THE SWITCH CONSIDERATIONS LIST: ‘CONSIDERATIONS FOR RX-TO-OTC SWITCH’ REFINED BY A CRITICAL SYNTHESIS OF FDA COMMENTS ON EXPANDED ACCESS FOR NALOXONE

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ABSTRACT

The Food and Drug Administration (FDA) recently held a meeting to explore new paradigms for drug availability under the regulatory rubric of novel conditions of nonprescription drug use. Subsequent to this meeting, FDA held a workshop on naloxone for prevention of death from opioid overdose. This represented the first publicly discussed switch candidate for novel conditions of nonprescription drug use. The workshop was in the form of an open pre-IND meeting to raise awareness about what considerations would be essential to address if a company were to pursue this switch candidate. Using the methodology previously reported in creating the published list of ‘Considerations for Rx-to-OTC Switch’, a critical synthesis of the FDA recommendations at the naloxone workshop was undertaken to determine if this Switch Considerations List should be refined. Overall, FDA reviewers used the same considerations for expanding nonprescription access to naloxone that have been used for first-in-class Rx-to-OTC switches in the past. However, because of the unique nature of naloxone as a possible intranasal antidote for opioid overdose and the emphasis on certain of the Switch Considerations, several recommendations are made to refine the list, including: addition of a Human Factors Section, renaming the list as ‘Considerations for Rx-to-Nonprescription Switch’; and adding a section on Regulatory Considerations, among others. Compiling and maintaining an up-to-date list of Switch Considerations is important, as it synthesizes the historical and current perspective to help companies predict FDA requirements, may be helpful to train new industry and government personnel, and provides a framework for persons without a regulatory science background to understand FDA switch decision making.

Key words: Rx-to-OTC Switch, Switch Considerations List, naloxone, opioid overdose

INTRODUCTION

In late 2011, Soller et al. published a critical synthesis of ‘OTC Considerations for Rx-to-OTC Switch’ (Appendix). This Switch Considerations List represents FDA’s composite perspective from selected first-in-class switches and other switch principles developed through FDA/industry dialogues in 1990 and 1998. The Switch Considerations List was derived from an analysis of FDA advisory committee transcripts, related meeting materials, and the regulatory science literature.
Subsequent to the 2011 publication of the Switch Considerations List, FDA convened a ground-breaking public meeting in March 2012 to consider ways to expand OTC accessibility through the switch of medicines for novel conditions of nonprescription drug use. A main emphasis was discussion on how to support consumer self-selection when indications for OTC use are too complex to convey key communication objectives through the OTC Drug Facts label. Possible solutions were presented, including pharmacy-only access and technologic solutions in retail settings using consumer survey kiosks. Others with a public health interest proposed the switch of naloxone to prevent fatalities due to heroin and opioid analgesic overdose (HOAO). In addition, a group of academic health professionals (i.e., the Self Care Collaborative) submitted comments to FDA elaborating core principles for new-era switches for medical therapies with novel conditions of use.

Shortly after the public meeting on novel conditions of nonprescription use, FDA held another public workshop to focus on potential nonprescription availability of naloxone for prevention of death in HOAO. This workshop was the first US public deliberation on a drug with potential novel nonprescription conditions of use. Discussion of the naloxone workshop represented a unique development, since nonprescription availability for naloxone is mainly driven by public health advocates, not the pharmaceutical industry. A naloxone switch also involves consideration of complex issues, such as: treatment of illicit and prescription drug abuse; and administration of the medical therapy by a ‘buddy’ (i.e., a person present at or near the time of an overdose event related to opioid use). Yet, these potentially risky novel conditions of use are balanced by an active ingredient that is recognized as having a remarkably positive safety profile, notwithstanding certain serious safety concerns.

Both FDA meetings had been preceded by publications from the US Centers for Disease Control and Prevention on a US update of the scope/extent of opioid-related overdose and a recent survey on community-based harm reduction programs using naloxone. This information was presented at the FDA meetings and is referenced below.

In a broader context, the UK Advisory Council on the Misuse of Drugs (ACMD) published a detailed report in May 2012 recommending wider UK availability of naloxone for harm reduction in HOAO. ACMD is an independent expert body within the UK Home Office established under the Misuse of Drugs Act of 1921 providing advice to government on drug-related issues in the UK. In Scotland and Wales, recent successful pilot projects have led to national programs. In 2011, Scotland permitted naloxone to be provided to some services without prescription for use in emergency. In Wales, a national strategy for take-home naloxone was established in 2009, followed by a number of local projects. The evaluation of these projects was completed in March 2011 with the main recommendation that take-home naloxone is effective and should be made available across Wales. Considering the available evidence from local programs in the UK, the ACMD concluded that ‘naloxone provision is an evidence-based intervention, which can save lives.

