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The Limits of Risk and the Concept of the REMS

Risk Definition

"Risk" has been defined for regulatory purposes by a guideline from the International Council on Harmonisation (ICH) as "the combination of the probability of occurrence of harm and the severity of that harm." This definition has been called "the Probability x Severity concept."[1] There is no way to ensure a drug product has no serious safety risks, since every drug has the potential to cause adverse events. This potential for serious risks exists regardless of how extensively the drug was studied before approval and how many times it has been dispensed postapproval. It is a truism of drug development that clinical studies with a few thousand or even tens of thousands of subjects cannot predict the risks that will occur during use by millions of patients after approval. Even if a major risk is not identified during the first year after approval, it is not possible to conclude there is no serious risk; the failure to detect risk via surveillance during the first year of marketing experience only shows the risk is low. Nevertheless, the goal during drug development is to investigate safety as thoroughly as possible before the product is widely marketed, and to determine the risks' magnitude for patients using the drug.

A marketing application submitted to the US Food and Drug Administration (FDA) for new drug approval must demonstrate the drug is "safe and effective." In reality, a drug is approved not because it is safe, but because it is "safe for the proposed use," i.e., it has a favorable benefit-risk ratio. FDA has defined a "safe product" as one that has "acceptable risks, given the magnitude of the benefit expected in a specific population and within the context of alternatives [alternative treatments] available."[2] "Safe" does not mean "free of risk." FDA guidance has stated, "a product is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a product is considered safe if it has an appropriate benefit-risk balance for the intended population and use."[3]

Risk Management Definition

FDA defines "risk management" as a process of measures above and beyond basic safety measures routinely applied "throughout a product's lifecycle" to control risk. These risk management measures must be based on careful risk evaluation.[4] Under the Risk Minimization Action Plan (RiskMAP) program, a REMS predecessor, FDA spelled out risk management as an "iterative process" consisting of: 1) assessing the drug's benefit-risk ratio; 2) developing and applying risk minimization tools; 3) evaluating the tools' effectiveness, including their impact on the benefit-risk ratio; and 4) making adjustments to the tools as needed (see **Figure 1-1**). The FDA RiskMAP guidance document introduced the concept of evaluating the effectiveness of the risk minimization measures on an ongoing basis, although evaluation was voluntary. It also created the new term, "benefit-risk balance," to replace "risk-benefit ratio,"[5] perhaps to place the emphasis on the positive "benefit" rather than the negative "risk," and to emphasize the positive connotations of "balance."

Drug Product Risks Are Measured in Adverse Events

Drug product risks, like other consumer product risks, are among the potentially dangerous circumstances to which everyone is exposed throughout life. Drug product risks represent only one aspect of the risks patients are exposed to during an illness, particularly in the hospital setting.

Drug product risks are quantified by measuring adverse events. "Adverse event" was re-defined by FDA in September 2010 as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related," i.e., without regard to causality. At the same time, FDA defined "suspected adverse drug reaction" as any untoward occurrence when causality is "a reasonable possibility."[6] Nevertheless, in a risk mitigation discussion, it seems reasonable to insist on including some degree of suspected causality when using the term "adverse event."

Adverse events due to medical care are common. In a study of 1,000,000 Medicare patients,[7] almost one patient in seven (13.5%) had an adverse event while in the hospital. A deeper analysis of a smaller sample found that 41% of these adverse events were related to a medication.[8]

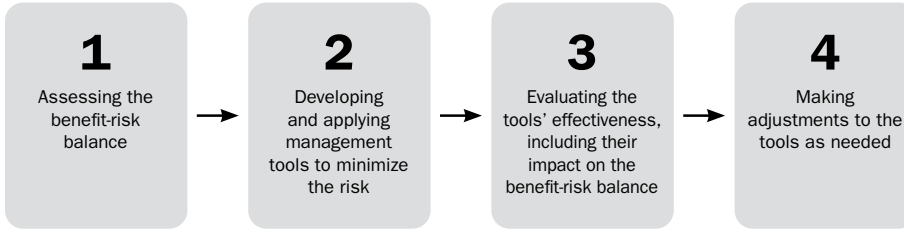
Adverse Events and Never Events

In 2010, the HHS Office of the Inspector General[9] defined two categories of untoward occurrences associated with drug products:

> The term "adverse event" describes harm to a patient as a result of medical care, such as infection associated with use of a catheter. The term "never events" refers to a specific list of serious events, such as surgery on the wrong patient, that the National Quality Forum (NQF) deemed "should never occur in a health care setting."

