REMS- Opportunities and Challenges for Industry

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• This presentation reflects the speaker’s perspective on this topic and does not necessarily represent the views of Mylan or other REMS sponsors.
REMS Landscape

• If a REMS is in place for the RLD, a REMS is needed for ANDA products referencing that RLD (Single Shared REMS, unless waiver granted by FDA)

• FDA REMS website currently lists 74 approved REMS
  – More than half with ETASU and/or Implementation system (i.e., not just Med Guide or Communication)

• Six Shared System REMS
  – Buprenorphine transmucosal, Clozapine, ER/LA opioids, Isotretinoin, Mycophenolate, TIRF

• Several other Shared System REMS in development/negotiation
The Way We Were…

• FDA would send a letter to ANDA applicant well into the review:
  – REMS exists for the RLD
  – A Single Shared REMS is required
  – Contact RLD holder to work out a SS REMS
  – Here’s their contact information

• RLD cooperation inconsistent- numerous issues
  – Getting prompt and timely movement, meetings, approvals
  – Negotiating terms of a CDA (or even getting started)
  – Challenges in agreeing MOU terms (e.g., veto power, distribution mechanism)

• FDA didn’t play a very active role, but could be engaged in egregious circumstances
Now- Some Great FDA Ideas Have Been Helping

• Sending REMS notification letters to initiate shared REMS work early in the ANDA review process

• FDA scheduling kick-off meeting/teleconference
  – Educate all involved sponsors on requirements
  – Establish expectations/timelines for initial CDAs, MOUs, REMS draft
  – Encourage everyone to play nicely in the same sandbox

• FDA requiring periodic (usually biweekly) status updates
  – Tends to keep the sponsors working in good faith

• Increased FDA engagement, communication and interaction
  – Trend toward FDA input on expectations before the first draft REMS submission- saves a review cycle
More Recent Great Moves From FDA

• FDA Guidance on REMS Modifications & Revisions
  – Delineates various changes and submission types (AR, CBE-30, PAS)
  – REMS Revisions- don’t change risk message or requirements
  – REMS Modifications- could be CBE-30 or PAS

• Use of a single Type V DMF to house the REMS documents, with sponsors simply submitting a LoA to cross-reference
  – Avoids extensive duplicate submissions from multiple sponsors
  – In place: TIRF, Clozapine Coming: Mycophenolate, ER/LA Opioid

• Removal of individual product details from REMS documents and moving to an FDA-managed website to avoid multiple revisions
Ongoing Development & Timeline Challenges

• Multiple sponsors involved:
  – Different levels of sophistication and understanding of REMS
  – Different individual review and decision processes (some very slow)
  – Varying meeting/telecon availabilities
  – May have differing views on important issues; can’t be forced to agree
  – Unequal levels of participation across sponsors; can lead to delay

• REMS Development Challenges
  – Often difficult to gain unanimous agreement on MOU
  – Initial REMS submission takes 3-4 months; Often 4-5 FDA review cycles
  – Finding common ground on contentious issues (e.g. majority vs unanimous rule, veto power, changes to distribution model)
  – Increased FDA interaction could be helpful in this phase to mediate or weigh in on these common issues
  – Launch for typical shared REMS- 2.5 years from initial contact with RLD
Practical Challenges

- RLD cooperation and sense of urgency
- Aligning timing of simultaneous REMS submissions for 20 sponsors

- The REMS space is very small
  - Very few REMS management vendors
  - Everyone needs to use the same few vendors for each new REMS in development, straining their resources
  - REMS groups at individual sponsors are stretched thin with the same people on multiple REMS at once

- Accommodating FDA preference for “switch” technology to facilitate dispensing and REMS operation in the field
  - Essentially only one key vendor
  - Resource limitations and lengthy lead times
Points for Agency Consideration

• Consider FDA/Industry Working Group to identify and evaluate practical alternatives to switch systems

• Avoid ANDA approval delay from inclusion of a new pending ANDA product into an existing approved REMS for that product
  – No substantive change to the REMS or risk calculus
  – No reason to substantially delay ANDA review/approval
  – Some OGD RPMs have pushed out TADs very far for such products

• Multiple review cycles add considerable time
  – FDA sets target timeline expectations for sponsors to develop CDA, MOU, REMS, but no similar timelines and expectations for FDA review
Points for Agency Consideration

• Inconsistency in FDA communication expectations for different REMS
  – For certain REMS, to have a telecon with FDA requires a formal Type B meeting request
  – For other REMS, sponsor POC can email the project manager and get a response or meeting within a few weeks [preferred approach]

• In some cases, midstream changes in FDA primary reviewers have resulted in re-vetting of decisions already agreed
  – Perhaps an ongoing decision log could be used to document decisions and agreements

• Combining multiple individual RiskMAPS into a shared REMS can present massive data migration/inconsistency challenges

• Continue to build on successful increased collaboration
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