These international activities in the US, UK and elsewhere, such as in Sweden and Italy where...
naloxone is available without a prescription, are consistent with the UN Commission on Narcotics Drugs encouragement to “… all Member States to include effective elements for the prevention and treatment of drug overdose, in particular opioid overdose, in national drug policies, where appropriate, and to share best practices and information on the prevention and treatment of drug overdose, in particular opioid overdose, including the use of opioid receptor antagonists such as naloxone.11.

With this background in mind, the following questions were formed: (a) when considering naloxone as a potential nonprescription medicine with novel conditions of use for prevention of fatalities associated with HOAO, did FDA convey any new perspectives that should be reflected in the ‘OTC Considerations’ previously compiled and reported in SelfCare in 2011 (Appendix); (b) what were the specific recommendations to interested nonprescription drug development teams regarding choice of formulation and data needed to support naloxone for prevention of death related to HOAO? The main focus of this paper is on the US consideration of naloxone as a nonprescription medicine.

METHODS

A similar critical synthesis methodology as employed to create the list of ‘OTC Considerations for Rx-to-OTC Switch’ based on first-in-class switches from 1999-2011 was used to assess meeting materials, transcripts and background materials for the March 2012 and April 2012 public hearings on novel conditions of nonprescription drug use and on naloxone1,2,7,8. In order to give context to this exercise, the evidence base for naloxone’s safety and effectiveness was also reviewed using materials presented by government and academic sources at the April naloxone meeting. This included obtaining and evaluating key original sources for information used by stakeholders at that meeting and conducting a review through established drug information resources. The output of the review was a synthesis of the regulatory scientific considerations and not a full discussion of the safety of naloxone. The results of our contextual review are presented.

Synthesis of the regulatory-scientific considerations set forth by FDA included: documenting the specific questions identified as important by FDA presenters or in FDA materials, consolidating questions if more than one FDA reviewer stated the same consideration in different terms but with the same meaning, mapping the core questions against the list of ‘Considerations for Rx-to-OTC Switch’ published by Soller et al. to determine what if any new considerations might relate to OTC availability of naloxone1. If differences in opinion between the investigators arose, a third party was asked for an opinion, which was then discussed to create resolution.

FINDINGS

Rationale for broader access to naloxone

US Epidemic of Opiate Overdose*: In the US, there is a prescription opioid epidemic especially

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*The initial results of this paper provide a sketch of the significant problem of prescription drug overdose affecting the US. The FDA meeting on naloxone is a rich source of information on this matter, as is the Center for Disease Control and Prevention (CDC) and the National Institute of Drug Abuse (NIDA).
affecting underserved populations. Recent US statistics paint a grim picture of this high profile public health issue\(^1\). In the US, one person dies every 19 minutes of unintentional drug overdose, amounting to about 27,000 unintentional drug overdose deaths per year. Among heroin users and persons who use prescription opioids, overdose is common. A case series of 329 drug users reported by Lagu et al. found 82% reported use of heroin, 64.6% had witnessed a drug overdose, and 34.6% had experienced an unintentional drug overdose\(^1\)

Prescription opioid abuse represents the fastest growing drug problem in the US. Since 2003 there have been more overdose deaths from prescription opioid analgesics than heroin and cocaine combined. Rates of overdose deaths, sales, and substance abuse treatment admissions relating to prescription opioid analgesics showed parallel increases of four- to six-fold over the 10-year period ending in 2008\(^1\) (Figure 1). CDC reported higher rates for these parameters among those under the federal poverty levels. Further, the highest rates of nonmedical use and prescription opiate analgesic sales have been reported among American Indians/Alaska Natives and non-Hispanic whites; lowest rates have been observed among Asians and African Americans\(^1\)\(^5\),\(^1\)\(^6\).

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**Figure 1: United States Rates of Overdose from Prescription Opioid Pain Relievers (POPR), treatment Admissions for POPR, and kilograms of POPR Sold, 1999-2010**

*SOURCE: Centers for Disease Control and Prevention\(^1\)*
Markers for opioid overdose are well characterized and include: gender (male for both opioid analgesic and heroin); age (45-54 years of age, opioid analgesics; 25-34 years of age, heroin); urbanization (i.e., non-metro, opioid analgesics; metro regions, heroin); low income/Medicaid at risk for opioids; and personal characteristics, such as history of substance abuse, other mental health diagnoses, non-medical use of prescription drugs (i.e., use without a prescription or non-medical routes of administration), and prescription history (i.e., multiple prescriptions, multiple prescribers and high daily dosage)\(^{17}\).

