

Regulation of Biomarkers

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Medical Device Amendments of 1976

– General Controls

- 1 Registration and listing
- 1 Good manufacturing practices
- 1 Postmarket reporting

Premarket Review

- 1 PMA
- 1 510(k)
- 1 Administrative differences
- 1 Core science same

Model for Evaluation of Diagnostics

- 1 Literature
- 1 Standards – CLSI, ISO
- 1 Guidances
- 1 STARD
- 1 FDA template

Analytical Performance

- 1 Accuracy
- 1 Precision
- 1 Analytical specificity
- 1 Analytical sensitivity*

Feasibility Study

- 1 Establish objectives (intended use and targeted performance)
- 1 Establish test population
- 1 Establish test sites
- 1 Establish cut-offs
- 1 Complete training exercises

Feasibility Study

- 1 Determination of hypotheses
- 1 Mechanistic
- 1 Transparent
- 1 Non-transparent
- 1 Biological and statistical “agnostics”

Clinical Study

- 1 Testing exercise
- 1 Independent validation of performance
- 1 Link to claim

Clinical Study

- 1 Clinical sensitivity
- 1 Clinical specificity
- 1 Predictive value of a positive
- 1 Predictive value of a negative
- 1 Likelihood ratios

Bad News

- 1 Cutting edge science with clinical nuances
- 1 Paucity of material and method standards
- 1 Complex bioinformatics
- 1 Lack of gold standards -- truth

Dickinson and Truth

He questioned softly why I failed?

“For beauty,” I replied.

“And I for truth,—the two are one;

We brethren are,” he said.

Bad News

- 1 Sampling bias
- 1 Selection bias
- 1 Verification bias
- 1 Spectrum bias
- 1 Impact of missing data sets (even small)
- 1 Discrepancy resolution

Good News

- 1 Interest and understanding of adaptive designs – burgeoning literature
- 1 Regulatory shortcuts based on limiting claims, transparency, cautionary labeling
- 1 Expertise in Bayesian statistics – untapped in diagnostics
- 1 Critical path initiatives at work on many fronts

Flexible Regulatory Tools

- 1 Expedited reviews
- 1 Real time work processes
- 1 De novo classifications
- 1 Pre-IDEs

Expedited Reviews

- 1 Not new process
- 1 Allow products to go to head of the queue
- 1 Quality counts

Real Time Work Processes

- 1 Just do it
- 1 Based on Real Time PMA Supplement
- 1 Applied broadly

De Novo Classifications

- 1 Risk based expedited down classifications
- 1 Broadly used in OIVD
- 1 Not without limits

Pre-IDEs

- 1 Protocol reviews
- 1 Antithesis of pop quiz
- 1 Bi-directional education
- 1 Reduced uncertainty

Results

- 1 Roche AmpliChip – 109 days
- 1 MammaPrint – 60 days
- 1 Avian Flu – 14 days
- 1 UGT1A1 – 9 days

Warning

- 1 Analytical performance
- 1 Feasibility studies
- 1 Clinical performance
- 1 -----
- 1 Not clinical utility based on outcomes;
not evidence based medicine*
- 1 Real world performance

Postmarket Safety

- 1 CDRH transformation
- 1 Conditions of approval studies
- 1 Active surveillance – LabNet
- 1 Integration of signals
- 1 Does not change premarket threshold

FDA – Dual Mission

- 1 Promote public health
- 1 Protect public health
- 1 Tension

Good Science

In the Desert

I saw a creature
Who, squatting upon the ground,
Held his heart in his hands,
And ate of it.

I said, "Is it good friend?"
"It is bitter-bitter," he answered,
"But I like it
Because it is bitter,
And because it is my heart."