Drug Shortages and the FDA
What Does Sugammadex Teach Us?

Sloan, Tod, MD, PhD
University of Colorado School of Medicine

Disclosures

- I have no current financial interests to disclose
- I did participate in Phase III studies with Sugammadex which was supported by the Manufacturer. I received no funds personally with these studies.
- I have not received funds nor spoken on sugammadex sponsored by the manufacturer
- I am not on any speakers bureaus

Sugammadex - History

- Early studies of Rocuronium done to identify autonomic side effects
- Sent to chemist in Scotland to assess effects in rat vas-deferens.
- Needed to squalubize the drug separate from diluent to separate effects of each.
- Cyclodextrins traditional solvent for steroid molecules

Put 2 and 2 together:

- Molecular design to maximize binding efficiency
- IND August 2003, NDA application October 2007

FDA Approval Process

- Drug Discovery and Development
- Preclinical phase
- Clinical Trials
- FDA Approval
- NDA Submission
- NDA Approval
- Marketing Authorization

Lexdon
The Business Library

FDA Advisory Committee Unanimously Recommends U.S. Approval of Sugammadex, the First and Only Selective Relaxant Binding Agent

http://www.marinebio.org/assets/images/54_chart_ceentar_be.jpg
Sloan, Tod, MD, PhD  
Panel: Drug Shortages and the FDA

**Schering-Plough gets not-approvable letter for sugammadex**  
By Michelle Donley  

NEW YORK (MarketWatch) -- Schering-Plough Corp. said Friday that the U.S. Food and Drug Administration issued a "not-approvable" letter for its sugammadex sodium injection, used to reverse muscle relaxation during general anesthesia. The company said it will work with the FDA to address the issues, which are mostly related to allergic reactions, not efficacy.

European Union's CHMP Issues Positive Opinion on Sugammadex  
Anaphylaxis can have new tool that works within minutes, open European approval.


**Anaphylaxis During the Perioperative Period**  
Ursula L. Hoyer, MD, and Mariana C. Castello, MD, PhD  

The Department of Anesthesiology, Perioperative and Pain Medicine, and Emergency Medicine and Clinical Informatics, Tufts University School of Medicine, Boston, Massachusetts.

Table 1: Drugs Involved in Perioperative Anaphylaxis (%)  

<table>
<thead>
<tr>
<th>Substance</th>
<th>Incidence of perioperative anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalbuphine</td>
<td>123</td>
</tr>
<tr>
<td>Ketamine</td>
<td>3</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>27</td>
</tr>
<tr>
<td>Morphine</td>
<td>28</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>20</td>
</tr>
<tr>
<td>Esmolol</td>
<td>20</td>
</tr>
<tr>
<td>Other antimicrobials</td>
<td>20</td>
</tr>
</tbody>
</table>

**Hypersensitivity: Case Description**  
1/1973  
- Subject had a first exposure to sugammadex in a volunteer study (Study 19.4.106)  
- Infusion stopped after 8.4 mg/kg sugammadex due to:  
  - Paresthesia  
  - Visual disturbance  
  - Nausea  
  - Rash  
  - Stomach discomfort  
  - Flushing  
- Reaction was self limiting, no treatment required  
- A slight increase in serum tryptase, suggestive for a possible allergy was found  
- Follow-up skin tests:  
  - Skin prick tests (SPT) inconclusive  
  - Intradermal skin test (IDT): The subject showed wheals > 50% of the wheal size of histamine (positive control) accompanied by flares at 1:1,000 dilution  
- Conclusion skin tests: Subject probably hypersensitive to sugammadex

**Special Populations (cont.)**  
- Bronchospasm (19.4.308)  
  - Two cases were reported as SAEs in asthmatic patients (considered possibly related by the investigator)  
    1. Bronchospasm shortly after reversal, around the time of extubation, successfully treated with terbutaline  
    2. Bronchodilator approximately one hour after reversal, close to the time of extubation, successfully treated with albuterol