**Layperson Administration of Naloxone:** Naloxone administration by laypersons has the following rationale:\(^5\):

- Naloxone is a safe, effective and relatively easy to use antidote for treatment of HOAO.
- Early administration of naloxone reduces risk to vital organs, including the brain.
- Many overdose fatalities are preventable with early recognition and treatment.
- Overdoses evolve over 1-3 hours, and there often are bystanders.
- People often fail to call 911.

**Successful US Public Programs for Distribution of Prescription Naloxone:** Community-based programs offering naloxone and other overdose prevention services to drug users, their family and friends, and providers started in the US in 1996. These services included education on overdose risk factors, early recognition of and appropriate responses to opioid overdose, and training for self- and buddy-administration of naloxone. Since that time, community groups and programs offering these services have increased in number. As noted above, other countries such as the UK have also been active in promoting local programs for harm reduction in opioid overdose.

In the US, naloxone is typically provided by medical professionals and through the use of standing orders. A number of States (e.g., California, Illinois, New Mexico, New York, and Washington) have recognized the value of administration of naloxone onsite by laypersons, and have passed laws that provide limited liability for prescribers in programs that provide naloxone to laypersons. Good Samaritan laws have been passed by Washington, Connecticut, New Mexico, and New York to provide protection from prosecution for bystanders at a drug overdose, and thereby encourage 911 emergency calls and use of naloxone if available\(^{18}\).

Recently, Wheeler et al. reported on a national US survey conducted by the Harm Reduction Coalition on 48 of 50 programs which included the experience with naloxone distribution by 188 local programs since 1996\(^{18}\). Respondents reported training and distributing naloxone to 53,032 persons (program range: zero to 16,220; median: 102.5; mean: 1,104.8), and receiving reports of 10,171 overdose reversals (range: zero to 2,385; median: 32; mean: 211.9). For a recent 12-month period, the 48 responding programs reported distributing 38,860 naloxone vials, including refills (range: zero to 12,070; median: 97; mean: 809.6). Overdose prevention
programs were characterized as small, medium, large, or very large, based on the number of naloxone vials distributed during that period. Six of 48 responding prevention programs were the largest accounting for over 84% of distributed vials (i.e., 32,812 vials). Over 43% of the responding programs reported difficulties in obtaining naloxone in recent months before the survey, mainly due to cost, available funding, and inability of suppliers to fill orders.

In sum, the prevailing US view of those working on naloxone training and distribution advocate strongly for providing opioid overdose education and naloxone to those who either use drugs, or might be present at an opioid overdose to help reduce opioid overdose mortality.

RX-TO-NONPRESCRIPTION CONSIDERATIONS: REGULATORY/SCIENTIFIC ISSUES

Adverse Events from Treatment: As a way to frame what a company might have to address in developing a safety profile for naloxone, it is instructive to review what health professionals use to obtain an initial read of a drug safety issue. Here, we use Lexicomp, a leading provider of drug information to health providers which seeks to represent prevailing evidence-based views on the safety and effectiveness of medical therapies.19 As such, it also represents an important source for regulatory scientists to obtain an overview perspective of selected medicines to help frame concerns regulatory authorities and the health professionals might have in relation to switch candidates. The following paragraphs summarize information on naloxone from Lexicomp. A similar approach was taken by one of the non-FDA presenters at the April workshop using information from AccessMedicine, which is very similar to Lexicomp. From Lexicomp:

‘Acute opioid withdrawal: Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids. Symptoms of acute withdrawal in opioid-dependent patients may include pain, hypertension, sweating, agitation, irritability...

‘Caution is recommended in Cardiovascular disease: Use with caution in patients with disease or in patients receiving medications with potential adverse cardiovascular effects (e.g., hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists.


Other safety issues identified in Lexicomp in the treatment of overdose with naloxone are:

‘…recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.’

‘…other resuscitative measures (e.g., maintenance of an adequate airway, artificial respiration, cardiac massage, vasopressor agents) should be readily available and used when necessary.” 19.
In sum, even if the benefit of reduced fatalities may appear to outweigh the risks from opioid withdrawal, it seems likely that a sponsor will need to objectively address the potential severity and extent of cardiovascular events and seizures from naloxone use. Additionally, there would likely need to be a characterization of the extent to which help from bystanders (i.e., “buddies”) is needed and feasible as well as steps taken after naloxone buddy-administration and prior to the appearance of emergency response teams.

