Use of serology in clinical trials: FDA perspective

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GREAT III

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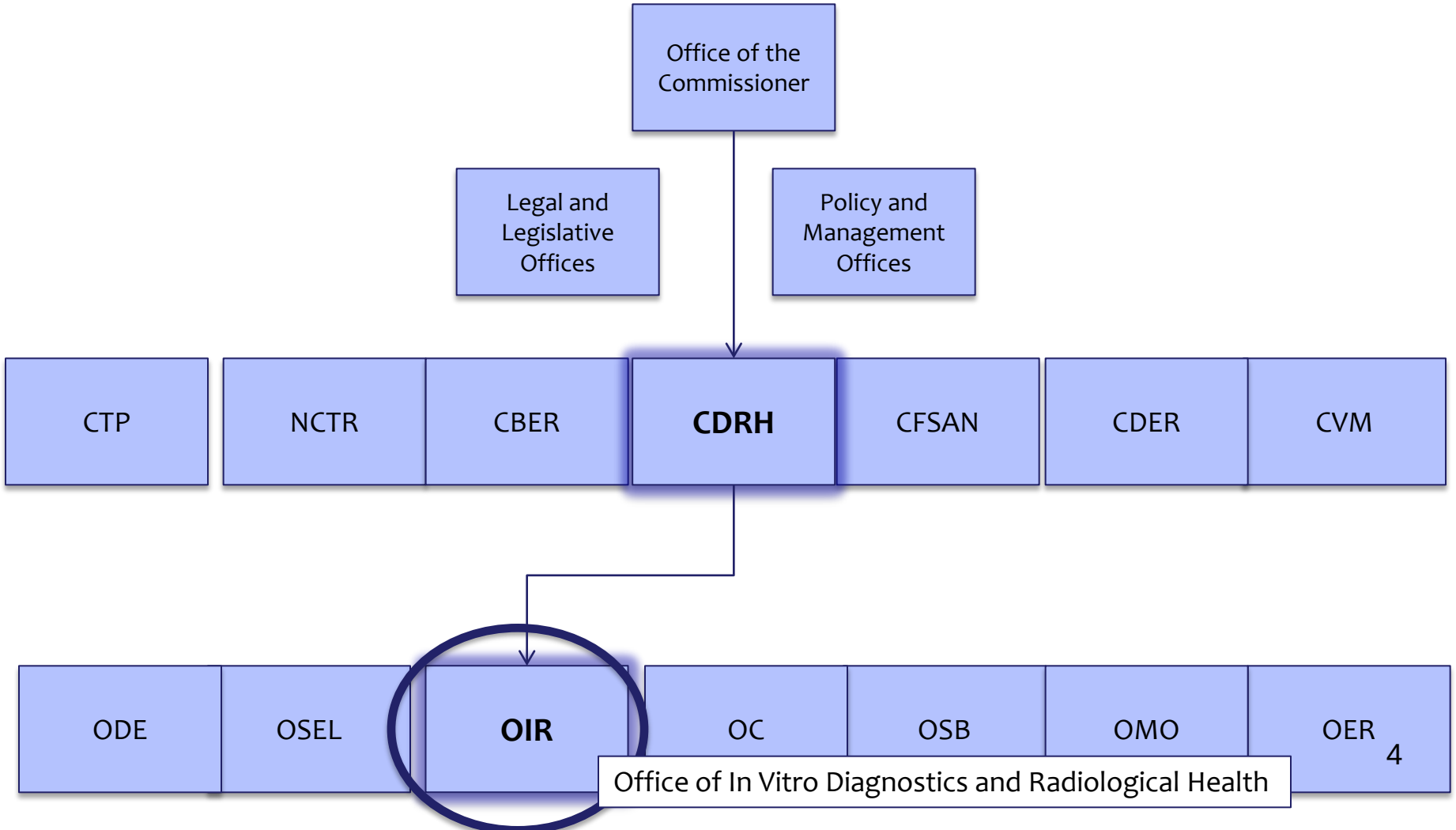
Disclosures

- I have no financial conflicts to disclose

OVERVIEW OF FDA REVIEW OF TESTS

FDA Organizational Structure



How FDA reviews IVD submissions

1. FDA reviews submissions based on *Intended Use* (e.g., screening, prognosis)/Indications for Use.
2. Intended Use determines the Risk of the marker- risk being *harm to patients from a wrong answer*
3. Risk determines Classification (Class I, II, III) and therefore type of submission (PMA, 510(k)).
4. Classification determines the scope of studies necessary to demonstrate performance of the device
5. You may need FDA OK before using your biomarker in a clinical trial - IDE process.
6. Use the PreSubmission process if you have questions

Highlights: What FDA means by…

- Safety [21 CFR860.7(d)(1)]:
  - What is the risk to patient of performing the test or of a wrong result?
    - False positive (FP) genotype as determination of treatment vs FP for diagnosis in conjunction with signs and symptoms
    - Blood test vs brain biopsy
    - Incorrect result in blood typing
  - How accurate are the results of the test?
  - *Analytical validation*
- Effectiveness [21 CFR 860.7(e)(1)]:
  - Is the test result relevant to the clinical condition?
  - *Clinical validation*

How FDA defines an Intended Use

- How is the device intended to be used- type of biomarker?
- For what population?
- For what disease?
- With what samples?
- With what other clinical information?

