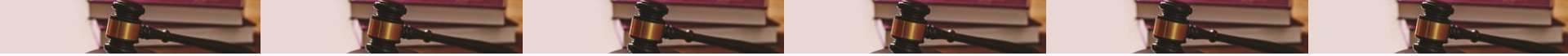
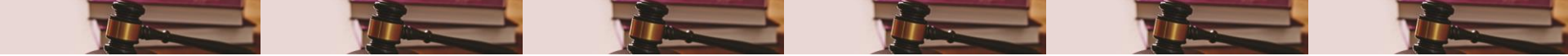


REMS as an Enforcement Tool

Jennifer L. Bragg, Partner, Skadden, Arps, Slate, Meagher & Flom LLP and Vice Chair, FDLI Board of Directors

Rachel Turow, Executive Counsel – Regulatory Law, Teva Pharmaceuticals USA, Inc.

FDLI



Single, Shared REMS and Generic Competition

Rachel Turow
Executive Counsel – Regulatory Law
Teva Pharmaceutical Industries Ltd.

FDLI

Background

- Food and Drug Administration Amendments Act of 2007 (FDAAA) added Section 505-1 to the FD&C Act regarding REMS.
- Prior to FDAAA, FDA had RiskMAPs for certain products with serious safety issues that could be addressed with postmarket mechanisms.
- REMS are similar strategies imposed by FDA to ensure that the benefits of the drug outweigh its risks.
- Some REMS include **E**lements **t**o **A**ssure **S**afe **U**se (ETASU)

The Single, Shared System Requirement

- Section 505-l(i)(l)(B) of the FD&C Act requires ANDAs and the RLD use a “single, shared system” for any REMS with ETASU.
- FDA can waive this requirement if the burden of creating the SSS outweighs the benefits.
- Historically, it has been very difficult for sponsors to reach agreement on formation of SSS and the SSS requirement has been seen as potential barrier to generic entry.

Restricted Distribution Systems Prior to FDAAA

• 1988:	Isotretinoin*	• 2002:	Alosetron
• 1989:	Clozapine	• 2002:	Sodium oxybate
• 1998:	Thalidomide Fentanyl citrate	• 2003:	Abarelix
		• 2005:	Lenalidomide
• 1999:	Dofetilide	• 2006:	Natalizumab
• 2000:	Mifepristone		Fentanyl PCA
• 2001:	Bosentan	• 2007:	Ambrisentan
			Small pox (Vaccinia) Vaccine

= shared system

Pre-FDAAA Shared Systems

Shared RiskMAP programs for Clozapine and Isotretinoin were significantly more successful than today's shared system REMS. What changed between then and now?

Clozapine	Clozaril	NDA 19–758	09/26/1989
		ANDA 74–949	11/26/97
		ANDA 75–417	5/27/99
		ANDA 75–713	11/15/02
		ANDA 75–162	4/26/05
		ANDA 76–809	12/16/05
	Fazaclo ODT	NDA 21–590	02/09/2004

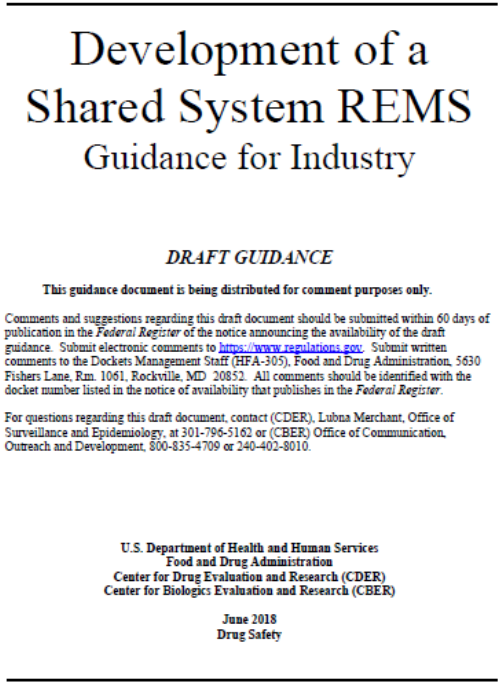
Isotretinoin	Accutane	NDA 18–662	05/07/1982
	Amnesteem	ANDA 75–945	11/2002
	Claravis	ANDA 76–135	04/2003
		ANDA 76–356	04/2003
	Sotret	ANDA 76–041	12/2002
		ANDA 76–503	06/2003

