



When Enough is Enough: When and how to push back at FDA

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Overview

- Regulatory changes/firsts
 - Case Studies
- How did we get here?
 - Some perspective
- Is There Anything We Can Do?
 - Available Tricks and Tools
 - Pre-IDE Process – an In-Depth Look
 - Going Global
- Your turn
 - Bring on your stories



Regulatory Changes/Firsts

- Anesthesia delivery device
 - That was then...
 - No clinical trial requirements
 - 510(k) clearance achieved for 154 similar devices
 - MDR reports for 0.0003% of devices sold
 - This is now...
 - Clinical trial requirements before 510(k) clearance will be considered



Regulatory Changes/Firsts

- Ophthalmic device HDE under review
 - FDA refused to meet to discuss deficiency letter unless pre-IDE meeting request was submitted
- Recent IDE application for Aneurysm Repair
 - Day 28 of review - FDA suggested pre-IDE because sterilization validation had not been submitted



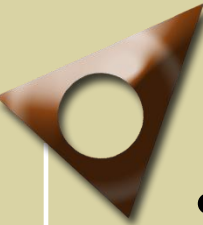
Regulatory Changes/Firsts

- Menaflex Cartilage Repair Device
 - 10 years on EU market, estm. 3,000 patients, no device-related safety issues
 - Per FDA – “unlikely that explanting the device will be appropriate or necessary”
 - 510(k) recission in process



Regulatory Changes/Firsts

- Watchman Embolic Protection Device
 - Class III device submitted for PMA
 - 800 patient pivotal trial
 - FDA panel recommended approval (7:5)
 - FDA disapproved (12 months later) – requires additional pivotal study



FDA on 510(k) Changes

- “...there will still be opportunities for comment, feedback, discussion and shaping.”
- "If substantive concerns were raised about a particular recommendation that we plan to adopt, we'll explain why we are moving forward."
 - Margaret Hamburg (AdvaMed MedTech Conference, October 2010)



General Trends and Observations

- Changes are aimed at improving FDA's reported performance
 - Disapproval is more common
 - Review cycles are limited
 - Hurried phone calls and e-mails need rapid response
- Regulatory practices are implemented, then (maybe) written down
- Practices vary by division, branch and reviewer
- Numerous instances of cancelled pre-IDE meetings, FDA requested meetings, etc. – often no/very short notice



How Did We Get Here?

- Accusations of “bad science” at ODE
 - Accusations of nine FDA staffers
 - Larry Kessler – former Director of OSEL
 - FDA, independent advisors, and Congress agree FDA science needs a “boost”
 - Wants more randomized trials, “hard clinical studies”
 - FDA defers to lowest level regulation previously accepted
 - “...flaws in both the thinking in the agency as well as the 510(k) program itself”



How Did We Get Here?

- Internal FDA challenges plus...
 - Economic downturn
 - Corporate excesses and ethical violations
 - Mistrust of profit motives
 - Promise of sweeping change from Obama administration
- FDA vulnerability to criticism, regulatory risk, attacks by consumer advocacy groups, political pressure...

Is There Anything We Can Do?



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Available Tricks and Tools

- Take advantage of the US need for small businesses
 - Small businesses employ over half the US workforce (<1000 employees)
 - Over 99% of all employers are small businesses
 - Medical device companies are mostly small businesses
 - Small business survival is linked to US economic recovery
- Stay well-connected to OCTANe, Advamed and trade groups that promote the message and importance of the industry



Available Tricks and Tools

- Engage in smart regulatory practices
 - Take advantage of opportunities for FDA communication
 - Pre-IDE process
 - E-mail/Skype
 - Training opportunities to educate FDA reviewers
 - Plan extra time
 - Research FDA reviewer background
 - Submit only **COMPLETE** submissions



More Tricks and Tools

- Evaluate all market approval options
 - HDE, *de novo*
- FDA wants to “co-develop” your protocol, test requirements, device
 - Manage this tendency
 - Encourage collaboration and discussion
 - Be respectful
 - Bring adequate support for your positions



Pre-IDE Meetings

- In-depth look
- Best tool for communication though currently misused/abused



Pre-IDEs - What they are...

