Berkeley School of Public Health

Forum for Collaborative HIV Research

HBV Forum 1
November 15th 2016
Hyatt Regency Hotel
Boston

www.hivforum.org

Berkeley School of Public Health

Forum for Collaborative HIV Research

Seeking FDA approval of assays that quantify HBsAg from patient blood

Timothy Block & Robert Gish

This involves bringing individuals from multiple organizations together

Facilitating collaborative research in drug development and health policy

(we, ourselves have motivation, but not the means, to accomplish this)

- Academics with clinical and scientific expertise
- Commercial scientists who possess the specimen and study information
- US FDA experts

Introduction

- Over-all Aims
  - Bring a q HBs into US FDA approval
- Objectives
  - Provide an assay, currently available for use in the management of CHB, to US patients, since it has shown to be clinically useful as positive and negative predictors of treatment outcome, and is likely to be a critical analyte in evaluation efficacy during mono and combination therapy *Liaw, 2012; Mocauri, 2009; Rickborst, 2010)*
  - In vitro experiments show HBsAg suppresses the function of monocytes, dendritic cells (DCs) and natural killer (NK) cells by direct interaction

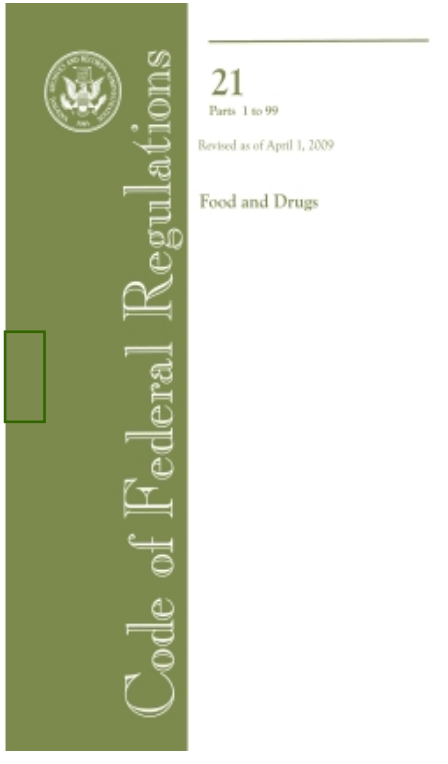
Activities

- Task 1: Convene working group of representative of expert academic, non profit, federal (FDA and NIH) and commercial stake holders
  - Conf. Call: October, 2016, with sub set of talent identified who have critical resources (specimen matched with outcome).
- Task 2: Dr. Subramanian and Wright, working with Drs Lok and Gish, will determine which specimen is still viable and which HBsAg indications it “proves” or supports, for an FDA filing.
  - Activity: Drs. Lok and others have been in communication since th conf call to urge location of the information.
- Task 3:
  - Letter sent from HBF, signed by others, explaining the process. This was received with welcome.
  - Follow up call scheduled for December 2016

Regulatory Authority established for FDA

Facilitating collaborative research in drug development and health policy

- Federal Food, Drug and Cosmetic Act
  - Established regulatory controls for Medical Devices (May 28, 1976)
- Code of Federal Regulations, Title 21, Part 800