Currently Approved SSS REMS*

Product	Approval Date	Participants
Alosetron	11/22/2016	3: 0 NDA; 3 ANDA
Buprenorphine Transmucosal Products for Opioid Dependence (BTOD)	2/22/2013	22: 3 NDA; 19 ANDA
Clozapine	9/15/2015	15: 3 NDA; 12 ANDA
Emtricitabine/tenofovir disoproxil fumarate	7/16/2012	5: 1 NDA; 4 ANDA
Isotretinoin iPLEDGE	10/22/2010	9: 1 NDA; 8 ANDA
Mycophenolate	9/25/2012	36: 5 NDA; 31 ANDA
Opioid Analgesic REMS	7/9/2012	347: 47 NDA; 300 ANDA
Sodium Oxybate	1/17/2017	1 ANDA
Transmucosal Immediate-Release Fentanyl (TIRF) Products	12/28/2011	10: 6 NDA; 4 ANDA
Vigabatrin	4/27/2017	6: 2 NDA; 4 ANDA

*Data from REMS@FDA

Recent FDA Guidance on SSS REMS



Development of a
Shared System REMS
Guidance for Industry

DRAFT GUIDANCE

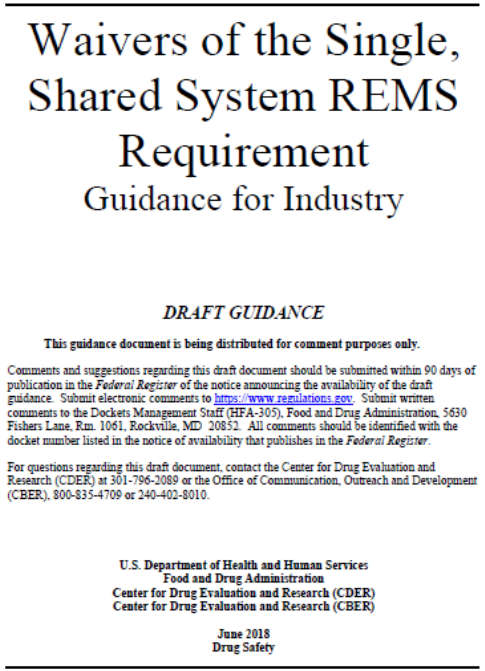
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER), Lubna Merchant, Office of Surveillance and Epidemiology, at 301-796-5162 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2018
Drug Safety



Waivers of the Single,
Shared System REMS
Requirement
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Drug Evaluation and Research (CBER)

June 2018
Drug Safety

SSS REMS Guidance

- Benefits of a SSS:
  - sharing the cost of:
    - developing and implementing the program,
    - analyses of adverse events or other safety data,
    - periodic assessments
  - Makes REMS modifications more efficient.

