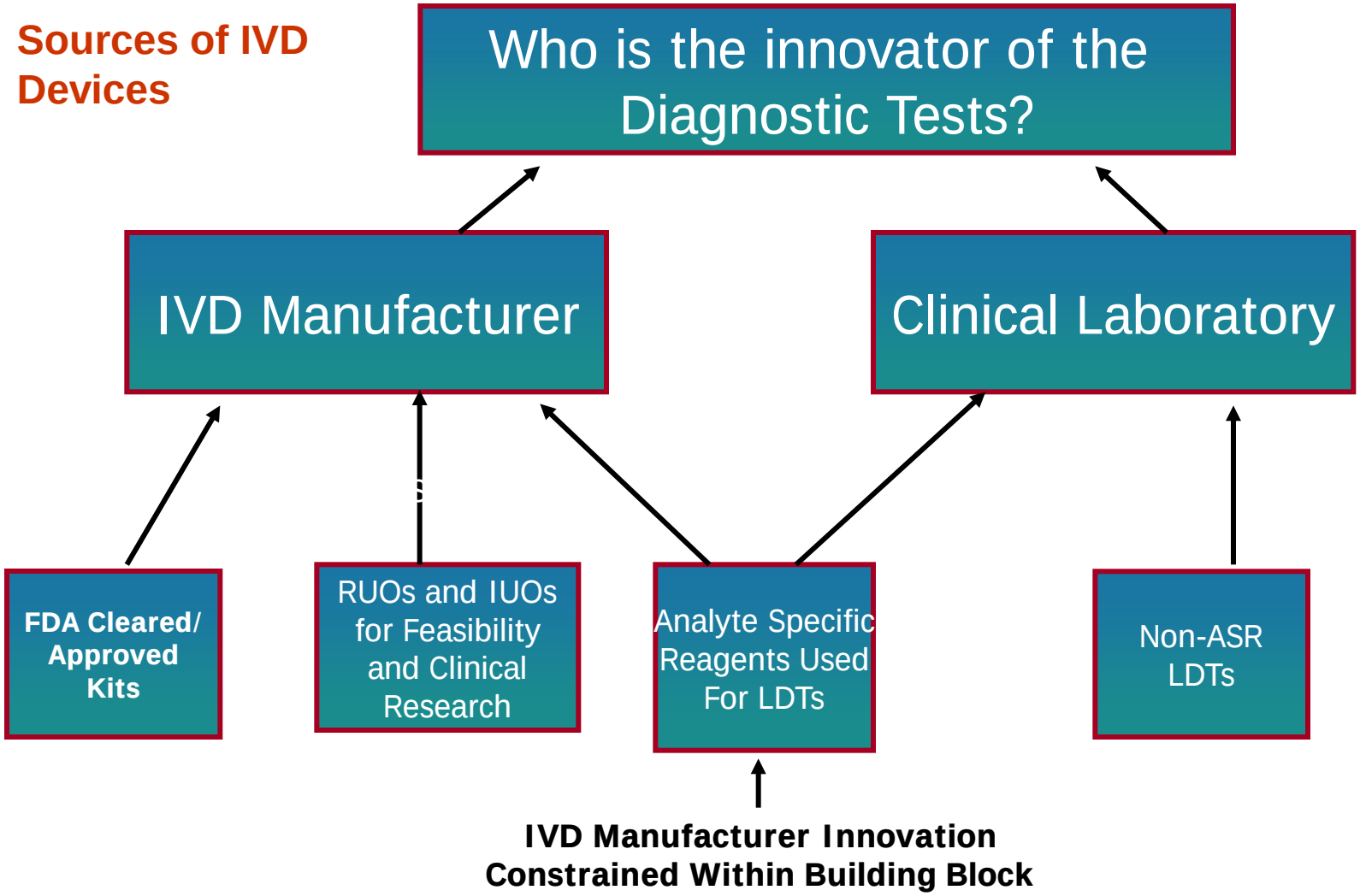
- U.S. FDA Current Requirements for *in vitro* Diagnostics and Companion Diagnostics