**Follow-up Study**  
- Confirmed hypersensitivity in previously seen patient  
- 182 subjects – some naive and some whom had previously had Sugammadex  
- No new hypersensitivity reactions seen

**Election to use experience in Europe where it is approved**

**FDA Under Fire**  
In early 2008, contaminated batches of Chinese-manufactured heparin, a widely used blood thinner, killed dozens of people in the United States. Since then, the U.S. Food and Drug Administration has taken its role much more seriously. While no one would fault the body for doing so, the switch in tactics in monitoring an industry full of potentially under-regulated factories has an impact.
The Federal Food and Drug Administration (FDA) has been stepping up its quality enforcement efforts—levying fines and forcing manufacturers to recall their facilities both here and abroad. Not only has this more rigorous regulatory oversight seemed to bring production levels up, but the FDA’s “zero tolerance” policy is forcing manufacturers to abide by rules that are rigid, inflexible, and unforgiving. For example, a drug manufacturer must get approval for how much of a drug it plans to produce, as well as the timetable. If a shortage develops, (because, say, the FDA shuts down a competitor’s plant), a drug manufacturer cannot increase its output of that drug without another round of approvals. Nor can it alter its timetable production (producing a shortage drug earlier than planned) without FDA approval.

The Globe and Mail

Why Canada is at risk of chronic drug shortages

With the number of chronic drug shortages perceived to peak at a rate of almost one per week, it’s been suggested that the problem is global. But the Canadian market is not free of the problem either. Why? Because the country’s drug purchasing process, and the fact that manufacturers are not obliged to give advance notice of pending shortages, makes a supply problem more likely to reach crisis level.

Learn Finance

Drug shortage as pharmacists sell medication abroad

The list of NHS patients seen being put at risk because of the lack of medication intended for British use is being handed out for profit by wholesalers and pharmacists.

CMS rules contribute to drug shortages, hospital pharmacists say

An Institute for Safe Medication Practices survey concludes that strict expiration dates on drug labels, despite certain evidence in national compendia, mean wasted medications.

Washington Federal guidance requiring strict adherence to manufacturer labels for injectable drugs has forced hospitals to throw away perfectly good drugs that are in short supply, according to a survey of pharmacy directors and managers.
March 23, 2012

AMA aims to alleviate drug shortages

Shortages of critically needed drugs hit a record high last year, nearly tripling since 2005, and continue to climb. As a result of shortages across the country, numerous patients have died or been harmed. Last July, it was reported that most U.S. hospitals have restricted the use of life-saving chemotherapy drugs and other critical medications to cope with the unprecedented shortages. Most of the drugs in question are generic and not highly profitable.

The FDA increased the number of staff for their drug shortages program and sent a survey urging drug manufacturers to voluntarily disclose potential prescription drug shortages even if not required by law.

Table 3. Type of Medication Errors Attributed to Medication Shortages Between 2004 and 2005

<table>
<thead>
<tr>
<th>Type of Error</th>
<th>No. of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing error</td>
<td>271</td>
<td>34.1</td>
</tr>
<tr>
<td>Improper dose/quantity</td>
<td>204</td>
<td>25.7</td>
</tr>
<tr>
<td>Omission error</td>
<td>178</td>
<td>22.2</td>
</tr>
<tr>
<td>Wrong administration timing</td>
<td>84</td>
<td>10.6</td>
</tr>
<tr>
<td>Unauthorized/incorrect medication</td>
<td>47</td>
<td>5.9</td>
</tr>
<tr>
<td>Wrong drug preparation</td>
<td>43</td>
<td>5.4</td>
</tr>
<tr>
<td>Wrong dosage form</td>
<td>21</td>
<td>2.6</td>
</tr>
<tr>
<td>Expired product</td>
<td>15</td>
<td>1.9</td>
</tr>
<tr>
<td>Extra dose</td>
<td>11</td>
<td>1.4</td>
</tr>
<tr>
<td>Wrong patient</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>Wrong route</td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td>Depleted product</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Wrong administration technique</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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De Oliveira, Aesch Acta 2011;115:1429