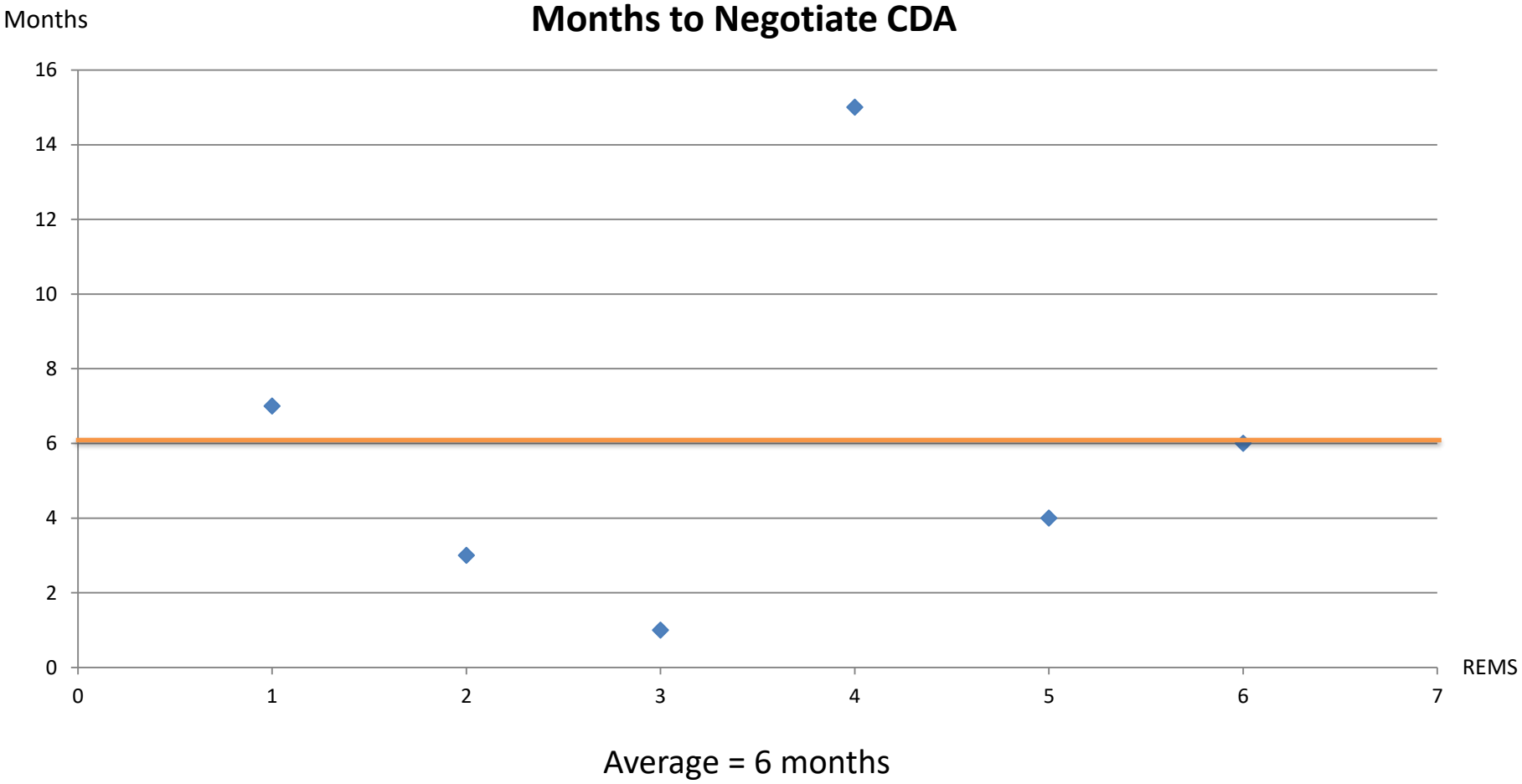
SSS Negotiations

- FDA notifies applicant of need for SSS when an ANDA is filed
- FDA recommends formation of industry working group (IWG)
- Needs to be one POC with FDA
- SSS should be submitted at midpoint of ANDA review
- SSS is condition for approval of ANDA, i.e. ANDA cannot be approved without SSS or waiver-granted REMS in place

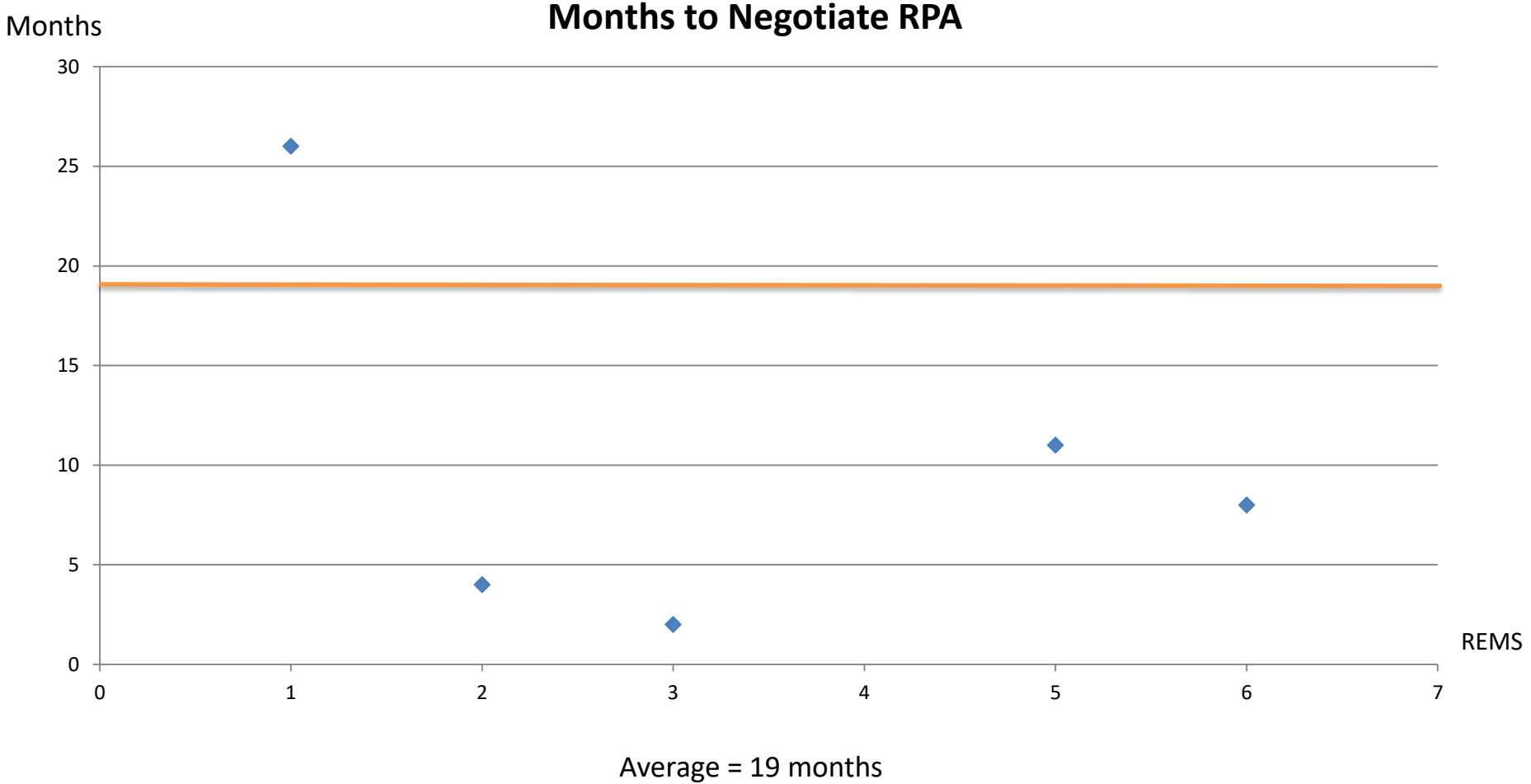
FDA-Identified Issues in SSS Negotiations

