An Update on REMS for Generic Drug Products

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A Key ANDA Regulation

The Hatch-Waxman Amendments to the Federal Food, Drug & Cosmetic (FD&C) Act (aka the Drug Price Competition and Patent Term Restoration Act or Hatch-Waxman Act) was enacted in September 1984 to expedite availability of less costly generic drugs by allowing the U.S. Food & Drug Administration (FDA) to approve generic versions of brand name drugs without the applicant having to conduct costly, duplicative clinical trials. The Act is predicated on FDA’s prior determination of the safety and effectiveness of the previously approved reference listed drug (RLD). Under the Hatch-Waxman Act, the prospective applicant of the Abbreviated New Drug Application (ANDA) must demonstrate that the proposed generic product is equivalent to the RLD in (among other criteria) bioavailability.\(^1\) Demonstration of such bioequivalence (BE) requires the generic product manufacturer to obtain samples of the RLD for testing purposes. Prospective ANDA applicants may also require access to RLD for additional testing such as dissolution and tests relating to retention samples.\(^2\)

Overview of the Current REMS Environment

Since September 2007, the FDA has been authorized under the FDA Amendments Act (FDAAA) to require a Risk Evaluation and Mitigation Strategy (REMS) for drug products with serious risks to ensure that the benefits outweigh those risks. REMS elements can include any or all of the following: Medication Guide, Communication Plan, Elements to Assure Safe Use (ETASU), an Implementation System, and Timetable for Submission of Assessments. One unintended, but not unanticipated, consequence of an ETASU is the potential for manufacturers of products approved under a New Drug Application (NDA) to use the ETASU to block or delay approval of a drug that is the subject of an ANDA;\(^3\) i.e., a generic drug product.

This is particularly the case when the ETASU restricts access to the NDA product. In such circumstances, it could be argued that the manufacturer of an approved NDA product would be violating the terms of the REMS restrictions if it were to sell drug samples to a prospective ANDA applicant.\(^4\) In fact, the FDA has become aware of

Abstract

ANDA regulations require that a generic drug be comparable to the reference listed drug (RLD) in active ingredient(s), dosage form, strength, route of administration, labeling, performance characteristics, and intended use. A key performance characteristic is bioequivalence (BE). Under FDAAA, if the RLD has a REMS with ETASU to ensure the benefits outweigh the risks, a drug subject to an ANDA is also subject to those controls. Manufacturers of generic drugs face some unique challenges in the current legislative and REMS environments, including obtaining samples of ETASU-restricted RLDs for BE testing and participation in Shared System REMS. These challenges and an overview of the current REMS landscape have implications for product lifecycle management and are discussed.
instances in which RLD sponsors have cited REMS ETASU as justification for refusal to sell.

The Evolving Legislative Environment Post FDAAA

Three legislative documents are noteworthy for manufacturers of generic drug products since the enactment of FDAAA: these are referred to below as the REMS Guidance, the FAST Act, and the FDA BE Letter Guidance.

REMS Guidance. Two years after FDAAA, the FDA distributed for comment its 2009 Draft Guidance for Industry: “Format and Content of Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications” (commonly referred to as the (draft) REMS Guidance). The scope was focused primarily on NDA products and did not address issues pertaining to new ANDA products. Such provisions were to be the subject of a future guidance. However, no guidance has been issued as of this writing. In fact, the 2009 guidance itself has not been finalized. Only the section on proposed REMS modifications has been further clarified in an April 2015 draft guidance.

FAST Act. As a result of the inadequacy of the enforcement provisions of the applicable section of FDAAA to prevent anti-competitive practices that interfere with access to RLDs, the Fair Access for Safe and Timely (FAST) Generics Act was introduced in the House of Representatives in September 2014. The goal of the FAST Act is to prevent manufacturers from using REMS as a basis to deny access to their products by generic drug sponsors. It 1) establishes a process whereby the Department of Health and Human Services (DHHS) authorizes a generic company’s request for test samples, 2) provides a cause of action against the RLD sponsor if it refuses to provide authorized samples, and 3) imposes penalties to the REMS drug sponsor for refusal to provide samples. As of this writing, this Bill was referred to the Subcommittee on Health and is not yet in effect.

FDA BE Letter Guidance. In December 2014, in recognition of RLD sponsors citing REMS ETASU to justify refusal to sell samples to prospective ANDA applicants, the FDA issued draft guidance for Industry “How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD.” If it so chooses, a prospective ANDA applicant can submit its BE study protocol for FDA to determine that it has protections comparable to those of the applicable REMS ETASU. If such a determination is made, the FDA will issue a letter to the RLD sponsor so stating and indicating that providing RLD to the prospective ANDA applicant would not violate the REMS. An important point is that the RLD sponsor is not legally obligated to comply with the FDA letter. Implications of this will be discussed further in the next section.