In 1999, the Institute of Medicine (IOM) (since 2015, the National Academy of Medicine) issued a landmark report on the problem of preventing death and disability in the healthcare system by preventing medical errors.[10] It set forth a goal of reducing preventable medical errors by 50% in five years. An evaluation in 2005 concluded that the

Figure 1-1. Evolution of Formal Risk Management Plans for Drugs With a High-Risk Profile*



*Defined in the Risk Minimization Action Plan (RiskMAP) program, a predecessor of REMS.

(Based on FDA's *Guidance for Industry: Development and Use of Risk Minimization Action Plans* (2005))

extent of improvement five years following the IOM report could not be quantitatively determined, but the level of medical errors remained high.[11]

To a great extent, the movement to require some new drugs to use a REMS for formal risk mitigation is a manifestation of the same desire to reduce preventable risk. Although the IOM report focused on "designing the health system at all levels to make it safer—to make it harder for people to do something wrong and easier for them to do it right,"[12] extending this approach to drug development means assessing the safety of new drugs after they are in wide use, analyzing the risk and, in the case of REMS, subsequently analyzing how well the risk minimization process worked.

Although the IOM report focused on medical errors, its emphasis on the need for healthcare systems to create a "culture of safety" became a component of many discussions on health policy and drug approval. Safety, it frequently was urged, should be an explicit organizational goal.[13]

The escalating discussion within both the medical community and the public at large about preventing "never events" reached its popular culmination in the writings of the surgeon and author, Atul Gawande. Gawande's first two books of essays scrutinized the potential for errors and the factors that cause them in surgery[14] and other aspects of medicine.[15] In his third book, *The Checklist Manifesto*, he proposed a solution, using checklists in medicine like those used by commercial aircraft pilots.[16] Gawande described formal studies that validated the ability of checklists to cut the incidence of surgical complications by half, preventing many deaths. Some critical discussion of Gawande's ideas subsequently appeared in the medical literature, including others' assertions that a culture of safety must already be present before checklists can work effectively. Regardless, Gawande's crusade helped energize the discussion about risk prevention and contributed to the atmosphere that led to the REMS concept

The Search for "Zero Risk"

In the US today, there is a relatively new societal expectation for "zero risk" in all activities and from all products. Zero risk, or nearly zero risk, is expected from every medical treatment, even though the risks of death and infirmity are far greater from many

everyday activities. As a result, the concept of risk has been widely studied and discussed. Specific discussions about drug product risks have occurred within the medical care system, as well as in Congress, the executive branch of government, the press and among the public.

"The One Percent Doctrine," a risk anticipation concept, developed in the midst of the "zero risk culture," as US government agencies sought to achieve an acceptable level of security against terrorist threats after the 11 September 2001 attacks on the World Trade Center and Pentagon. The One Percent Doctrine seeks to maintain a risk level in which there is less than a 1% chance a serious event will occur. A corollary to this philosophy, as described by Sunstein,[17] is that when the risk's results would be devastating, such as an attack that could cause many deaths, it becomes reasonable to consider a 1% risk the same as certainty of risk. Thus, "if there's a one percent chance [of an attack] … we have to treat it as a certainty in terms of our response."[18] This means trying to keep the risk far lower than 1%.