Issues to be Addressed in Negotiations

- Confidentiality
- Voting structure
- Cost-sharing
- Product liability concerns
- Anti-trust concerns
- Experience/trust gap(s)

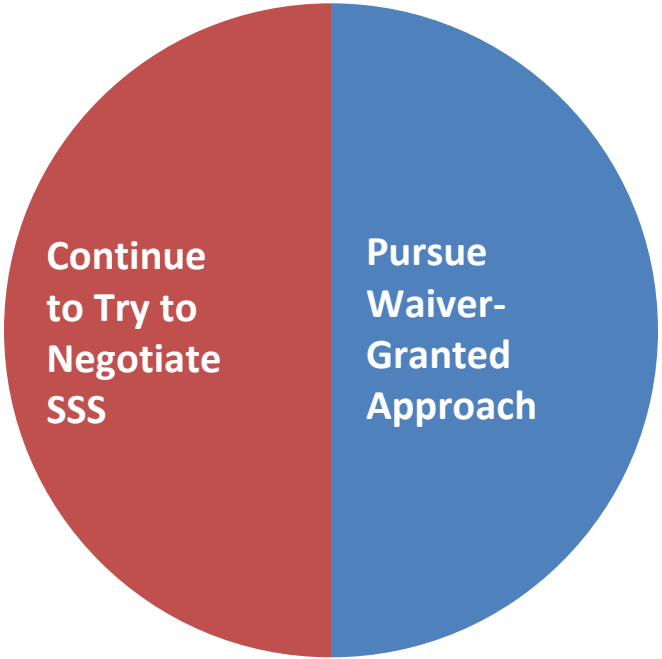

Months to Negotiate CDA
Months
16
14
12
10
8
6
4
2
0
0
1
2
3
4
5
6
7
REMS
Average = 6 months

Months to Negotiate RPA



Average = 19 months

Half the Time, SSS Not Achieved



Getting Across the Finish Line

- Even when negotiations on the CDA and Contract go smoothly, there are still opportunities for delay.
- FDA review can be inconsistent.
  - FDA is still learning how to review SSS and inexperience can lead to regulatory and other related delays.
- When a sponsor chooses to forego the waiver-granted approach, there are hurdles beyond just the CDA and RPA.

Waiver-Granted Approach

- New FDA Guidance on waiver-granted REMS changes waiver from “last resort” to “at any time.”
- Gives alternative for sponsors who have not already pursued SSS
- Not a solution when SSS is already well underway but still delayed due to contractual or regulatory issues.

FDA's Authority to Address REMS Delays

- **Section 505-1(f)(8) of the FD&C Act:**
  - **LIMITATION** No holder of an approved covered application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application under section 355(b)(2) or (j) of this title or to prevent application of such element under subsection (i)(1)(B) to a drug that is the subject of an abbreviated new drug application.
- In other words, innovators should not use ETASU to block generic competition.

CREATES Act of 2016 (S.3056)

(2) FAILURE TO REACH AGREEMENT ON SHARED SYSTEM.—

(A) IN GENERAL.—An eligible product developer may bring a civil action against the license holder for a covered product seeking relief under this paragraph in an appropriate district court of the United States alleging the license holder—

(i) failed to reach agreement with respect to a single, shared system of elements to assure safe use with respect to the covered product; or

(ii) refused to allow the eligible product developer to join a previously approved system of elements to assure safe use with respect to that product.