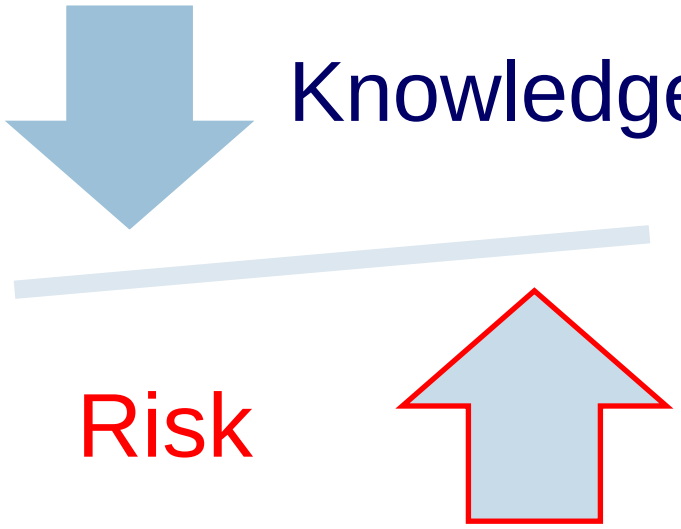
  Why the Agency has Requirements

Sources of IVD Devices



Risk Based Regulation of IVDs

Class I most 510(k) exempt



Class III - PMA

Knowledge Mitigates Risk

Class I - Low likelihood of harm
Register & list 21CFR §807
General Controls

Class II - Moderate likelihood of harm or risk can be mitigated
Special Controls

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

Level the playing field…Basics of Device Review: Safety and Effectiveness

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)]*

Advantages to IVD Co-development

Evaluate drug and device in one trial

For pharmaceutical companies

- potential for optimum patient population and smaller future trials
- improved drug effect if marker effective
- assured performance of diagnostic device- not guaranteed using a Lab Developed Test (LDT)

For diagnostic companies:

- new type of diagnostic claim
- well characterized subjects
- extensive patient follow-up

Review of Proposed Solutions

- Coalition for 21st Century Medicine: Support developers to offer proof of clinical validity in order to obtain coverage. Reimbursement should be based on the performance of each test and evidence that supports it.
- Advamed: Agree that tests should be regulated according to risk.
- ACLA: Clinical validity not addressed.
- CAP: Defining analyte for drug efficacy does not encompass the test technology and variability from different assay methodology.
- ASCO: Agree that regulatory uncertainty of FDA oversight of LDT CoDx is an issue.

Coding and Payment for CDx

- Need transparent coding, especially for Next Generation Sequencing (NGS)
  - Current CPT system, payers do not know what they are paying for
  - Palmetto imposed PTIs and Z-codes
- Stakeholder involvement is need in pricing assays
  - Currently lack of predictability
- Differential payment for clinically validated (FDA PMA) approved assays
  - Similar to innovator drugs for pharma

U.S. FDA Current Dilemma
For Consideration

Expectation of Agency is that an Approved IVD Device is available for the assessment of a patient prior to treatment initiation or adjustment of therapy.

- Continue to require joint meetings with CDER/CBER, CDRH, Pharmaceutical Sponsor and IVD Device Sponsor
- IVD Device intended for commercialization at the time of drug approval is clearly outlined in the device and compound labeling
- FDA to define the requirement for “adding” second, third, etc. compound to the IVD Device labeling
- Total data set, as tested for the original approval should not be required.
  - Test a statistical “n” to allow calculation of negative and positive predictive value.
  - Use consented patient medical information, from specimens tested for NPV and PPV, to “gather” medical outcome information for “truth”

Ultra High Throughput Sequencing for Clinical Diagnostic Applications

- Ultra high throughput sequencing has exerted considerable impact on basic, applied and clinical research.
  - Possible to sequence a complete human genome in a single instrument run.
- Ultra high throughput sequencing technologies, commonly referred to as next-generation sequencing or NGS, have many applications
- With the emergence of these novel technologies, the FDA needs to prepare for new regulatory challenges while continuing to apply scientific evidence-based oversight.
  - To achieve this regulatory goal, the first step is to understand how to analytically evaluate the data generated by the emerging NGS platforms.
- Analytical evaluation of technologies capable of sequencing whole human genomes poses novel regulatory challenges both in terms of biology-related and technical questions, as well as computational resources.
  - One of the important issues is the selection of suitable reference human genomes for validation purposes.
  - Requirements for extensive computer data storage capacity and powerful computational capability to analyze complex data sets also need to be considered.
  - The availability of a variety of platforms employing an array of different sequencing techniques and strategies dictates that any regulatory requirement should have the flexibility to adapt to rapidly changing technology in terms of the wet-lab procedures and the bioinformatics pipeline.

Ultra High Throughput Sequencing for Clinical Diagnostic Applications

- The FDA ultimately has to balance public safety concerns with the goal of fostering innovation and enabling the translation of these new technologies to benefit public health.
  - To evaluate a new technology, the experimental data need to be in accordance with the claim, and the platform performance needs to be adequate for its intended use.
  - The sequencing process can be divided into three phases, with some steps varying between platforms or absent entirely: (1) nucleic acid preparation and amplification (including library preparation, as applicable), (2) signal generation and detection, and (3) bioinformatics analysis.

Conclusion

- FDA Enforcement Discretion of Laboratory Developed Test IVDs creates an un-level playing field compared to IVD Manufacturer requirements to provide evidence to support both safety and efficacy with clinical utility.
- Encourage FDA to define requirements for development of subsequent assays after first CDx approval since samples from the original pivotal trial will not be available. Suggest use of a representative patient population for equivalence testing to the previously approved CDx.