- A basic communication tool to obtain informal feedback on:
 - Preclinical test plans
 - Clinical plans/ statistical plan
 - Regulatory status, NSR/exempt investigations
 - OUS investigations
- An opportunity to meet FDA face-to-face to:
 - Demonstrate the credibility and integrity of the company
 - Learn who FDA is and what they expect
- Optional!



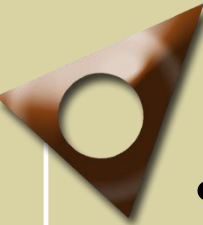
Why face-to-face meetings?

- Potential Benefits (to sponsors and FDA)
 - Design testing and development plans that will expedite review and approval
 - Save money and time in the long run
 - Improves understanding (both ways)
 - Minimize surprises
 - Improves FDA performance on MDUFMA goals
- Cost (to sponsors and FDA)
 - More work, higher costs early in the development process



Pre-IDEs – What they're not...

- A tool for negotiation
- An iterative process
- Modular review
- Review of data (“pre-510(k)”, “pre-PMA”)
- As in-depth as an IDE or marketing application review meeting
- Legally binding
- Method for dispute resolution



Timing – When in the development cycle?

- At key decision points
 - Prior to conducting “proof of concept” animal studies
 - During preclinical phase
 - Prior to expanding clinical trials from feasibility to pivotal phase
- Prior to big expense activities
 - Prior to GLP Study
 - Prior to first US clinical experience
 - Prior to initiating substantive OUS trial



Example: Prior to Proof of Concept

- Discuss concept(s), provide outline of test plan including:
 - Bench tests
 - Applicability of various standards
 - Animal studies – need and type
 - Clinical studies – need and type
- Discuss possible regulatory pathways
- Discuss potential combination product issues
- Be sure plans are well defined and you've got specific questions for FDA to address



Example: During Preclinical Phase

- Request FDA feedback on:
 - Bench testing plan – methods, standards
 - Animal study protocols
 - Feasibility/pilot clinical study protocols
 - Preliminary guidance on SR/NSR (need for IDE) if appropriate
 - Preliminary (non-binding) guidance on regulatory pathway
- Quality of feedback depends on targeted questions
- Pre-IDE meetings/teleconferences encouraged at this stage



Example: Prior to Initiating Pivotal Trials

- FDA will give feedback on:
 - Need for further bench/animal testing
 - Need for pilot study prior to initiating pivotal study
 - Proposed pivotal study protocol: endpoints, duration, evaluation, statistical analysis plan
 - Proposed regulatory pathway
 - Proposed indication for use
 - Preliminary assessment of expedited status, need for advisory panel meeting



Pre-IDE Meeting Process

- Meeting Request
- Submit Pre-IDE Packet
- Meeting Conduct
- Post-Meeting Activities/Follow-up



The Process – Meeting Request

- Contact the appropriate branch for a general discussion or written request
- Provide specific agenda – required
- Allocate realistic proposal of time for topics
- Make the most of your time (minimize background, maximize discussion)
- Meeting will begin and end on time (typically one hour)
- Provide list of attendees (affiliations, expertise)

Scheduling Pre-IDE meetings

- Planning/scheduling done by FDA project manager (usually 3-4 weeks after pre-IDE packet is received)
- FDA will not schedule meeting until pre-IDE packet is received
- Meeting request can precede packet submission by *only* up to 3 weeks



The Process – Pre-IDE Submission Packet

- Not a full IDE – not intended as pre-review of your IDE application
- FDA expects 10 – 20 page document
- Don't fill up with detailed attachments
- Focus on what's critical for FDA to know in order to answer your questions



Pre-IDE Packet Contents

- Device description
- Analysis of potential failure modes
- Outline of proposed conditions of use, including:
 - Proposed intended use and indications
 - Target population and environment of use
- Summary of instructions for use of the product*
- Any known warnings, precautions, contraindications, restrictions or training requirements*



Pre-IDE Packet Contents

- Proposed plan for clinical evaluation of the product (if needed), including:
 - Primary & secondary endpoints and how they will be measured
 - Success/fail criteria
 - Study design and justification for study design
 - Type of control (historical, concurrent, active, none, etc.), identification of control, and justification
 - FDA wants randomization to concurrent controls much more often



Pre-IDE Packet Contents

- Summary of the risk analysis*
- Device performance information
 - Published and/or unpublished data
 - Summary of bench and/or animal test data OR plan
 - Summary of prior clinical experience
- Regulatory path information, regulatory plan
- Specific questions to be addressed