(B) ELEMENTS.—To prevail in a civil action brought under subparagraph (A), an eligible product developer shall prove, by a preponderance of the evidence, that—

(i) the eligible product developer has sought approval of an application for approval under subsection (b)(2) or (j) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) or has sought a license for a biological product under section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)) referencing a covered product subject to a REMS with ETASU;

(ii) the covered product is subject to a REMS with ETASU that requires a single, shared system of elements to assure safe use with respect to the covered product;

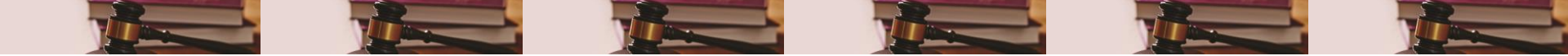
(iii) at least 120 days have elapsed since the developer first initiated an attempt to reach an agreement with the license holder that would allow the product developer to participate in a single, shared system of elements to assure safe use;

(iv) the license holder and eligible product developer have not reached an agreement that would allow the eligible product developer to participate in a single, shared system of elements to assure safe use on commercially reasonable terms; and

(v) the Secretary has not waived the requirement for the covered product to be part of such a single, shared system.

Conclusion

- SSS REMS are very difficult, and in some cases impossible, to achieve and are considered to be a potential reason for delayed generic entry.
- Other than 505-1(f)(8) of the FD&C Act, FDA has little authority to force RLD holders to cooperate during SSS negotiations.
- Given the fraught nature of some SSS negotiations, legal or legislative action (or both) may be the only solution.



REMS as an Enforcement Tool

Jennifer L. Bragg
Skadden, Arps, Slate, Meagher & Flom LLP
Jennifer.bragg@skadden.com
(202) 371-7980

FDLI

Cautionary Notes

- Company-specific citations in slides and accompanying discussion are based on public sources – no privileged or confidential information
- With respect to discussion of indictments and/or civil FCA allegations, these involve allegations of wrongful conduct – and are not themselves proof
- In each of the civil settlements, the companies have denied wrongdoing and the settlements do not include admissions of liability
- The purpose of today's discussion is to describe and analyze theories of liability/risks (and potential defenses and mitigation strategies) – not to judge or criticize the conduct of any particular company

REMS Enforcement Remedies: Criminal, Civil & Administrative

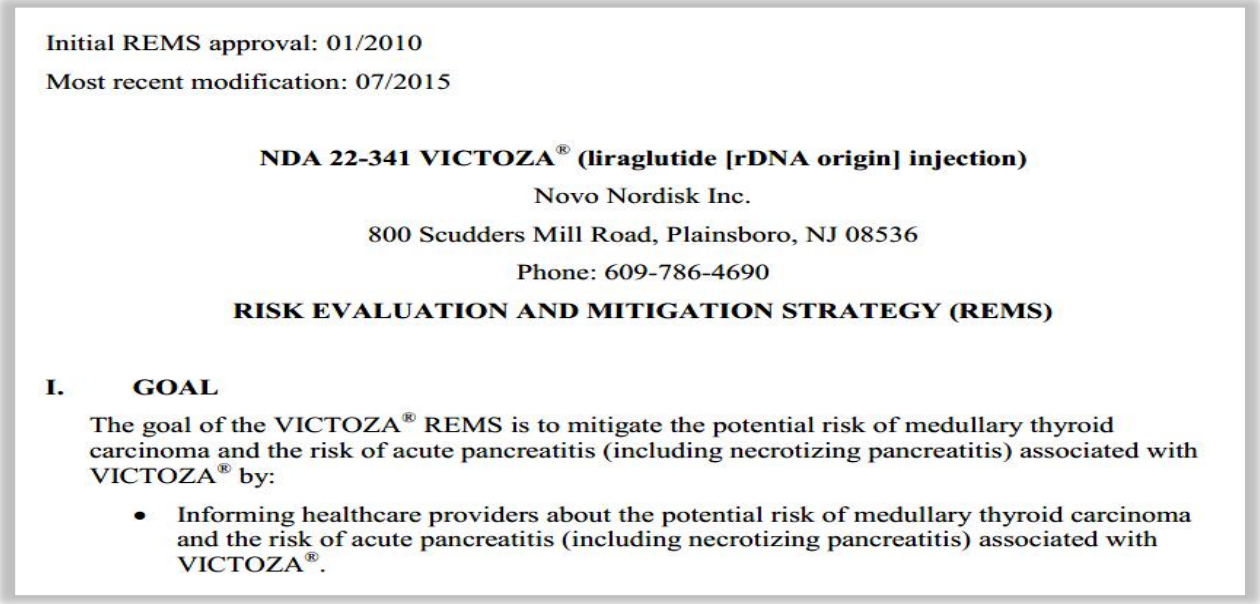
- A drug covered by a REMS is misbranded if the manufacturer fails to comply with a required element of a REMS – *e.g.*, timetable, medication guide, communication plan, or other required elements to assure safe use (ETASU)
- The introduction into interstate commerce of a misbranded drug is a prohibited act and subjects the manufacturer to criminal liability
  - Misdemeanor *(strict liability)*
  - Felony liability *(repeat offenders or violations committed with intent to defraud or mislead)*
- In addition, a knowing submission of false REMS documents or reports to FDA may trigger liability under 18 U.S.C. 1001