FDA’s Considerations for Switching Naloxone: Overall, FDA presenters at the FDA’s public workshop on naloxone appeared supportive of sponsors seeking approval of a nonprescription form of naloxone and seem to favor development of a new intranasal version, although their comments addressed the i.m. auto-injector form as well. It is notable that the April 2012 workshop carried the tone of a pre-investigational new drug (pre-IND) meeting between a drug sponsor and the agency, except that it was in public with invited stakeholders.

Virtually all recommendations from FDA presenters on an OTC development plan for naloxone derive from those typically used in the development and approval process for past Rx-to-OTC switches, as outlined in the Appendix. This section summarizes the FDA’s recommendations. As described in the Synthesis section of Results and in the Discussion, revisions are made to the list of “OTC Considerations for Rx-to-OTC Switch” to include an amplification of the Switch Considerations List to emphasize certain of FDA’s standard switch questions and add a section on Human Factors Research.

Leonard-Segal† noted, ‘An OTC application for naloxone, depending upon the formulation, may need to contain new data to address all of these components’ (i.e., as noted in the following regulatory science questions)‡. All of this represents important commentary, even for other (non-naloxone) switches.

- Would a clinically meaningful difference exist between an OTC naloxone and Rx naloxone so the current Rx product(s) would remain after the OTC switch? †
- Would a difference in dosage form between the Rx products and the proposed OTC product be interpreted as a clinically meaningful difference?
- Would all important information necessary for effective and safe use of OTC product be able to be contained in the nonprescription Drug Facts Label?
- Would a Consumer Information Leaflet (CIL) be needed for safe and effective use of the OTC product?

† Andrea Leonard-Segal, MD, MS – Director, Division of Nonprescription Clinical Evaluation, Food and Drug Administration.
‡ The Food Drug Cosmetic Act has been interpreted in such a way that a medicine may not be marketed as both an Rx and an OTC medicine for the same indication, population, and same conditions of use. Marketing of same active ingredient in products that are both Rx and OTC (i.e., ‘dual marketing’) can only occur when a clinically meaningful difference exists between the two that makes the Rx product safe only under the supervision of a licensed practitioner. An example of this is Motrin, which is marketed as an OTC medicine at a 200 mg nonprescription dosage unit for pain and fever relief, and in a 400 mg prescription dosage unit for long-term anti-inflammatory therapy in arthritis (i.e., not an OTC condition).
• Because of the nature of the active ingredient or its formulation, does the drug application for the switch candidate need all or some of the following components?

  Chemistry (e.g., new formulation, stability, packaging, etc.):

  Pharmacology/Toxicology (e.g., new formulation, new method of delivery, new combination of ingredients, possibility of longer duration of exposure in the OTC venue because of repeated use, etc.):

  Microbiology (if applicable; e.g., drug resistance issues raised by the OTC setting, sterility issues):

  Clinical Pharmacology (e.g., new formulation, new combination, etc.):

  Efficacy data (if e.g., nonprescription and Rx indications differ, if reduced dose, if not bioequivalent to approved reference drug, etc.):

  Safety data (e.g., clinical trials):

  Postmarketing worldwide safety data to identify new signals after broad time-and-extent of Rx product use and to assess safety in markets in which this product may already be nonprescription (e.g., Sweden, Italy), including use of FDA’s Adverse Event Reporting System; WHO International Drug Monitoring Program; Literature review; Drug abuse and overdose data):

  Consumer studies (i.e., those that are unique to drug evaluation, especially for a new OTC indication, new warnings, nonprescription new directions for use, etc.); see below for types of studies.

  Complete Labeling:

  Other issues specific to the product intended for novel conditions of use (e.g., public health considerations, advertising, potential unintended consequences, etc.).

From these basic questions, Leonard-Segal and Herz†† tailored specific considerations for nonprescription naloxone, which itself is a process used for the case-by-case approach to Rx to OTC switch that is typically used by FDA.

**Efficacy**: For the switch of an approved Rx product such as naloxone, no additional efficacy data (i.e., as distinguished from actual use studies in a naturalistic setting, see below) may be needed, while a new naloxone formulation may need new efficacy data because of differences in the clinical pharmacology profile compared with that of the approved reference drug.20,21

**Safety**: For the switch of an approved Rx product, substantial support is likely available in the current safety database through clinical studies and postmarketing surveillance data. For a new formulation, new clinical safety data may be needed (e.g., intranasal formulation). If the new formulation is more bioavailable than the reference drug, seeking approval for...
Rx use first would allow acquisition of the needed postmarketing safety information before nonprescription availability. Specific to naloxone, information would be needed to understand the potential for its conversion into an opioid agonist that could be abused\textsuperscript{20, 21}.