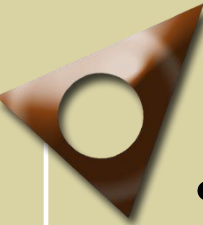
Pre-Meeting Packet: Must be Submitted in Advance

- FDA prepares copies and distributes
- FDA schedules internal pre-meeting and sponsor meeting
- FDA team members review package, prepare memos/feedback prior to internal pre-meeting
- FDA internal pre-meeting held to discuss issues, reach consensus and obtain further information from team/management



Meeting Conduct

- Go prepared to LISTEN
 - Use this meeting to gather information, not answer questions and resolve differences
 - Avoid getting confrontive/emotional
- Usually little/no time for company presentations
 - Put what you need into the pre-IDE packet
 - Don't use the meeting time to explain something new/complex to FDA



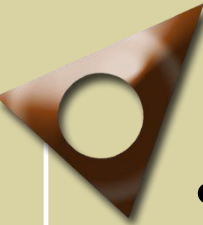
Meeting Conduct - Strategies for Success

- Know the:
 - Applicable regulations
 - Regulatory history/precedent
 - FDA review team
- Strive for:
 - Collaboration
 - Transparency
 - Accessibility
 - Responsiveness
 - High quality submissions



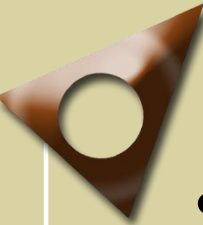
The Process - Post-Meeting Activities

- Get list of meeting attendees from FDA
- Prepare and send meeting notes to FDA
 - Typically FDA doesn't share/prepare meeting notes
 - Meeting notes should be sent to FDA within 7-10 days post-meeting
- FDA will provide feedback/changes on notes (or you should request)
- Incorporate changes to IDE application



Tips for Effectively Using the Process

- FDA will do their homework before meeting with you - you should too!
- Think carefully about what you want to get from a meeting – are you ready to talk with FDA?
- Changes to device or protocol after pre-IDE packet has been submitted could cause delay or cancellation; ask reviewer/branch chief



Tips for Effectively Using the Process

- Manage your meeting time carefully
- Bring right people (no more, no fewer) to discuss focused questions
- FDA will include attendees related to specific questions – do the same
- Ask for clarification if something is not clear



What not to expect...

- Do not expect FDA to:
 - Make any guarantees or binding commitments (unless it is a determination or agreement meeting)
 - Approve a study or clear/approve a device at the meeting
 - Act as a consultant
 - Give special treatment or favors
 - Hold to informal feedback provided years ago
 - technology, medicine not constant
 - Have a series of meetings on the same topics
 - make the most of THIS meeting



Going Global

- Take advantage of the global economy
 - Europe is well known and well supported
 - Plan clinical strategies to develop data cost effectively OUS
 - Brazil, India, Jordan, South Africa, Venezuela
 - More rapid to first-in-man/feasibility
 - More rapid/predictable trials approvals
 - More rapid enrollment
 - Lower cost per patient



Going Global

- Market approval OUS
 - Think “fastest path to revenue”
 - Europe continues to be more predictable
 - Japan/Canada/Australia – well established paths and distribution
 - Countries with large market potential – Brazil, China, India
 - Countries with low levels of regulation – Malaysia, Singapore, India



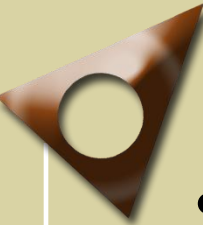
A Note for Suppliers/Service Providers

- Your success depends on your customers success
 - Be prepared to give extra support/justifications
 - Recognize the challenges the industry is facing
 - Manage your financial arrangements
- Consider your own global options



Final Thoughts

- Focus on funded areas for research
 - Preventable chronic diseases and infectious disease
 - \$3 billion in proposed stimulus legislation
 - Opportunities for new/improved delivery methods
 - Funding extended for developing new vaccines
 - Increased focus on stem cell research
- Focus on the continued demand for excellent healthcare
 - Aging population pressures will continue
 - Pendulum will swing back if US patients determine they're not getting the best care/products



Your Turn

- Bring on your stories...

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