REMS Enforcement Remedies: Criminal, Civil & Administrative

- Responsible manufacturers also may face civil liability
  - Civil False Claims Act
  - Equitable relief (injunction and/or seizure) and accompanying disgorgement
  - Civil monetary penalties
    - up to $250,000 per violation of REMS requirements, not to exceed $1 million in a single proceeding
    - If the violation continues after FDA notice, the fine doubles every 30 days (up to $10 million in a single proceeding)

- FDA may also rely on administrative remedies to address non-compliance

Recent REMS Enforcement Actions: Novo Nordisk



Initial REMS approval: 01/2010

Most recent modification: 07/2015

NDA 22-341 VICTOZA® (liraglutide [rDNA origin] injection)

Novo Nordisk Inc.

800 Scudders Mill Road, Plainsboro, NJ 08536

Phone: 609-786-4690

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the VICTOZA® REMS is to mitigate the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with VICTOZA® by:

- Informing healthcare providers about the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis (including necrotizing pancreatitis) associated with VICTOZA®.

- Product-specific (Victoza) REMS
- Imposed at launch to mitigate the risk of a rare form of cancer (MTC) seen in animals
- REMS required a Communication Plan, including a Dear HCP Letter and an information sheet provided to HCPs who were being detailed

Novo Nordisk Allegations

- NNI allegedly used tactics to counter-detail the required REMS message
  - "Sandwiching" the risk message between promotional messages
  - Authorizing messaging that downplayed the potential cancer risk
- "Overall effect" of the training allegedly created the false impression that the REMS-required message was "erroneous, irrelevant, or unimportant."
- One year after product launch, REMS survey revealed that only 50% of surveyed PCPs were aware of the MTC risk
  - FDA deemed this lack of knowledge to be "new safety information" and required NNI to provide an additional HCP letter
- NNI allegedly flouted FDA's admonition and continued to downplay the MTC risk
  - Voicemail from VP of Marketing allegedly instructed sales force to state that no new safety concerns had been identified
- No allegations that NNI failed to adhere to the REMS' pancreatitis requirements

Recent REMS Enforcement Actions: Novo Nordisk

JUSTICE NEWS

Department of Justice

Office of Public Affairs

FOR IMMEDIATE RELEASE — Tuesday, September 5, 2017

Novo Nordisk Agrees to Pay $58 Million for Failure to Comply with FDA-Mandated Risk Program

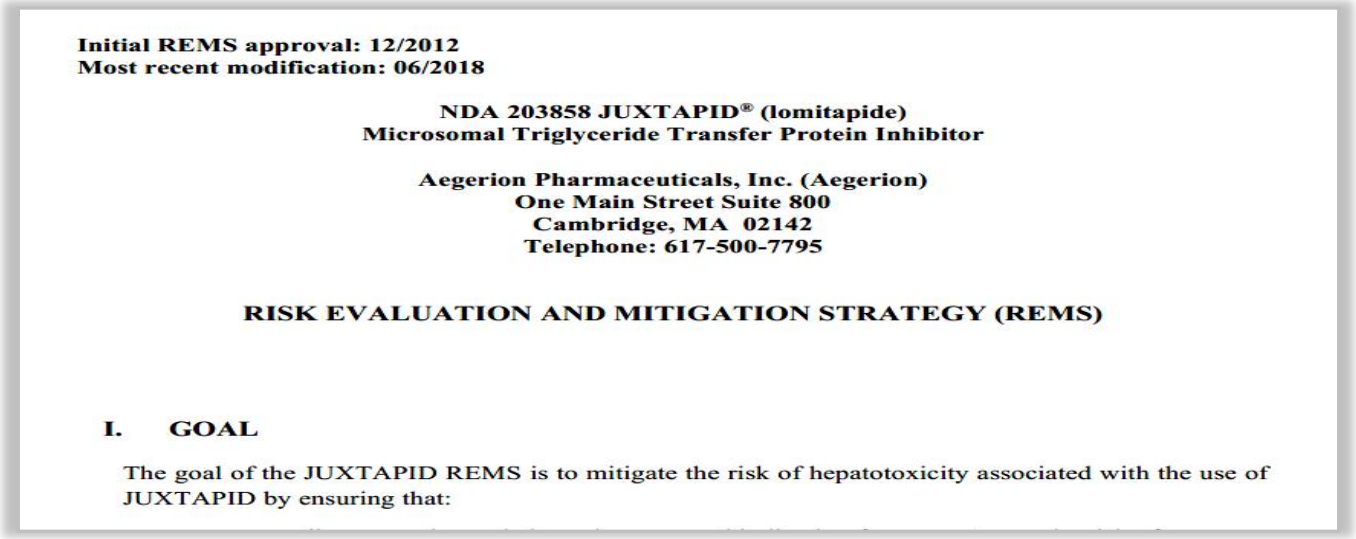
Payments Resolve Allegations Highlighted in DOJ Civil Complaint and Recently Unsealed Whistleblower Actions