FDA Human Subject Protection Regulations

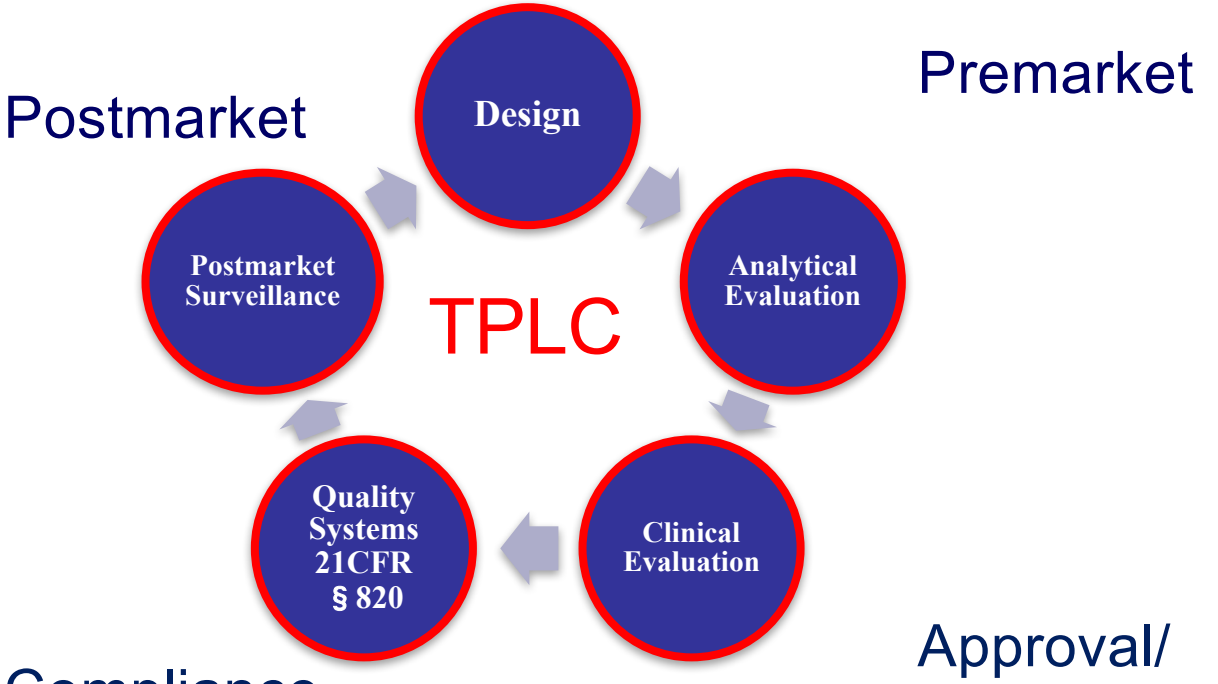
Facilitating collaborative research in drug development and health policy

- 21 CFR Part 50: Informed consent and limited emergency exceptions
- 21 CFR Part 56: IRB review
- 21CFR 812: Disqualification of an Investigator (812.119)

– Apply to all FDA clinical investigations

CDRH Total Product Life Cycle Regulatory Approach

Facilitating collaborative research in drug development and health policy



http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTPLC/tplc.cfm

FDA Regulated Uses of In Vitro Diagnostics (IVD)

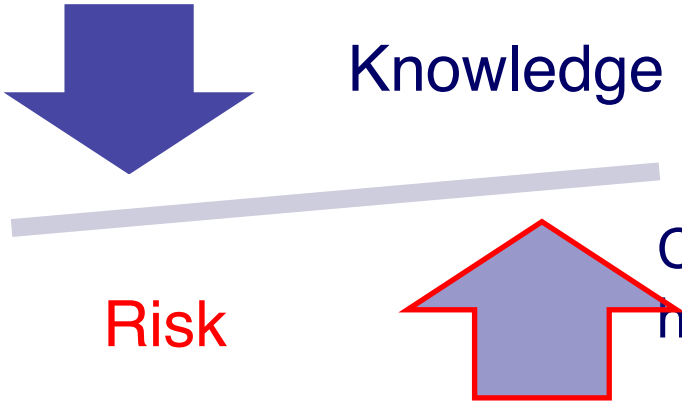
- Diagnosis – Diagnose disease, identify pathogens, confirm, or rule out infection in symptomatic patients
- Screening - Intended use population includes individuals **without** signs or symptoms of disease, infection
- Epidemiology/Surveillance - To detect and monitor incidence or prevalence of infection for targeting and evaluating health programs
- Monitoring, prognosis, prediction

Basis of Pre-Market Device Approval: Risk - Safety and Effectiveness

Facilitating collaborative research in drug development and health policy

- Safety
  - *Are there reasonable assurances, based on valid scientific evidence that probable benefits to health from use of the device outweigh any probable risks? [860.7(d)(1)]*
- Effectiveness
  - *Is there reasonable assurance based on valid scientific evidence that the use of the device in the target population will provide clinically significant results? [860.7(e)(1)]*

Pre-Market Risk Based Classification



Knowledge Mitigates Risk

Class I - Low likelihood of harm
Register & list
General Controls.510(k)

Class II - Moderate likelihood of harm

or risk can be mitigated
Special Controls. 510(k)

Class III - High or unknown likelihood of harm
Significant Risk
Pre-Market Approval-PMA

Pre-Market Risk Based Regulation

- Risk (and subsequently classification and submission type) is inherently tied to Intended Use of a device

- Can any potential risks to a patient be mitigated by special controls such as labeling, analysis of benefit/risk etc.