"The Acme PROTEEN™ test kit is intended for the qualitative or semi-quantitative determination of IgG class autoantibodies against receptor A-1 in human serum. It is used as an aid in the diagnosis of primary A1 deficiency in adults in conjunction with other laboratory and clinical findings."

Some definitions of different Intended Uses

- *Screening*- Aid in detection of disease in patients having no signs or symptoms
- *Diagnosis*- Aid in the diagnosis of disease in patients have signs and symptoms
- *Prognosis*- Aid in determining the natural history of disease, disregarding treatment
- *Monitoring*- Following course of disease: usually in response to treatment in subjects already diagnosed
- *Prediction*- Recommending a course of treatment based on biomarker status for a patient already diagnosed
- *Risk*- Probability of patient developing the disease

Different Intended Uses pose different risks to patients: *Risks* determine classification

- *Screening*- Miss subjects with the disease or select patients without for unnecessary interventions- CLASS III
- *Diagnosis*- Miss patients with disease and treat patients without- CLASS II or CLASS III
- *Prognosis*- Incorrectly predict outcome- CLASS II
- *Monitoring*- Inappropriately change treatment- CLASS II
- *Prediction*- Recommend wrong treatment and deny correct treatment- CLASS III
- *Risk*- Patient acts irrevocably on wrong probability of disease- CLASS III

CHALLENGES TO USING CELIAC SEROLOGY IN CLINICAL TRIALS

Evaluation of the use of tests in clinical trials

- Is the device intended to be used to make patient treatment decisions?
  - Research use only (RUO) vs investigational use only (IUO) vs in vitro diagnostic (IVD)
  - Studies may be exempt from IDE regulations
- Does the planned use of the device in the trial pose more than non-significant risk to the patient?
  - Subject population, sample type, sampling technique
  - Based on use of the test, not necessarily the test itself
  - Significant risk (SR) vs Non-significant risk (NSR) study design

Highlights: RUO vs IUO

- For a product in the laboratory research phase of development, and not represented as an effective in vitro diagnostic product, all labeling bears the statement, prominently placed: "For Research Use Only. Not for use in diagnostic procedures."
- For a product being shipped or delivered for product testing prior to full commercial marketing (e.g., to collect data on the performance of the test during clinical validation), all labeling bears the statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."

http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm

Using celiac serology in clinical trials

- Celiac serology tests have been cleared for aid in diagnosis of celiac disease when clinical truth was established by biopsy
- Celiac serology tests have not been cleared or approved for other uses

Current FDA status of celiac serology tests

Typical cleared Intended Use/Indications for Use statement:

"*The Acme SEALIAK test is an in vitro diagnostic test for the semi-quantitative detection of the IgA and IgG immunoglobulin classes of antibodies to tissue transglutaminase (tTG) in human serum in adults over age 20. The test is intended for use in clinical laboratories as an aid in the diagnosis of celiac disease in conjunction with other laboratory and clinical findings*"

- >45 tests cleared as aid in diagnosis since 1997, variety of technologies
- Class II (general and special controls)
- Reg: 21 CFR 866.5750, 866.5660
- ProCodes MVM (tTG), MST (gliadin)

Challenges with serology in clinical trials-FDA status

- Compared with an "aid in diagnosis claim", a monitoring claim relates changes in the concentration of the marker to *clinically meaningful* changes in disease
- Manufacturers have not yet submitted devices that demonstrate a correlation between tTG levels and histological status for monitoring, only for diagnosis
- Other uses might be included in a clinical trial, e.g., for investigational use only or under an IDE

Challenges with serology in clinical trials- biology of the disease

- Literature indicates that tTG levels decrease in response to GFD and increase with gluten exposure
- Changes in tTG levels may not be reflective of underlying pathology, so changes in tTG have to be understood in the context of therapy
- If tTG levels are low due to adherence to GFD, there may be no meaningful change in tTG levels to monitor the response to therapy

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PRE-SUBMISSION PROCESS

Contacting FDA catches problems early and reduces time to the clinic/to the market

PreSubmission process

- **FREE**
- Non-binding
- FDA review team provides recommendations on approach
- Early involvement can cut *years* off the development time
- http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

Types of PreSubmissions

- Study risk determination—determine risk use in a trial (SR or NSR), or if an IDE is needed
- PreSubmission— Can get written response to questions on analytical and clinical design
- Determination meeting—decide on type of data needed to demonstrate effectiveness
- Agreement meeting—agree on investigational plan
- Informational meeting—info provided to FDA w/o feedback
- Submission issue meeting—to discuss specific concerns during a review

Conclusions

- The Intended Use guides all study design
- Understanding failure modes of the device is key to safety
- Both regulatory status and biology of celiac disease can complicate use of serology tests in clinical trials
- Talk to FDA!

Thank you!

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