To FDA, the risk of a devastating adverse event, such as loss of life, loss of sight, etc., justifies application of something similar to the One Percent Doctrine. For instance, the drug Sabril (vigabatrin), approved in August 2009, is a GABA transaminase inhibitor indicated for treating infantile spasms and refractory complex partial seizures in adults. Safety concerns in children were based on visual field loss in 30% of adults taking the drug, although the risk for pediatric patients had never been clearly defined. Abnormal changes in MRI scans were seen in some infants' brains, although the neurological significance was unknown. Following a philosophy resembling the One Percent Doctrine, FDA required a REMS for Sabril,[19] in part to address a potential risk for children that had not been seen yet, based in a 30% risk in adults and the devastating character of the untoward event in question (i.e., visual field loss).

The "Potential Risk" Concept

The medical community's focus on zero risk eventually led to a backlash, a reactive concept based on the realization that, in many situations, risk may be so difficult to quantify that all of the worries and preventive measures are focused on "potential risk" rather than risk. "Potential risk" in drug products has been defined as "an untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed."[20] These occurrences include:

- safety concerns based on nonclinical studies that have not been observed or have been resolved in clinical studies
- adverse events observed in clinical trials or epidemiological studies for which the difference from the comparator group (in which patients were given either placebo, another active substance or no treatment) is large enough to raise a suspicion, but only a suspicion, of a causal relationship
- a signal arising from a spontaneous adverse event reporting system
- an event known to be associated with other products of the same class or that could be expected to occur based on the product's properties[21]

In some cases, "potential risks" have been identified, but not verified or clarified, such as risks based only on clinical trials that were small or were not designed to detect them. "Potential risks" also can appear in clinical trials that included specific racial groups or

age groups that are at higher risk for the adverse event than the general population, but in which too few patients were included from those subpopulations to draw meaningful conclusions.

Quantifying Risk

Risk can be quantified in various ways and then compared for different events. The incidence of a particular adverse event or of all adverse events can be measured. The type of adverse event and how soon it follows exposure to the drug product can be quantified.

As discussed earlier in this chapter, ICH defines risk as "the combination of the probability of occurrence of harm and the severity of that harm,"[22] which is known as "the Probability x Severity concept."[23] Thus, the risk is quantifiable because the degree of severity is a significant quantifiable measurement. How often is the adverse event life-threatening? How often does it cause hospitalization or an extension of hospitalization? How many days of work loss does it cause? To what extent does it reduce the quality of life, which can be measured as Quality-Adjusted Life Years (QALYs) or with other metrics? The financial impact of the adverse event, including the societal cost or the total cost from both the resulting medical care and the loss of the patient's role in the workforce, also can be measured.

Anxieties About Risk

It could be said that anxieties about risks are relative. For instance, in one discussion[24] about the risk of developing progressive multifocal leukoencephalopathy (PML), a neurologic disease, as a complication of treatment with Tysabri (natalizumab) for multiple sclerosis (MS), the risk was 1:1,000. Patients were asked if they were willing to assume this amount of risk in exchange for controlling their MS, and many were unwilling to do so. However, compared to a 1:100 lifetime risk of dying in a car accident, a 1:625 lifetime risk of being killed by a car while walking across the street and a 1:1,000 lifetime risk of drowning, the risk of PML from this drug did not seem so high. In fact, the 1:1,000 lifetime risk of dying by drowning sounds almost unbelievably high for an event we consider rare, which makes the risk of PML as an adverse event associated with Tysabri seem even smaller.

Responses to a comparison of measured risks are a reflection of how well individuals are able to handle anxiety about risks in general. Any individual patient's response to a quantifiable risk may be high or low due to innate personality characteristics, the disease severity or the presence of other anxieties unrelated to the disease.

FDA's Risk Management Process

Risk management is a process that involves multiple activities aimed at the single goal of minimizing risk. This process consists of "identifying, assessing, analyzing, treating, monitoring, and communicating" risks,[25] whether they are linked to using drug products or to air travel. One FDA official has suggested drug product risks are risks to "pharmaceutical quality," a risk of impairing "a consistent delivery of label performance, lack of contamination, and product availability."[26] In addition, risk management includes the selection, implementation and evaluation of measures to reduce risk.

