FDA Post-Marketing Surveillance

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Post-Approval Studies
Credits

- This presentation is a collaborative effort:
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Post-Approval Studies
Background

- Post-market studies may include post-approval studies
- Statutory basis for post-approval studies
  - 21 CFR §814.82 Postapproval requirements
  - “Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use.”
- Post-approval studies may be a Condition of Approval of a PMA or may be ordered by regulation subsequent to approval

Post-Approval Studies
Reasons for Studies

- Assess the generalizability of a new device or technology
- Continuing long-term follow-up to ensure reasonable assurance of continued safety and effectiveness
- Evaluate the effectiveness of training programs
- Identify and assess rare events
- Gather data on real-world “off-label” usage

Post-Approval Studies
Generalizability - Issues

- Pre-approval clinical trials tend to have experienced, high-volume thought leaders as investigators
- Tend to be early adopters and believers
- High-volume case load provides significant in-depth experience
- May take on higher risk cases, especially referrals
- Case mix may not accurately reflect general experience once device becomes widely available

Post-Approval Studies
Generalizability - Assessment

- Larger sample sizes from dispersed sites preferable
- Mix of high- and low-volume sites
- Mix of more and less experienced operators
- Sequential enrollment: “all comers”;
  - Assess frequency and types of off-label usage
  - May be affected by reimbursement disparities
- Can be linked to assessment of effectiveness of training programs

Post-Approval Studies
Long-Term Follow-up

- Continuing periodic assessment to ensure reasonable assurance of safety and effectiveness for intended use
- Augments pre-approval S&E evaluation
- Particularly important for devices with long-term effects such as permanent implants e.g.
  - Pacemakers / ICDs
  - Carotid Stents
  - Aortic Stent-Grafts

Post-Approval Studies
Long-Term Follow-up

- Pre-clinical “bench” testing is not always completely predictive of long-term reliability
- Permanent implants may function for years before showing systematic signs of failure
- Unanticipated failure modes may appear at long intervals post-implant
- Not practical to conduct very long term pre-clinical evaluation in all cases

Post-Approval Studies
Long-Term Follow-up

- Intelligent mix of pre- and post-approval evaluation can help mitigate time-to-market issues
- Extensive bench testing and design evaluations prior to clinical trials
- Clinical trials designed to evaluate short-term safety and effectiveness and uncover possible unanticipated adverse effects
- Reasonable assurance of S&E prior to approval
- Post-approval study to provide longer-term assessment

Post-Approval Studies
Training Program Assessment

- Post-approval studies can evaluate the effectiveness of training programs in successfully generalizing a new device
- Training usually structured in levels based on experience
- Data collected in post-approval studies links outcomes and adverse events to level of expertise and amount of training provided
- Training programs can be revised based on results to optimize outcomes

Post-Approval Studies
Rare Adverse Events

- Post-approval studies can be designed to capture and assess rare adverse events e.g. mortality, unanticipated device failure modes
- Sample sizes for post-approval studies can be much larger than pre-approval, providing data statistically powered to detect rare events
- Post-approval study design should provide for analyses of rare adverse events

Post-Approval Studies
Rare Adverse Events

- Rare adverse events may be more prominent or likely with widespread use of new device
- For truly rare adverse events, may need to combine post-approval study with active surveillance – company contacts physicians directly to inquire about rare events

Post-Approval Studies
Off-Label Usage

- Post-approval studies designed for sequential enrollment or all-comers should reflect real-world device usage
- Physician practice may drive toward off-label use, ex: device approved for high-risk patients also used off-label for low-risk patients
- Post-approval data collection and analysis can detect significant trends toward off-label use

Post-Approval Studies
Off-Label Usage

- Further pre-approval trials can assess safety and effectiveness of new device for additional indications
- Off-label use of devices in post-approval studies may be confounded by reimbursement issues
  - Sequential enrollment will likely include off-label use
  - CMS coverage may not extend to all subjects in post-approval study if some uses are off-label; depends on details of coverage decision

Post-Approval Studies
Structure of Studies

- Post-approval studies are frequently comprised of several components
  - Continuing long-term follow-up of pre-approval clinical study cohort to gather data on device performance over extended time periods
  - Patients treated post-approval may be enrolled to assess generalizability of device and effectiveness of training program
  - Post-approval study may have several phases to evaluate different aspects of device performance and utilization

Post-Approval Studies
Structure of Studies

- Post-approval studies may be designed to gather data to support reimbursement decisions or expansion of coverage
- Post-approval studies can be structured to gather information on real-world, off-label usage patterns that may drive further pre-approval studies and marketing applications

Post-Approval Studies
Structure of Studies

- Post-approval studies can be designed so that data can be provided in various forms:
  - Physician updates to help physicians to make informed usage decisions
  - Disseminate updated information on device performance and adverse event rates
  - Provide information on mitigations and corrective actions for observed adverse events
  - May be reflected in labeling updates, notifications

Post-Approval Studies
Other Factors

- Data from post-approval studies can help both manufacturers and FDA better characterize the risk-benefit profiles of devices
- Analysis of post-approval data improves FDA's ability to ensure adequate pre-market assessment of device safety and effectiveness
- Post-approval studies can be an important component of post-market surveillance, in conjunction with other data sources

Post-Approval Studies
Real-World Example – Carotid Stents

- First device approved August 2004
- Permanent implant with possible long-term consequences and a sensitive end-organ
- Pre-approval clinical studies conducted on 300-500 subjects at 30-50 high-volume sites
- Low incidence of major adverse events
- Investigators were generally very experienced and already believed in the technology

Post-Approval Studies
Real-World Example – Carotid Stents

- Pre-approval assessment indicated favorable risk-benefit profile and device was approved
- Approved indication is for high-risk symptomatic and asymptomatic patients
- Post-approval studies included as conditions of approval
- Training program included as condition of approval

Post-Approval Studies
Real-World Example – Carotid Stents

- Condition-of-approval studies
  - Continue to follow pre-approval study subjects out to three years post-implantation for long-term assessment of device performance
  - Sequential enrollment of 1500 patients treated since device approval: follow 1000 for 30 days, 500 for one year
  - Categorize post-approval enrollment by high, moderate, low volume center; Level 1, 2 or 3 physician training

Post-Approval Studies
Real-World Example – Carotid Stents

- Condition-of-approval studies
  - If primary endpoint rates or device-related adverse event rates are higher than anticipated, apply stopping rules to reassess risk-benefit profile
  - Link outcomes and adverse events to effectiveness of training program
  - Perform data analyses to uncover off-label usage patterns
  - Provide regular clinical updates to physician users including data from post-approval studies

Post-Approval Studies
In Relation to CMS Coverage Decisions

- FDA & CMS both part of HHS but separate agencies with different mantras
- FDA: "device is safe and effective for intended use"
- CMS: "procedure is reasonable and necessary"
- In designing post-approval studies, companies may want to consider differing FDA and CMS perspectives

Post-Approval Studies
Summary

- Post-approval studies are explicitly called out in the regulations
- Intelligent mix of pre-approval assessments and post-approval studies can ameliorate time-to-market issues while providing reasonable assurance of device safety and effectiveness
- Post-approval studies can be an important component in post-market surveillance of devices

Post-Approval Studies
Summary

- Studies can lend support to coverage decisions or expansion of coverage
- Companies may want to take into consideration the differences in FDA, CMS perspectives when contemplating design of post-approval study


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