factors**.*

Performance Goals Drive Sample Size

- Sample size

  How good is your device?

  Appropriateness of banked specimens

  Clinical performance needed

- Not one size fits all:

  Genotyping, Basic Clinical Chemistry, Hematology, Flu

Protocols for Analytical studies

- CLSI guidelines:

EP05-A2 - Establishing precision
EP06-A - Establishing linearity
EP07-A2 - Interference studies
EP09-A2-IR - Method comparison studies
EP12-A2 - Qualitative tests
EP17-A - Limits of detection & limits of quantitation
EP21-A - Total error
EP25-A – Reagent stability
C28-A3 - Reference ranges

- MM17-A - Multiplex
- Statistical Guidance for Reporting diagnostic tests (www.fda.gov/cdrh/osb/guidance/1620.html)

Conclusions

- Pre-IDEs are useful for sponsors & FDA
- Effective pre-IDEs require preparation
- Statisticians should be involved early