Manufacturers of Generic Drug Products Face Challenges Post FDAAA

The post-FDAAA legislative environment has created a number of challenges for manufacturers of generic drug products.

In December 2009, the Generic Pharmaceutical Association (GPhA) issued a response to the September 2009 draft REMS Guidance citing several challenges posed by the Guidance and providing recommendations. These are summarized in the table on the next page.
<table>
<thead>
<tr>
<th>Challenge</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Limited or closed distribution systems | 1. Publish procedure to obtain FDA letter indicating ANDA applicant agreed to applicable restrictions during BE testing.  
   **[Author’s Note: this was subsequently achieved through the December 2014 draft guidance “How to Obtain a Letter from FDA...” which was discussed previously.]**  
   2. Enforce FD&C Act against sponsors who continue refusing to sell product.  
   3. Require that REMS include requirement for manufacturer to certify it will not use REMS as pretext to delay or block generic competition. |
| Cost of Shared System (SS) REMS | 1. Where cost to join may be disproportionate to generic companies, the FDA should state it will invoke the FDAAA “exceptions” provision.  
   2. FDA should implement a separate comparable aspect of the ETASU for generic companies.  
   **[Author’s Note: SS REMS will be discussed further in the next section of this whitepaper.]** |
| Access to shared databases | 1. FDA should require a data sharing arrangement with fair and equitable payment.  
   2. Amend guidance to include data sharing provisions and permit generic companies to develop other systems to comply with ETASU  
   **[Author’s Note: this is the FDAAA “exceptions” provision to be discussed further in the SS REMS section of this whitepaper.]** |
| REMS implementation timeframe | Extend implementation timeframe from 120 to 180d from issuance of the REMS letter. |
| Delay in getting to market when NDA holder submits a REMS modification via Prior Approval Supplement (PAS) | 1. For REMS with multiple approved applications, include all stakeholders in discussion to assure timely communication and implementation.  
   2. Otherwise, if the ANDA holder’s modification conforms to those of the NDA holder, permit ANDA holder to file a Changes Being Effecte in 30-days Supplement (CBE-30).  
   **[Author’s Note: NDA PAS approval time is ~4mo; ANDA PAS approval time is ≥12mo.]** |

**REMS or Restricted Access Programs Used to Block Market Access.** In July 2014, a report “Lost Prescription Drug Savings from Use of REMS Programs to Delay Generic Market Entry” was issued from a GPhA-commissioned study involving a survey of generic drug manufacturers from December 2013 to March 2014. Results showed that, in addition to significant economic impact, REMS or other restricted access programs are being used to deny generic manufacturers access to drug samples for BE testing and product development, thereby blocking market access to generic drugs. It was noted that brand manufacturers had started applying restricted access programs to drugs for which the FDA had not required a REMS. Based on private reports from generic manufacturers and, in one case, a

**Disclosure of Confidential Information.** Another challenge for manufacturers of generic drug products is inherent in the draft FDA BE Letter Guidance (described previously); viz., the requirement to disclose certain confidential information. If the generic manufacturer chooses to request that an FDA Letter be sent to the RLD sponsor, it must first complete a Disclosure of Authorization Form authorizing the FDA to disclose to the RLD sponsor the name of the prospective
ANDA applicant and the active ingredient of the proposed generic drug product. The Form also states that the prospective ANDA applicant agrees to hold the Agency harmless for injuries caused by sharing this information with the RLD sponsor in the FDA Letter.2 The “catch” here is that the prospective ANDA applicant must first authorize the FDA to disclose certain confidential information in the letter to the RLD sponsor, but the RLD sponsor is not legally obligated to comply with the FDA letter. Thus, manufacturers of generic drugs have to make a benefit-risk decision of whether or not to avail themselves of the draft guidance by allowing disclosure of confidential information in hopes of obtaining RLD samples for the required testing.