**Consumer Studies:** A naloxone switch would need consumer studies, including those pertaining to self-selection, human factors and actual use\textsuperscript{20}.

**Label Comprehension Study**, to assess whether laypersons (i.e., opioid users or buddies) can understand the steps outlined in the directions of use. This type of study is needed in the US because naloxone is (a) first in its class to OTC market; (b) for a new nonprescription target population; (c) for a new nonprescription indication; (d) may have substantive labeling change to the existing Rx product; and (d) new directions for use (not previously seen in the OTC marketplace).

**Human Factors Study**, to determine if laypersons can properly prepare or use the product syringe or intranasal device based upon the directions.

**Self-Selection Study**, to determine ‘whether the individual administering naloxone could properly diagnose the opioid overdose and determine that it is appropriate to give naloxone based upon the information on the [proposed nonprescription] Drug Facts Label.’

**Actual Use Study**, in a naturalistic setting where ‘access to study medication simulates what would occur if the drug were approved OTC’ to ‘help predict if a drug will be used properly and safely in the OTC setting.’

**Use of Devices:**

**Intranasal:** The sponsor should: (a) describe the modification(s) of an approved device, if any, in the NDA; (b) provide spray characterization data, e.g., spray pattern, droplet size distribution, and pump delivery; and (c) provide a three-point droplet size distribution, including the percentage of droplets $\leq 10 \mu$, so as to understand the smallest fraction that may expose the lungs directly as opposed to the nasal mucosa. Any novel devices will require review by Center for Devices and Radiological Health (CDRH).

**Intramuscular:** The sponsor should provide a full description of the approved device. Any novel devices will require review by CDRH\textsuperscript{21}.

**Nonclinical:** The amount of nonclinical data required will depend on the route of the planned drug application. For 505(b)(2) applications, the amount of information may be less, since the sponsor can rely on the agency’s previous findings for naloxone. The sponsor should include local tolerance studies of adequate duration in two species. If clinical monitoring of local tissues during any clinical studies is an acceptable alternative based on the novel route (e.g., intranasal), the requirement for nonclinical studies might be waived, assuming no novel excipients. Factors favoring limited nonclinical studies for naloxone relate to its single- or two-dose use and the amount of clinical experience with naloxone that provides supportive human data\textsuperscript{21}. 
Relative Bioavailability: Evaluate the relative bioavailability of at least two different doses compared to parenteral injection of naloxone (IM, IV or SC). The objective is for the plasma naloxone levels to be detectable and comparable and present for a meaningful duration relative to the approved product, so that dose selection can be based on a variety of assumptions of different levels of absolute bioavailability of the intranasal naloxone. This information guides what additional information may or may not be needed for the rest of the drug development program for naloxone. Based on the results of the first bioavailability study, a second pivotal relative bioavailability study may be needed to assess a parenteral dose of naloxone of at least 0.4 mg in comparison to dose(s) of the new product that would be expected to result in similar or greater drug exposure. If the product is not bioequivalent, particularly if the exposure is less than the approved product, then efficacy studies would be required.

Challenges to Conducting Clinical Trials for Naloxone: Typically the individual for whom naloxone is intended is unconscious, unable to provide informed consent. Product users are ‘buddies’ who encounter the drug overdose event, first responders, and emergency department personnel. In this type of setting, regulations provide for exemptions from informed consent. Nelson concluded that ‘[A]n efficacy study of the use of IN Naloxone for complete or partial reversal of narcotic depression, including respiratory depression, meets all of the criteria for an exception from informed consent, provided that the research process includes community consultation and public disclosure’. If the systemic bioavailability is low, clinical trials may not be ethical.

Additional public health considerations were identified without detailed discussion by Leonard-Segal: (a) needle safety for the injectable formulation; (b) the impact of the injectable no longer being a prescription drug; (c) management of withdrawal reactions; (c) promotion of opioid misuse through nonprescription access of naloxone; (d) potential adverse impact on the use of 911 calls; (e) the need for educational campaigns; and (f) advertising, which is controlled not by FDA but by the Federal Trade Commission (FTC).