Pharmaceutical Manufacturer Novo Nordisk Inc. will pay $58.65 million to resolve allegations that the company failed to comply with the FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) for its Type II diabetes medication Victoza, the Justice Department announced today. The resolution includes disgorgement of $12.15 million for alleged violations of the Federal Food, Drug, and Cosmetic Act (FDCA) from

"Novo Nordisk's actions unnecessarily put vulnerable patients at risk," said U.S. Attorney Channing D. Phillips for the District of Columbia. "We are committed to holding companies accountable for violating the integrity of the FDA's efforts to ensure that doctors and patients have accurate information that allows them to make appropriate decisions about which drugs to use in their care. Working with the FDA and other law enforcement partners, we have sent a strong signal to the drug industry today."

- **$58.65 million civil settlement**
  - $12.15 million in disgorgement
  - $46.5 million to resolve FCA allegations that REMS-related activities caused the submission of false claims
- No CIA
- Settlement resolved 7 *qui tam* suits

Recent REMS Enforcement Actions : Aegerion



Initial REMS approval: 12/2012
Most recent modification: 06/2018

NDA 203858 JUXTAPID® (lomitapide)
Microsomal Triglyceride Transfer Protein Inhibitor

Aegerion Pharmaceuticals, Inc. (Aegerion)
One Main Street Suite 800
Cambridge, MA 02142
Telephone: 617-500-7795

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

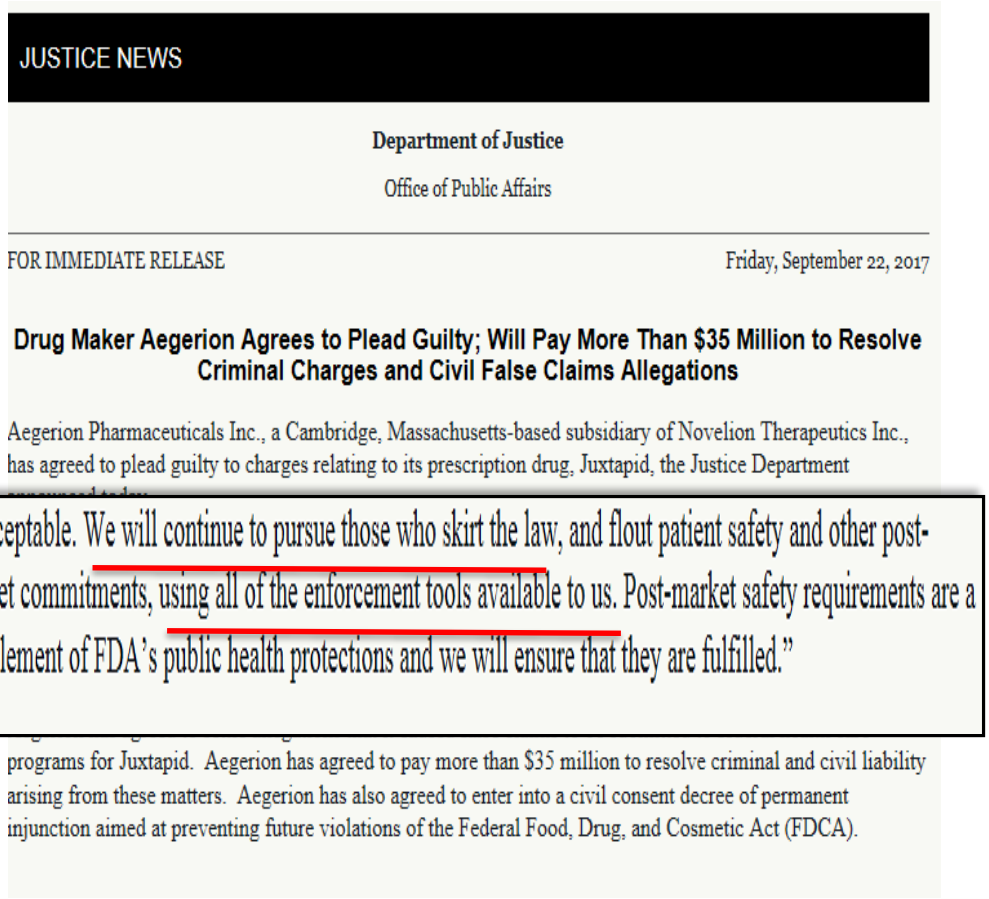
The goal of the JUXTAPID REMS is to mitigate the risk of hepatotoxicity associated with the use of JUXTAPID by ensuring that:

- Product-specific (Juxtapid) REMS
- Designed to educate HCPS about the risks of liver toxicity and restrict access to Juxtapid to patients with a clinical or laboratory diagnosis consistent with HoFH
- REMS requires (among other things) pharmacy and HCP certifications

Recent REMS Enforcement Actions: Aegerion Allegations

- Aegerion allegedly caused the submission of false and misleading REMS attestations
  - Sales representatives advised HCPs that REMS attestations could be completed for patients whose clinical profiles did not meet established diagnostic criteria for HoFH
  - Sales representatives completed attestations without the HCP's knowledge
  - Sales representatives completed attestations that included false and misleading
- Aegerion allegedly "REMS-trained" nurse practitioners but failed to conduct REMS training for physicians who ultimately signed off on the prescriptions
- Aegerion allegedly provided misleading information regarding who was being prescribed Juxtapid to FDA in a required REMS assessment report.
- In November 2013, FDA issued a Warning Letter admonishing Aegerion for making misleading statements about Juxtapid's safety and efficacy

Recent REMS Enforcement Examples: Aegerion



JUSTICE NEWS

Department of Justice

Office of Public Affairs

FOR IMMEDIATE RELEASE — Friday, September 22, 2017

Drug Maker Aegerion Agrees to Plead Guilty; Will Pay More Than $35 Million to Resolve Criminal Charges and Civil False Claims Allegations

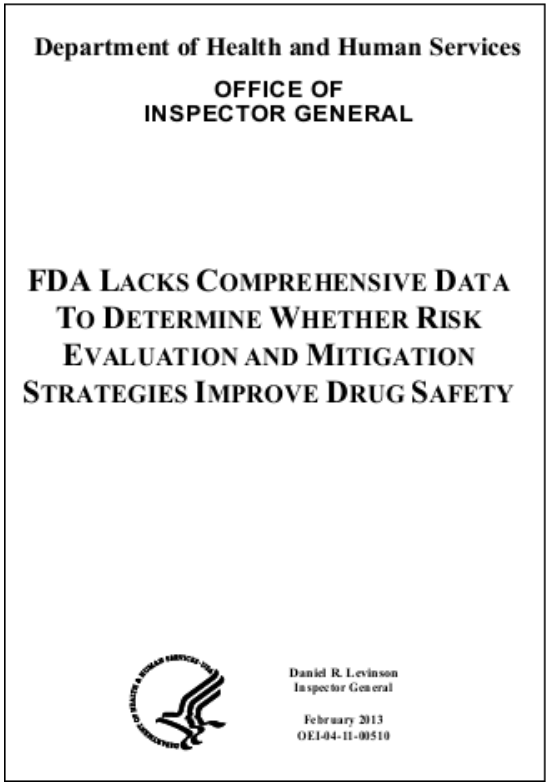
Aegerion Pharmaceuticals Inc., a Cambridge, Massachusetts-based subsidiary of Novelion Therapeutics Inc., has agreed to plead guilty to charges relating to its prescription drug, Juxtapid, the Justice Department

unacceptable. We will continue to pursue those who skirt the law, and flout patient safety and other post-market commitments, using all of the enforcement tools available to us. Post-market safety requirements are a key element of FDA's public health protections and we will ensure that they are fulfilled."

programs for Juxtapid. Aegerion has agreed to pay more than $35 million to resolve criminal and civil liability arising from these matters. Aegerion has also agreed to enter into a civil consent decree of permanent injunction aimed at preventing future violations of the Federal Food, Drug, and Cosmetic Act (FDCA).

- **$35 million criminal and civil resolution**
- REMS (and off-label promotion) misbranding charges resulted in:
  - 2 FDA misdemeanor pleas
  - Annual compliance certifications by company president and BoD
  - $7.2 million in criminal fines and forfeiture
  - Consent Decree
- FCA settlement alleged that statements made in violation of REMS requirements resulted in false claims
- Global resolution also included a DPA and CIA

Environmental Signals



Department of Health and Human Services

OFFICE OF
INSPECTOR GENERAL

FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY

Daniel R. Levinson
Inspector General

February 2013
OEI-04-11-00510

Key Observations

- Only 7 of the REMS reviewed met all of the goals
- FDA most often determined that REMS were not met as a result of deficiencies in patient and HCP awareness of drug risks
- ~50% of the REMS assessments did not include all of requested information
- Nearly all deficiencies identified by prior FDA assessment reviews were still present in the sponsors' most recent assessments

Key Takeaways

- Utilizing the REMS theory of misbranding as an enforcement tool may be appealing to DOJ because it is a relatively straightforward way to charge under the FDCA

- DOJ's REMS-based enforcement efforts have focused on companies that disregarded FDA's attempts to ensure HCPs and patients are informed of the product's risk profile

- As evidenced by the OIG report, lack of risk awareness is a prevalent issue, and FDA may use the various tools at its disposal to address this information gap