**Supply Chain**

Injectable Generic Drugs

- Shortage and cost of raw materials
- Few manufacturers (1-3) 7 total in US
- Cost malpractice concerns
- Cost of regulatory compliance and good manufacturing practices
- High cost of specialized manufacturing equipment
- Inability to use manufacturing line for other drugs

- Supply chain problems/ Natural Disasters
- Sale of drugs outside US (Canada)
- Gray market availability
- Poor price responsiveness
- Cost of maintaining inventory
- Short shelf life
- Low cost of drug: pre-negotiated price of buying groups
- Low reimbursement rate insurers and Medicare
- Unexpected increased demand, change in practice/usage

**Economics of Drug Shortage**

Sloan, Tod, MD, PhD

Panel: Drug Shortages and the FDA

Survey: 7 Deaths From Anesthesia Drug Shortage


April 2012. Based on survey of American Society of Anesthesiologists (3,603 members.)
**Etiology of Shortages**

- Limitation of raw materials (30% outside US)
- Manufacturing difficulties
- Regulatory limitations: FDA enforcement
- FDA facilitation (CDER)
- Drug Recalls
- Change in formulation
- Manufacturing business decisions (profitability, other drugs, selling drugs elsewhere)
- Distributor inventory (incl. non-US availability)
- Availability alternative sources, or agents

**Summit 2010**

- American Society of Health-System Pharmacists, American Society of Anesthesiologists, the Institute for Safe Medication Practices, pharmaceutical manufacturers, wholesalers, health care organizations, the federal government and others
- For the purpose of improving the supply of medications in our health care system.
- The summit produced recommendations in the four domains of regulation and legislation, raw material sourcing and manufacturing, business and marketing, and product distribution

**FDA Limitations to Respond**

Report to Congress Nov 2011

- FDA responds to drug shortages
  - taking actions to address the underlying causes
  - enhance product availability, for example by providing assistance to manufacturers to resolve manufacturing or quality problems that can result in a shortage
- FDA is constrained in its ability to protect public health from drug shortages due to its lack of authority

**FDA Resources**

FDA enforcement actions are intended to protect the public from potentially unsafe drug products

- Advisory Panels
- DSAI: Division of Scientific Investigations conducts inspections of clinical investigators’ study sites
- CDER: Center for Drug Evaluation and Research (responsible for response to shortage)(1987)
- CBER: Center for Biologics Evaluation and Research (blood and vaccines)(1987)
- PDUFA: Prescription Drug Users Fee Act Reauthorization (requires shortage tracking, expedited inspections and applications, user fees)(1992)
- FDASIA: Food and Drug Administration Safety and Innovation Act (requires reporting of shortages)(2012)

**Center for Drug Evaluation and Research (CDER)**

- Established 1987 by FDA to deal with shortages, charged with Biologics in 2002
- FDA’s Drug Shortage Program
  - Provide awareness of shortages
  - Conduct medical necessity assessments
  - Consider appropriate action on inspection reports
  - Assess proposals of firms as they attempt to avoid supply disruption or increase production
Prescription Drug User Fee Act


Thursday, May 31, 2012

On May 30, the U.S. House of Representatives, by a vote of 387-0 passed the Food and Drug Administration Safety and Innovation Act of 2012, H.R. 3587, commonly referred to as the Prescription Drug User Fee Act (PDUFA) reauthorization, a legislative package of important Food and Drug Administration (FDA) provisions including ones to prevent and mitigate national drug shortages. Last week, the U.S. Senate passed a separate PDUFA reauthorization that also addresses the drug shortage issue.