Synthesis: In assessing the questions that FDA has set forth for nonprescription naloxone there appear to be two areas where the 2011 Switch Considerations List can be updated. The first pertains to the inclusion of a heading for Human Factors Research (see Switch Consideration 8 in Table 1). Such studies relate to whether a layperson can properly prepare and use the proposed switch product. This is an essential consideration for emergency access to naloxone in terms of its intended use to prevent mortality, the potential complexity of use, and anticipated timing of peak effect. Switch Consideration 12 is particularly relevant to the issue of Human Factor Studies, (HFS) which are not new and have been discussed in relation to use of asthma inhalers in the past. HFS may be particularly important for switches with novel conditions of use, such as use of kiosks as product self-selection aids.

** Robert Nelson, MD PhD, Senior Pediatric Ethicist/Lead Medical Officer, Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration
**Table 1: The Switch Considerations List**

<table>
<thead>
<tr>
<th>Considerations for Rx-to-Nonprescription Switch *</th>
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<tbody>
<tr>
<td>Derived from Selected Post-2002 First-in-Class Switches, FDA 1990 and 1998 Switch Principles and an Analysis of Naloxone as a Switch for Novel Conditions of Use</td>
</tr>
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**Overarching Consideration:**
1. Because of the nature of the active ingredient or its formulation, does the drug application for the switch candidate need all or some of the following components?

**Rx Fundamentals Safety**
2. Has the Rx product been on the market for a sufficient time and extent to enable full characterization of the drug's safety profile, including:
   a) Margin of safety;
   b) Safety across the drug's therapeutic range and at high doses;
   c) Potential masking of serious disease by short or long term use;
   d) Potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity;
   e) Any known special toxicity with discontinuation of therapy;
   f) Drug-drug interactions;
   g) Safety in special populations (e.g., women of child-bearing age, children, elderly);
   h) Other special conditions or toxicity in its class that may be associated with the acute, chronic or chronic intermittent use;

3. Can the condition be adequately self-diagnosed, or is there a need for physician diagnosis?
   a) To what extent is misdiagnosis associated with current Rx practices relating to the intended OTC use of the product?

**Efficacy**
4. Is the minimally effective dose known?
5. Are there efficacy studies needed to support the intended OTC use of the switch candidate?

**Rx Use Pattern**
6. What are the patterns of diagnosing, prescribing and patient use in the Rx setting related to OTC intended use?

**OTCness General**
7. Are the studies supporting OTCness generalizable to the intended OTC target population?

**Human Factors Studies**
8. Are human factors studies needed to determine if laypersons can properly prepare or use the product (e.g., syringe; monitoring meter, etc.) based upon the directions?

**Label Comprehension:**
9. Would all important information necessary for effective and safe use of OTC product be able to be contained in the nonprescription Drug Facts Label?
10. Do consumers understand key communication objectives of the label, relating to directions of use, contraindications, in-use warnings and precautions?
11. Do consumers show they would be likely to be able to assess and take action on the treatment effect (e.g., take appropriate action if the drug is not working, serious side effects emerge, or self-monitoring is needed)?
12. Would a consumer leaflet be needed for nonprescription drug use?

**Actual Use:**
13. Do consumers demonstrate successful self-selection and de-selection of the product under conditions (or simulated conditions) of actual use?
14. Does the pattern of actual use support that the label can be successfully used in practice? That is, does the pattern of use show that consumers will likely:
   a) Know when they should see a physician before using the product and once they have begun using the product.
   b) Use the drug on an acute or chronic basis for conditions other than that intended by labeling;
   c) Use the correct dosage for the period of time specified in the label;
   d) Evaluate response(s) to treatment and successfully monitor progress with therapy, including identifying serious adverse events symptomatically or, for example, with periodic lab tests;
   e) Or other actions, as specific to the switch candidate.

**Overall**
15. Do the benefits of OTC availability outweigh the risks?

**Regulatory Considerations**
16. Would a clinically meaningful difference exist between the Rx product and the proposed OTC product so that the Rx product(s) would remain on the market after OTC switch (e.g., difference in dosage form)?

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*SOURCES: (1) Soller RW, Chan PV, Shaheen C. OTC considerations for expanding access to nonprescription medicines: A critical synthesis of questions from the Food and Drug Administration to its advisory committees on Rx-to-OTC switch. SelfCare. 2011:2(3);117–138. Reprinted with permission of SelfCare. (2) Soller RW, Shaheen C. SelfCare. 2012:3(6);121-137*
In addition, the FDA presentations at the naloxone meeting offered relevant amplifications of issues raised in past switch decisions. As a result, the Switch Considerations List now includes Switch Considerations 1, 9, and 16. Switch Consideration 1 is a standard overarching question, which FDA posed for naloxone and has been used regularly in the past, for example, as part of FDA-company switch discussions prior to advisory committee deliberations on switch. Because FDA has stated this issue publicly in relation to naloxone for garnering interest by companies or coalitions interested in switching naloxone, it is included in the revised list. Switch Consideration 9 is pertinent, since it reflects a move by FDA to emphasize the need for consumers to receive essential drug information. This concept has a counterpart in the US prescription drug labeling. Companies are required to include in the Rx Medication Guides for high-risk drugs a major initial heading that states: ‘what is the most important information I should know about “drug name”‘ or words to that effect. Switch Consideration 16 addresses the regulatory issue of ensuring identical drugs are not simultaneously marketed as Rx and nonprescription medicines. Although these Switch Considerations are not new, they are included in the revised Switch Considerations List because they were important to FDA in the context of naloxone – the first proposed switch for novel conditions of use.

