RAPS Webcasts

Postmarket Safety Reporting for Combination Products: Understanding and Exploring the Proposed Rule

Bradley Merrill Thompson
General Counsel, Combination Products Coalition
Shareholder, Epstein Becker & Green, P.C.
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Agenda

- Background
- Basic Framework
- Questions & Ambiguities
- Implementation Issues

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Background

- History of postmarket safety reporting for combination products
  - Discussed in Nov. 2002 public hearing and July 2003 public workshop
  - Concept paper published in 2005
  - OCP solicited comments (CPC comments available at: http://combinationproducts.com/images/CPCAEConceptPaperFiled3.23.06.pdf)
  - Content of the proposed rule is similar to the Concept Paper

- So what have manufacturers been doing?
  - Following requirements associated with the marketing application used for its approval/clearance
  - Talking with the agency to develop a plan
  - Over-reporting, under-reporting, just-right reporting – just depends

CPC Comments

- Let’s remember that combination products come in three flavors:
  - Cross labeled
  - Kits
  - Single entity
- CPC in its 2006 comment letter put together a table showing how interim and unified safety reporting systems could be accomplished.

Conceptual alternatives

Option	1	2	3	4	5	6
Basic rule	File based on the sub-mission or center type	Always file two	FDA should use discretion to decide at the time of approval	The manufact-urer should have the discretion to decide which best applies	Always file 1½, that is a primary sub-mission and a supple-mental sub-mission	FDA should develop a single unified reporting process for combin-ation products

Background

- Proposed rule
  - Published Oct. 1, 2009 (http://edocket.access.gpo.gov/2009/pdf/E9-23519.pdf)
  - Original comment date Dec. 30, 2009; extended to Jan. 29, 2010
- Publication of the proposed rule is an important milestone
  - Enables public dialogue between agency and industry on the details of the regulation
  - This dialogue to review the details will help to pave the way for a more effective implementation

Background

- Postmarket safety reporting requirements for drugs, devices, and biological products share many similarities, for example:
  - Deaths
  - Serious/expedited events
  - Periodic reporting
- However, also unique requirements based on the specific products, for example:
  - Device malfunctions
  - Blood-related events

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Basic Framework

- The proposed rule combines the approaches that apply to constituents parts
  - Manufacturer follows a single set of adverse event reporting rules
    - Rules associated with the marketing application under which the product cleared or approved
  - Add on portions of other rules that are different
  - All reports submitted to the lead Center (except for field alert reports submitted to field offices)

Basic Framework

- Five general areas where rules are different and “supplemental” requirements would apply
  - 5-Day report for devices (event requires “remedial action” to prevent substantial harm)
  - 30-Day device malfunction report
  - 15-Day “alert report” for drugs and biological products (serious and unexpected event)
  - 3-Day field alert report for drugs (major problems with drugs in distribution)
  - 7-Day expedited blood fatality report
- These reports only necessary if not otherwise/already required to provide them under the reporting framework for the combination product

Basic Framework

- The rule also would add a completely new requirement
  - Where there are multiple application holders
  - Each applicant subject to:
    - Applicable requirements for postmarket safety reporting for their constituent part
    - Requirement to report “information received about events” to manufacturer of companion constituent part or to FDA within 5 calendar days of receipt of information
    - Requirement to investigate such information received by another applicant

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Questions & Ambiguities

1. Reporting events to manufacturer of companion constituent part or to FDA

- *When* does information need to be reported?
  - Rule says reporter needs to report “information” received
  - Need clarity that a *potentially reportable event* triggers the reporting requirement
  - If an applicant can reasonably determine an event does not concern the other applicant’s constituent part, no reporting requirement
- *What* information is required to be reported?
  - Should include all available information on the event, including information reporter used to determine if the event was potentially reportable

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Questions & Ambiguities

1. Reporting events to manufacturer of companion constituent part or to FDA

- Reporting to FDA “or” another applicant
  - When is reporting to FDA the right choice?
  - Default should be if reporting to other manufacturers not practical

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Questions & Ambiguities

1. Reporting events to manufacturer of companion constituent part or to FDA

- Possible confusion based on regulation and preamble that non-applicants may need to file reports with FDA
- Possible scenario:
  - Person A must report information to a non-application holder (Person B). Proposed 4.104(b) then requires Person B (who doesn't hold an application) to investigate and possibly report the event relating to their product
  - E.g., prefilled syringe approved under an NDA where no 510(k) exists for the container closure/device constituent part
    - Manufacturer of the syringe sells to other entities
    - Under § 4.104(b), the syringe manufacturer would have to investigate information received from the NDA holder and report events per § 4.103(a) and (b).
- Not the right result – marketing application holder is in the best position to investigate and report; component manufacturers and other non-registered entities should not have reporting obligation

Questions & Ambiguities

1. Reporting events to manufacturer of companion constituent part or to FDA

- 5 day reporting timeframe
  - Some reports may not be able to be investigated within this timeframe
  - Possible solution – tie reporting timeframe to the identified event
- Proposed rule says required reports should be submitted under existing methods
  - These are brand new requirements; unclear what reporting mechanism and format should be used
  - Reporters should be able to choose their usual or other internally-developed format

