

Ophthalmology Innovation Summit Medical Device Update

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Regulation of Medical Devices

- Prior to 1976, medical devices did not require FDA pre-market approval
 - Dalkon Shield IUD, an implantable contraceptive device, recalled after 12 deaths
- Congress passed the 1976 Medical Devices Amendments to strengthen FDA's authority to oversee medical devices:
 - Classification of devices
 - Premarket approval for life-supporting/life-sustaining devices
 - Records and reporting requirements
 - Establishment registration
 - Investigational device exemptions

1976 Medical Device Amendments

- Classification based on risk, history of safe use prior to 1976
- Class I and II
 - Premarket notification or 510(k)
 - Demonstration of **substantial equivalence** to pre-1976 or Class I/Class II devices
- Class III
 - Premarket approval (PMA) for life-supporting, life-sustaining devices and new technology
 - Establish reasonable evidence of safety and effectiveness

Temple Report - 1993

- Device approval process source of concern for David Kessler, MD, FDA commissioner
- Formal review of IDEs, PMAs, 510(k)s by Committee for Clinical Review under leadership of Robert Temple, MD, CDER
- Temple Report identified deficiencies in design, conduct and analysis of clinical trials of medical devices
- Led to requirements for randomized, controlled, masked studies in support of PMA applications and increased number of medical reviewers

Food and Drug Modernization Act FDAMA – 1997

- Increased burden on device manufacturers, delays in device approvals led to FDAMA and “least burdensome” mandate for FDA to:
 - Facilitate timely availability of new products, patient access
 - Accelerate review of devices
 - Regulate advertising of unapproved uses of drugs & devices
 - Establish reasonable postmarket controls
 - Improve the regulatory review process

CDRH in the Firing Line

- HHS Inspector General highly critical of CDRH performance in:
 - Product reviews
 - Oversight of clinical investigations
 - Protection of rights of study subjects
 - Review of annual reports, adverse events, MDRs
- Guidant, Medtronic defibrillator issues
 - FDA slow to recall

CDRH in the Press

- Clearance decisions criticized by medical community
 - Concentric Merci device for clot removal and recanalization in acute ischemic stroke cleared without demonstrating clinical benefit ^{1,2}
 - Cyberonics vagal neurostimulation for refractory depression cleared against recommendation of review team, based on an open-label, single-arm clinical trial
 - Regen's Menaflex device cleared for use in meniscus repair, no predicate device with same indication for use, political pressure on FDA

¹Furlan AJ, Fisher M. Devices, drugs and the Food and Drug Administration. Increasing implications for ischemic stroke. *Stroke* 2005;36:398-399.

²Goldstein LB. Regulatory device approval for stroke. Fair and balanced? *Stroke* 2007;38:1737-1738.

What's new at the Division of Ophthalmic Devices?

- Division of Ophthalmic, Neurologic, and ENT Devices (DONED)
 - Many new reviewers, loss of institutional "memory" with experienced long-time personnel retiring as a result of move to White Oak
- Transition from prospective single-arm, open-label clinical trials in "normal" eyes, well-established endpoints
 - Intraocular lenses, excimer lasers
- Novel Class III devices for new indications for use, more sophisticated study designs (RCT, masking), new endpoints
 - Presbyopia
 - Non-refractory glaucoma
 - Choroidal neovascularization (wet AMD)

Class III Devices - IDE Review Trends

- Approval of IDE pivotal trials increasingly difficult for novel devices
 - OUS clinical data is important to support initiation of pivotal trial, and increasing numbers of cases are needed to avoid U.S. feasibility study
 - Phased pivotal trial will be more acceptable than enrollment of full PMA cohort with no interim assessment of data by FDA
 - Agreement on primary effectiveness endpoint and statistical analysis plan prior to trial initiation in the absence of masking
 - Introduction of bias based on sponsor's ability to see data

Class III Devices – Study Endpoints

- FDA pressure on sponsors to pre-specify effectiveness and safety targets for pivotal trials
 - No scientific or regulatory need to pre-specify effect size other than to “power” the study
 - Safety is meaningful only when considered in the context of effectiveness
- Composite or co-primary endpoints
 - Includes effectiveness **and** safety outcomes in a combined endpoint, precludes assessment of benefit versus risk
- Reasonable assurance of safety and effectiveness is established when the benefit is clinically meaningful and exceeds the risk of the device

Class I/II Devices – 510(k) Trends

- Indication for use – a clear predicate device is critical!
- A 510(k) doesn't look like a 510(k)
 - Statistically valid samples sizes for performance testing, bench testing, animal studies
 - Complete software documentation required for software-driven devices
 - For anything novel, clinical data will likely be requested
- Human factors studies – new group at CDRH
- Longer review times

CDRH Enforcement and Compliance Trends

- Inspections, field corrections, recalls
- Current FDA approach is to act fast, investigate later
- Clinical protocol compliance elevated to study validity issue
 - *Question to Advisory Panel, December 2008:*
Based on 19% ineligible subjects; missing data, missed visits, out-of-window visits, loss to follow-up in over 35% of cases, please comment on interpretability and validity of the statistical results for effectiveness, in light of the extent of protocol violations and missing data
 - Sponsor showed that protocol deviations represented 2,492 of 79,240 or 3% of monitored CRF fields, other monitored assessments

Managing the Regulatory Environment

- Design controls and thorough risk analysis are critical
- Maintain compliance with required elements of QSR but keep the quality system simple to make sure that compliance can be consistently achieved
- Same approach for clinical trial compliance
 - Wide visit windows where possible
 - Minimize case report form fields – every missed field is a protocol violation
 - Keep clinical procedures and compliance activities separate from quality systems and CAPA

Managing to a Successful IDE, PMA or 510(k)

- Good science – non-clinical and clinical studies with a rationale, strong design and methodology
- In-depth analyses and understanding of data
- Define safety concerns for informed consent form, labeling
- This is not the right time to do the minimum possible for a submission
- Facilitate FDA's work with thorough, well-organized submissions that are clearly written and easy to review
- Manage expectations – the process is less predictable, strong and steadfast effort is important

Thank you

(and good luck!)