DISCUSSION

The Food and Drug Administration developed an exemplary workshop. Principal stakeholders presented key issues on expanded access of naloxone at the place and time when care is most needed. FDA presenters provided essential feedback for potential sponsors, not unlike the type of feedback seen at pre-Investigational New Drug (pre-IND) development meetings.

The emphasis of the FDA presenters appeared to favor the intranasal route of administration which is not approved for use in the US and would require substantially more studies than an application based on the approved i.m. product. However, the intranasal option appears attractive from a public health standpoint, as it avoids the risk of needle-stick injuries from the injectable naloxone, needle disposal, and blood-borne virus transmission. Despite no large randomized clinical trials, intranasal naloxone has been assessed in several studies, with little evidence of adverse events. Naloxone is rapidly absorbed by the intranasal route, and has been evaluated as statistically comparable to IV naloxone when administered by paramedics in terms of average improvements in respiratory rates and the Glasgow Coma Scale.

Of note is the fact that the FDA recommendations for new studies to answer essential regulatory scientific questions pertaining to the switch of naloxone are basically in line with the ‘Considerations for Rx-to-OTC Switch’ published in 2011 in SelfCare. While naloxone would be a drug with novel conditions of nonprescription use, the basic Chemistry Manufacturing and Controls (CMC), bioavailability, and development plan for consumer studies focus on many of the key considerations used for most Rx-to-OTC switch products in the US. As a result, revision of the Switch Considerations List is mainly an inclusion of direct commentary by FDA reviewers amplifying issues of known importance when considering a specific agent for novel
conditions of nonprescription use. As such, they add an important dimension to the Switch Considerations List. Most notable, however, is the new section on Human Factors Research, which may become more prominent if technology solutions (e.g., kiosks) are explored by companies for aiding consumers in the self-selection of products, as discussed by Schifkvitz at the March 2012 FDA hearing on novel conditions of nonprescription drug use in relation to switching statins.32

Furthermore, the name, ‘Considerations for Rx-to-OTC Switch’, has been changed in the revised Switch Considerations List (Table 1). The reasons are twofold. First, this is mainly an acknowledgment of FDA’s NSURE (Non-prescription Safe Use Regulatory Expansion) initiative started at the March 2012 FDA public hearing on novel conditions of nonprescription drug use. NSURE marks a new period hopefully characterized by a willingness of US regulators to consider a broader US view of the potential consumer availability of products not needing a prescription. Second, the term ‘Rx-to-Over-the-Counter Switch’, covers only a subset, albeit a large one, of previously switched nonprescription medicines. However, current examples exist of behind-the-counter nonprescription medicines (e.g., insulin, Plan B and pseudoephedrine).

Despite one FDA presenter sharing a view that much is known of naloxone and its safety profile, it is not surprising that FDA is asking for a comprehensive application addressing safety. Naloxone would be a first-in-class switch, and its conditions of use distinguish it from all other current nonprescription medicines. While we are not including a review of naloxone’s safety in this manuscript, it is nonetheless notable that cardiovascular concerns and seizure are recognized and potentially serious side effects that need to be balanced as risks against the potential benefit of saving lives.

Additionally, how FDA will handle the strong recommendations from those running local naloxone programs about the importance of bystander (i.e., ‘buddy’) training may represent a unique aspect of novel conditions of use. Parents and other caretakers of children are the only other ‘secondary form’ of self-care. In a caretaker-child setting, training is based simply on reading the label. Is that sufficient for naloxone? The naloxone programs emphasize training and education concerning early signs of opioid overdose, calling 911 immediately, and addressing signs of treatment and support post-administration until early responders arrive. For example, the Boston community outreach program for naloxone use in potential fatal overdose required a 15-minute bystander training that included techniques in overdose prevention and documentation by staff that participants comprehended the training. If the decision is to pursue only the ‘OTC Drug Facts’ type of label as the ‘intermediary’ defining safe and effective use, then the consumer studies recommended by Leonard-Segal will be essential. Additionally, certain of the extant clinical studies that included training as part of the intervention will be only supportive at best.