Questions & Ambiguities

2. Reports for combination products with multiple applications

- Rule ambiguous on what reports need filed and by whom when the event relates to the combination product as opposed to a single constituent part
  - E.g., cleared device (1) incorporated into a combo product approved under an NDA, but also (2) separately marketed
  - Need for device manufacturer also to file a report?
- Final rule should clarify that the application holder for the finished combination product should file

Questions & Ambiguities

3. Constituent parts

- Line between a component v. constituent part -- when are components subject to the rules?
- Under existing combination product regulations:
  - Device constituent part is considered a finished device
  - Drug constituent part is considered a drug product
- Proposed rule defines a constituent part to include any drug or any device or biological product that is part of a combination product
- Is a component or sub-assembly or drug ingredient that is part of a combination product a constituent part and therefore in effect considered a finished device or drug product?

Questions & Ambiguities

3. Constituent parts

– Determining which constituent part is associated with an adverse event
  - Not much detail in the proposed rule; this topic would benefit from additional guidance
  - Investigational steps an applicant should take in determining whether a constituent part "reasonably" caused the adverse event

Questions & Ambiguities

4. Reconciling overlapping reporting requirements

- Rule recognizes that supplemental and sometimes duplicate reports will be required
- Supplemental reports are only necessary if the reporter "would not otherwise (already) be required to provide them under the reporting framework associated with the application under which your product is approved, or if they would be required, but at a later timeframe"
  - Criteria for drug v. device reportable event are very different -- default to most demanding?
  - Clarify that capturing reports at a later time is intended for situations in which multiple constituent parts are involved in an event
  - Implementing guidance needs to provide examples

Questions & Ambiguities

5. Assumption that reports always filed with lead Center

- May not always be the case
  - Multiple marketing applications – rule should clarify that constituent part applicants will continue to report to individual centers
  - If lead Center requests a marketing application for a constituent part, that applicant should file reports with Center under which the new application is cleared or approved
  - E.g., CDER tells a manufacturer it needs a 510(k), which leads to MDRs
- Cross-labeled products
  - Do both applicants report to a lead Center?

Questions & Ambiguities

6. Cross-labeled versus concomitant use

- Clarification is needed in order to clarify the application of these rules
- Re-affirm that concomitant use of two differently regulated articles is not a combination product

Questions & Ambiguities

7. Other issues

- Issues specific to medical devices
  - Device malfunctions
    - Rule references and relies upon new provisions in FDAAA (summary reporting for malfunctions for class I devices)
    - Clarify that FDAAA requirements not yet in effect
- Interaction with ex-US reporting requirements
  - Consider harmonization with global requirements
  - Also, when manufacturers must submit field reports when the report is from an ex-US manufacturing site

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Implementation Issues

- What the rule says about implementation
  - "[N]o significant operating and maintenance costs associated with this collection of information because … reporters are required to develop and maintain systems for reporting and maintaining records of postmarketing safety events"
  - Because these systems are already in place, "reporters will accrue no significant additional costs"
  - Estimates the time associated with preparing reports as minimal – only 1 hour to prepare and submit a report and only a 1/2 hour to fulfill corresponding record-keeping requirements
  - 180 days to delay effectiveness

Implementation Issues

- Greater impact on regulated industry
- How will the rules be implemented for existing, “legacy” products?
  - Reporting frameworks currently established through:
    - Product approvals
    - Commercial agreements
  - Established technological reporting mechanisms
    - Heavily automated systems – complex issues in terms of gateways and information flow
    - E.g., Combo product approved under an NDA – only way to input information relating to a device is through the NDA gateway

Implementation Issues

- Impact on new products and market entrants
  - Rule seems to assume most will be familiar with requirements
  - However, until now, agency interpretation was in a draft concept paper
  - New market entrants may need to create completely new systems

Implementation Issues

- Agency implementation challenges
  - Personnel handling certain reports with which they're unfamiliar
  - Personnel and training issues
  - IT challenges
  - As mentioned above, currently no mechanism to handle new requirements for reporting requirements in 4.104

Implementation Issues

- Bottom lines
  - Implementation will require coordination of many functions and time- and labor-intensive changes to existing systems (both within agency and industry)
  - There is a need for coordinating guidance to address and clarify the details
    - Flowcharts
    - Tables
    - Examples
  - Current estimates for compliance burden are too low
  - 180 days may not be sufficient to delay effectiveness

Implementation Issues

- Another bottom line
  - How should this rule fit into the overall scheme for regulating combination products? For example:
    - Permanent solution? *OR*
    - Interim solution until a unified combination product regulatory framework is developed?
  - Unified framework
    - One report that asks for all relevant information about the regulated article
    - One integrated set of reporting timeframes
    - Administratively easier for the agency, thereby allowing them to better protect public health
    - Easier for regulated industry to comply

Questions or Comments?

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