Title IX of the House PDUFA reauthorization includes specific requirements for enhanced manufacturer notification to FDA that would enable the agency to use its existing authority to respond in a timely fashion to a manufacturer’s declaration to halt or restrict production of a key drug. Other provisions in Title IX of the PDUFA reauthorization would authorize the Secretary of the Department of Health and Human Services (HHS) to enter into expedited inspections and reviews of drug applications and manufacturing facilities if such actions could help identify or mitigate ongoing drug shortages. Advocates were pleased to see that the Committee included language to “require the Drug Enforcement Administration (DEA) to provide timely approval of details on the scope of controlled substances in instances where an increase could help address a drug shortage.” Also, the legislation requires a Government Accountability Office (GAO) study to examine the issue of drug shortages.

FDA Safety and Innovation Act

Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012

Regulatory Information

Fact Sheet: Drug Products in Shortage in the United States

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. In the new law, Congress provided FDA with new authorities to combat shortages of drug products in the United States and imposed new requirements on manufacturers regarding early notification to FDA of issues that could lead to a potential shortage or disruption in supply of a product.

Manufacturers are required to report

- information about shortages to FDA, and
- are required to report the reasons for shortages and
- the expected duration of shortages

News Release

For Immediate Release
July 5, 2012

Statement from HHS Secretary Kathleen Sebelius on the signing of the Food and Drug Administration Safety and Innovation Act

Today, the President signed into law S. 3587, the “Food and Drug Administration Safety and Innovation Act.” This legislation, which passed both the House and Senate with overwhelming bipartisan support, will help ensure safe and effective medical products to patients and maintain our nation’s role as a leader in biopharmaceutical innovation.

S. 3587 is the culmination of the work of the Administration and Congress, in partnership with patients, the pharmaceutical and medical device industries, the clinical community, and other stakeholders, to provide the Food and Drug Administration with the tools needed to continue to bring drugs and devices to market safely and quickly and promote innovation in the biopharmaceutical industry, and to help secure the jobs supported by drug and device development.

This legislation will drive innovation, improve new drug and medical device reviews, and implement the program proposed in the President’s Budget to accelerate approval of lower cost generic drugs, and fund the new approval pathway for biomarker based treatments in the Affordable Care Act. These new programs are important to increasing patient access to affordable medications and to promoting health care reform.

S. 3587 also enhances the tools available to the FDA to combat drug shortages by requiring manufacturers of certain drugs to notify the agency when they anticipate shortages of critical drugs. The legislation also requires the Administration to request Congress to complement the actions directed by the 2011 Executive Order to address this significant public health issue.

Provisions in the legislation also will help ensure the safety of the drug supply chain in an increasingly globalized market, increase transparency by providing manufacturers, patients and providers with information on drug shortage decisions. It is consistent with the Administration’s request to Congress to complement the actions directed by the 2011 Executive Order to address this significant public health issue.

While enactment of S. 3587 makes an important moment for innovation across industries, research and clinical care settings, its most immediate benefits are the patients and families that will be helped to the next generation of affordable medical products this bill will help to foster.
Sugammadex – Where are we?

YAHOO! FINANCE

Merck Announces FDA Acceptance of Resubmission of New Drug Application for Sugammadex Sodium Injection

WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--

Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the resubmissions of the New Drug Application (NDA) for sugammadex sodium injection has been accepted for review by the U.S. Food and Drug Administration (FDA). Licensure for the drug is expected to be completed at the fourth quarter of 2013.

Sugammadex sodium injection is the company’s investigational agent for the reversal of neuromuscular blockade (NMB) induced by non-depolarizing or depolarizing (succinylcholine chloride) agents. Sugammadex is used in a number of single-dose, stepwise dosing regimens, designed to induce single-dose, stepwise dosing regimens, designed to induce muscle relaxation during surgery. Sugammadex is designed to work by inactivating or reversing neuromuscular blockade directly to neuromuscular junctions. If approved, it would be the first in a new class of medications in the U.S. known as selective relaxant binding agents to be used in the surgical setting.