While there are a handful of manufacturers of naloxone, it is interesting that the consideration of naloxone gaining nonprescription status appears to be principally driven by public health and not pharmaceutical company interests. Naloxone is a relatively inexpensive generic active. It is unclear what the marketing plan would be, although extending the market to all first
responder (i.e., naloxone in every police car, and ambulance) across the nation as well as potential ‘buddies’ of heroin users and prescription opioid analgesic users would seem to represent a sizable market. Nevertheless, consistent with FDA policy on switch decisions, economic considerations are not discussed as a part of the approval process. Similarly, Leonard-Segal’s additional issue on product advertising was left unaddressed, but certainly will get future discussion if one or more companies step forward to pursue nonprescription naloxone.

LIMITATIONS

Our review does not include the large amount of information available on naloxone for prevention of fatalities from HOAO. Our purpose was to assess whether this first detailed workshop on a potential switch candidate with novel conditions of use, required consideration of unique regulatory scientific questions that had not been associated with past Rx-to-OTC switch decisions by FDA. We found that the core questions raised by FDA are those that can be expected from our recent publication on ‘OTC Considerations’ for Rx-to-OTC switch

CONCLUSION

FDA’s public meeting in 2012 on novel conditions of nonprescription drug use and its subsequent workshop on naloxone for prevention of fatalities from opioid overdose are landmark events in the history of Rx-to-OTC switch in the US. Of note is that the first switch candidate with novel conditions of use was scrutinized by FDA in the context of tried and tested Switch Considerations for OTC access. Nevertheless, certain refinements to the Switch Considerations List, which was developed prior to these public meetings, are recommended as a way to keep the list current with the evolving discussion around Rx-to-nonprescription switch. Compiling and maintaining an up-to-date list of Switch Considerations synthesizes the historical and current FDA perspective to help predict agency requirements, can be used to train new industry and government personnel, and offers a framework for persons without a regulatory science background to understand FDA switch decision making.

Conflict of Interests: None

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### OTC Considerations*

*Derived from Selected Post-2002 First-in-Class Switches and FDA 1990 and 1998 Switch Principles*

#### Rx Fundamentals

**Safety**

1. Has the Rx product been on the market for a sufficient time and extent to enable full characterization of the drug’s safety profile, including:
   - a) Margin of safety;
   - b) Safety across the drug’s therapeutic range and at high doses;
   - c) Potential masking of serious disease by short or long term use;
   - d) Potential for genotoxicity, tumorigenicity, and fetal and developmental toxicity;
   - e) Any known special toxicity with discontinuation of therapy;
   - f) Drug-drug interactions;
   - g) Safety in special populations (e.g., women of child-bearing age, children, elderly);
   - h) Other special conditions or toxicity in its class that may be associated with the acute, chronic or chronic intermittent use;

2. Can the condition be adequately self-diagnosed, or is there a need for physician diagnosis?
   - a) To what extent is misdiagnosis associated with current Rx practices relating to the intended OTC use of the product?

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### Efficacy

3. Is the minimally effective dose known?

4. Are there efficacy studies needed to support the intended OTC use of the switch candidate?

#### Rx Use Pattern

5. What are the patterns of diagnosing, prescribing and patient use in the Rx setting related to OTC intended use?

#### OTCness

**General**

6. Are the studies supporting OTCness generalizable to the intended OTC target population?

**Label Comprehension:**

7. Do consumers understand key communication objectives of the label, relating to directions of use, contraindications, in-use warnings and precautions?

8. Do consumers show they would be likely to be able to assess and take action on the treatment effect (e.g., take appropriate action if the drug is not working, serious side effects emerge, or self-monitoring is needed)?

#### Actual Use:

9. Do consumers demonstrate successful self-selection and de-selection of the product under conditions (or simulated conditions) of actual use?

10. Does the pattern of actual use support that the label can be successfully used in practice? That is, does the pattern of use show that consumers will likely:
   - a) Know when they should see a physician before using the product and once they have begun using the product.
   - b) Use the drug on an acute or chronic basis for conditions other than that intended by labeling;
   - c) Use the correct dosage for the period of time specified in the label;
   - d) Evaluate response(s) to treatment and successfully monitor progress with therapy, including identifying serious adverse events symptomatically or, for example, with periodic lab tests;
   - e) Or other actions, as specific to the switch candidate.

#### Overall

11. Do the benefits of OTC availability outweigh the risks?

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