Legal Liability of Manufacturers of Products with REMS. As mentioned previously, it could be (and has been) argued that the manufacturer of an approved NDA product would be violating the terms of its REMS if it were to sell drug samples to a prospective ANDA applicant/generic competitor.4 The FDA has become aware of instances in which RLD sponsors have cited REMS ETASU as justification for refusal to sell.2 One source noted that the effectiveness of the December 2014 FDA BE Letter Guidance in enabling generic companies to access REMS drug products will likely be based on courts determining whether or not refusal to provide drug samples violates antitrust laws.4

The Current REMS Landscape for Generic Drug Products: Shared System REMS

Pursuant to Section 505-1(j) of the FDCA, a drug subject to an ANDA and its RLD must use a shared system (SS) for ETASU unless the FDA waives the requirement (also referred to as the “exceptions” provision). As a result, the FDA has been directing sponsors of ANDA products to contact the RLD sponsor regarding development of a SS REMS.

As of the latest update of the SS REMS webpage (April 7, 2015), there were six SS REMS involving a total of 108 products of which 77 are generic.10 These are listed in the table below by initial REMS approval date.

<table>
<thead>
<tr>
<th>Name of SS REMS</th>
<th>SS REMS Initial Approval Date</th>
<th>Number of Products (NDA/ANDA)</th>
<th>SS REMS Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotretinoin IPLEDGE REMS</td>
<td>Oct 22, 2010</td>
<td>8 (1/7)</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Transmucosal Immediate-Release Fentanyl (TIRF) Products REMS</td>
<td>Dec 28, 2011</td>
<td>8 (6/2)</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Extended-Release and Long-Acting Opioid Analgesics REMS</td>
<td>Jul 9, 2012</td>
<td>47 (14/33)</td>
<td>MG, ETASU</td>
</tr>
<tr>
<td>Mycophenolate REMS</td>
<td>Sep 25, 2012</td>
<td>29 (5/24)</td>
<td>MG, ETASU</td>
</tr>
<tr>
<td>Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS</td>
<td>Feb 22, 2013</td>
<td>11 (2/9)</td>
<td>MG, ETASU, IS</td>
</tr>
<tr>
<td>Rosiglitazone REMS</td>
<td>Sep 16, 2013</td>
<td>5 (3/2)</td>
<td>ETASU</td>
</tr>
</tbody>
</table>

Five of the six SS REMS involve multiple NDA holders. Four of the six involve more ANDA than NDA holders. All ANDA products are included in SS REMS; none have individual REMS.

The Unique Challenges of SS REMS

Several challenges for ANDA as well as NDA sponsors are inherent in their participating in a SS REMS. Most, but not all, are a consequence of the nature of SS REMS. The remainder are a consequence of the current state of legislation. These are outlined below.
Challenges Attributed to the Nature of SS REMS

- Collaborating with competitors
- Antitrust and competitive confidentiality issues
- Building trust
- Familiarity with developing SS REMS programs
- Understanding the complexity of program requirements
- Ensuring sponsors have an equal voice and access to program information
- Gaining consensus on REMS framework and operation
- Sponsors entering and leaving the program
- Working “at risk” ahead of FDA program design approval
- Dividing responsibilities and costs
- Timely decision-making to meet program deadlines and goals (which is true for any REMS but particularly challenging for SS REMS because of the need to involve multiple sponsors)
- Turnaround time in responding to FDA inquiries due to the need to involve multiple sponsors
- Version control between the FDA and sponsors for REMS modifications

Challenges Attributed to Legislation

- Few precedents (currently only six approved SS REMS)
- Absence of regulations or guidance on SS REMS (currently, the FDA provides its expectations in REMS notification letters to individual sponsors)

What to Watch for in 2015

Three areas are on the “watch” list in 2015. Two involve legislation. One involves the continuing evolution of SS REMS. With regard to legislation, we await:

- The outcome of the referral of the FAST Act of 2014 (H.R. Bill 5657) to the Subcommittee on Health
- Actions resulting from the compilation of public comments on the draft FDA BE Letter Guidance

With regard to SS REMS, we can expect the number of SS REMS to increase as individual products with REMS with ETASU face loss of exclusivity and entry of generic drug products into the market. We can also expect an increase in standardization. The anticipated increase in the number of SS REMS should lead to more standardized methods and tools to help the FDA and sponsor companies develop and manage these programs on an ongoing basis. We’ll see FDA fulfilling its PDUFA V commitment to continue developing techniques to standardize REMS to better integrate into current and evolving healthcare systems as evidenced by stakeholder outreach activities such as public meetings, workshops, teleconferences, symposia, etc. from 2010 to 2013 and issuance of the 2014 FDA draft report “Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS).”

We’ve come a long way, but we’re not there yet!
References


3. FDA Amendments Act (FDAAA) Sep 2007, Title IX, Sec. 505-1(f)(8)


7. House of Representatives (H.R.) 5657: Fair Access for Safe and Timely (FAST) Generics Act of 2014; F:\M13\Stiver\Stiver_381.xml