Intended Use of the IVD

"Intended Use"-driving force of the scientific review

- Understanding :
  Integration of disease(s)/condition(s).
  Integration of patient clinical management and public health (surveillance)
  - Who will be tested, where and when: outpatients, inpatients, pediatrics, adults, acutely ill, etc.
  - What are the appropriate specimens: timing, handling
  - How result(s) may be used: patient management

When is a Device Class III?

- Class III devices are those:

  a) that cannot be classified as class II because insufficient information exists to determine that special controls would provide reasonable assurance of its safety and effectiveness;

  a) that cannot be classified as class I because "insufficient information exists to determine that the application of general controls [is] sufficient to provide reasonable assurance of safety and effectiveness of the device";

AND…

Facilitating collaborative research in drug development and health policy

When is a Device Class III? *cont…*

c) and that "(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health,

d) or (II) presents a potential unreasonable risk of illness or injury." Section 513(a)(1)(C) (21 U.S.C. 360c(a)(1)(C)).

Facilitating collaborative research in drug development and health policy

Facilitating collaborative research in drug development and health policy

2012 meeting with FDA:
Roche Question: HBsAg Q Pre-IDE 2011

- Tumor Markers are Class II devices when used for therapy monitoring and Class III when used for diagnosis. Why not HBsAg Q?

- FDA Response: The intended use for a HBsAg Q assay is for assessing sustained response to treatment and for predicting treatment outcome and not for assessing response to drug therapy.

Jump to 2016

- qHBsAg possible uses
  - Stage liver disease
  - Prognosis /risk of progression to HCC or cirrhosis
  - Decide who is candidate for therapy
    - Nucs
    - INF
    - Clinical trials
  - Early on treatment response (NPV)
  - Late on treatment response
  - SVR: newest and best endpoint = “functional cure”

Downclassification of Class III Devices

- Class III devices can be downclassified to Class II when sufficient information becomes available to establish special controls that reasonably assure safety and effectiveness. Process is slow and complicated by recent Congressional Legislation (7/12)

Downclassification of Existing Class III Devices

- Example: Hepatitis A infection diagnostic devices. Reassessment of level of risk

- Hepatitis B and C infection diagnostic devices remain as Class III
  - {by regulation but not by reality (RGG) }

Basis of Pre-Market Device Approval : Risk - Safety and Effectiveness

Facilitating collaborative research in drug development and health policy

- Safety
  - *Are there reasonable assurances, based on valid scientific evidence that probable benefits to health from use of the device outweigh any probable risks? [860.7(d)(1)]*
- Effectiveness
  - *Is there reasonable assurance based on valid scientific evidence that the use of the device in the target population will provide clinically significant results? [860.7(e)(1)]*

Scientific / Clinical Evidence for Safety and Effectiveness

Facilitating collaborative research in drug development and health policy

Other FDA concerns :

- A lot of papers/abstracts and lots of use of the word "may" aid……
- Lack of endorsement/recommendations by EASL and US. Professional Organizations

Action items

- Current peer review articles need to be more assertive with wording
- FDA needs to lower to Class II (requires and act of Congress) or establish an expedited pathway for viral ancillary testing (proposed)

Facilitating collaborative research in drug development and health policy

Scientific Review: Device Performance

- Analytical Performance Characteristics

  Reliability and accuracy of analyte measurements

- Clinical Performance Characteristics

  Clinical sensitivity and specificity

  Positive and negative predictive values

- Labeling

  Intended use, device design, directions for use, warnings/limitations, result interpretation, performance

Demonstrating Evidence for Safety: Analytical Studies

- Likelihood of false positives?
  - Cross-reactivity and other interferences
  - Carryover and contamination
- Likelihood of false negatives?
  - Limits of detection
  - Matrix effects
  - Interference

Demonstrating Evidence for Effectiveness: Clinical Studies

Facilitating collaborative research in drug development and health policy

- Well-controlled clinical evaluations:
  - Clinical plan and protocol
  - Defined objective(s) and methods
- A test device with standardized design and performance
- Other evidence: case histories, literature, reproducibility etc. where appropriate

Outcomes and Products

- Product 1: Abbott
- Product 2: Roche
- Product 3: Others ?

Facilitating collaborative research in drug development and health policy

Questions

Facilitating collaborative research in drug development and health policy