



Comparison of EU and US Regulatory Frameworks



Timothy Stenzel, MD, PhD
Senior Director, Medical, Regulatory,
and Clinical Affairs

Disclaimer

- **I speak only for myself. Ideas contained in this presentation do not represent an official Abbott position.**

Abbott Molecular Registered Products

US

- **PMA: PathVysion (Her-2), UroVysion (Bladder Cancer)**
- **510(k): AneuVysion (Prenatal), AutoVysion (Her-2), CEP8 (Leukemia), CEP12 (Leukemia), XY FISH (Bone Marrow Transplantation)**

EU

- **Annex II A or B: 12 registered products in the areas of HIV-1, CT, CT/NG, HCV, and HBV**
- **Self-declared: PathVysion (Her-2), Vysis AutoVysion System (Her-2), UroVysion (Bladder Cancer), AneuVysion (Prenatal), TriGen (Prenatal), CEP8 (Leukemia), CEP12 (Leukemia), XY FISH (Bone Marrow Transplantation) plus about 12 others with more in process**

Key U.S. Requirements Compared with E.U. Requirements

U.S.

- Device Characteristics
- Labeling
- Performance Standards (QSR)
- Risk Analysis
- Analytical validation (int. & ext.)
- External Clinical Studies
- Mfg & Testing Docs & Summary
- Environmental Assessment

E.U.

- Device Characteristics
- Labeling
- Performance Standards (ISO)
- Risk Analysis
- Analytical validation (int. & ext.)
- External Clinical Studies, opt.
- Mfg & Testing Summary
- *Essential Requirement Checklist*

Draft ASR Guidance Document

- Released in September 2006
- The final (original) ASR rule mentions that ASRs are useful to “...identify one specific disease or condition.”
- The draft guidance appears to alter the original intent of the final ASR rule by introducing the concept that an ASR is a “single moiety”, two words not mentioned in the final ASR rule or any subsequent final documents on ASRs
- Further, the FDA proposes to prohibit manufacturers of ASRs, that have received an unsolicited specific request from a customer, from providing the customer with peer-reviewed, published literature on the use of an ASR
- The draft guidance would limit all ASR nucleic acid products to a single probe or primer. The consequence of this would be to virtually eliminate manufactured ASR PCR products because of labeling restrictions which would leave customers with almost no way of figuring out how to combine the necessary primers and probes into a functioning product

Draft IVDMIA Guidance Document

- **The IVDMIA document (In Vitro Diagnostic Multivariate Index Assays) was released for comment in September 2006**
 - **“1. Use clinical data -- including data from one or more in vitro assays and, in some cases, demographic data -- to empirically identify variables and to derive weights or coefficients employed in an algorithm;**
 - **2. Employ the algorithm to integrate these variables in order to calculate a patient-specific result (e.g., a “classification,” “score,” or “index”). This result cannot be independently derived and confirmed by another laboratory without access to the proprietary information used in the development and derivation of the test; and**
 - **3. Report this result, which cannot be interpreted by the well-trained health care practitioner using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness.”**
- **This proposal would apply to laboratory developed tests with no limit on the size and type of laboratory**
- **The same regulatory pathways would apply to laboratories that now apply to IVD manufacturers**
- **There is confusion among U.S. laboratories about which tests are covered under this new guidance**
- **Many laboratories have expressed concern that this is a prelude to much more extensive FDA regulation of clinical laboratories**

Kennedy Bill

- Introduced March 1, 2007 by Senators Kennedy (D-MA) and Smith (R-OR).
- Requires labs using LDTs (laboratory developed tests) to submit information to FDA supporting the validity of the test. Would include an approved or cleared IVD that has been modified by the laboratory
- All information will be entered into a public Internet database
- 270 days after passage, FDA is to issue a Guidance to facilitate the use of reviews of the peer-reviewed biomedical literature and other information and data about the clinical validity of LDTs
- 18 months after enactment, FDA is to issue a Guidance clarifying when modifications to an LDT will require submission of additional information
- A 510(k) or PMA application may ultimately be required of an LDT
- Laboratories will be required to be GMP compliant and have an adverse event reporting mechanism

Obama Bill (Introduced in 2007)

- **Genomics and personalized medicine interagency working group**
 - Standardized genomics terminology, definitions, and data code sets
 - Quality standards and guidelines
 - Privacy protections
 - Patient control and access, informed consent
 - Research guidelines
- **National bio-banking initiative**
- **Genomics workforce and training**
 - Genetics and Genomics Training
 - Integration across health professional disciplines
- **Realizing the potential of personalized medicine**
 - National Academy of Sciences study
 - Regulation of genomic tests
 - Establishment of CMS specialty area for genetic tests
 - Reimbursement - CPT & HCPCS codes
 - DTC marketing and education/awareness
 - Clinical and cost effectiveness research

Summary

- **The current US system is complex, burdensome, inhibitory, expensive, time-consuming and appears at least somewhat dependent on which FDA individuals/branches are involved.**
 - **Safety concerns may exist since unlike self-declared CE Marked products, ASR manufacturers are not allowed to provide instructions for use**
 - **The current US system may encourage the use of the RUO labeling**
- **The EU system is well-designed, transparent to manufacturers, easily allows for innovation/improvement, and appears to be both safe and to work extremely well.**
- **The US would see many more genetic test kits manufactured and marketed, if it would adopt a more EU-like system, even if all kits were all required to have pre-market review**
- **Any changes to the EU system should be carefully reviewed**
- **Most genetic tests, including higher risk tests, are of relatively small volume which is an inherent disincentive for manufacturers**