Figure 1-2. Basis for FDA's Process of Determining Risk of a Drug

- Estimated size of the intended patient population
- Seriousness of the disease or condition
- Expected benefit of the drug
- Expected duration of treatment
- Seriousness of the known or potential adverse events
- Whether the drug is an NME

(Based on FDA's *Draft Guidance For Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications* (2009))

FDA has a specific process for evaluating the need for risk management, i.e., the need for a REMS. When FDA is deciding whether to require a REMS for a drug product, the reviewers go through a process (see **Figure 1-2**) that includes evaluating:[27–29]

- estimated size of the patient population for the drug
- seriousness of the disease or condition
- expected drug benefit
- expected treatment duration
- seriousness of known or potential adverse events
- whether the drug is a New Molecular Entity (NME)

Although the *Food and Drug Administration Amendments Act* of 2007 (*FDAAA*) only applied these factors to REMS that begin at the time of a drug's initial approval, REMS guidance documents published since have stated that these criteria and this process also would be used to determine the need for a REMS at any point in a drug's lifecycle,[30,31] whenever significant safety concerns arise.

In practice, the manufacturer's perception of risk also is an important part of the process. If there is an indication that any drug may have safety issues that could delay approval or result in non-approval, the manufacturer should anticipate a possible REMS. Beginning at the time of Phase 3 clinical studies, steps should be taken that include drafting a preliminary REMS submission and discussing it at the pre-NDA meeting with FDA.

The Concept of the REMS as a Counterbalance to Risk

The REMS program was created by *FDAAA* and was signed into law 27 September 2007.[32] (*FDAAA*, in giving FDA authority to impose REMS requirements, in fact amended the *Federal Food, Drug, and Cosmetic Act* (*FD&C Act*), inserting the REMS narrative as "Section 505-1" in Chapter V of the act.[33]) High-risk products would be required to have a REMS as part of a New Drug Application (NDA) or Biologics License Application (BLA) beginning 25 March 2008.[34] The transition period was short, but its duration was reasonable in view of the fact many companies already had internal procedures in place for preparing RiskMAPs (see Chapter 2),[35] which could be used to prepare REMS.

The REMS concept grew out of the RiskMAP program in response to the high-profile adverse events associated with some major drug products in the four years preceding *FDAAA* enactment. The adverse events due to Vioxx (rofecoxib, an NSAID

with increased risks of heart attack and stroke that was withdrawn from the market in September 2004) and Avandia (rosiglitizone, for the treatment of type 2 diabetes, a drug whose high risk of heart attacks was recognized in 2007 and which today is subject to severely restricted distribution) contributed to the environment in which tighter risk management was sought for high-risk drug products.

The REMS concept reflected a desire to make valuable yet high-risk drugs available to patients while preventing harm, by calling for cautious observation of their use, informing and alerting patients about possible adverse events and controlling prescribing and dispensing to restrict the drugs to those who really need them. In concept and in practice, the REMS program permitted FDA to approve or leave on the market certain high-risk drugs that were needed by patients because of proven efficacy. Without the REMS, the benefit-risk balance of these drugs might have made it impossible for them to be approved or, in the case of previously approved drugs, impossible to leave them on the market. For instance (see Chapter 11), the REMS has been used to try to avoid more-stringent measures suggested by members of Congress seeking greater controls for long-acting and extended-release opioids. One FDA official even suggested that the clarity and control the REMS provides for these opioids might help funnel the products to patients who could benefit from them but whose physicians otherwise might not prescribe them because of safety concerns.[36]

REMS Flexibility

One important REMS characteristic is its flexibility: the manufacturer or FDA can request changes in the REMS as the prescribing situation evolves. Every REMS is required to undergo a formal assessment of its effectiveness at pre-specified intervals, usually 18 months, three years and seven years after approval (see Chapter 7). This assessment is an essential requirement for all REMS and enables FDA to quantify specific REMS actions' effects on the benefit-risk balance and require any needed changes to improve measures that are not functioning adequately. A REMS can be adjusted incrementally (see Chapter 9) to increase a product's safety, or some or all REMS controls can be removed when they no longer are needed. It is easier to adjust a REMS than to withdraw a product from the market, a factor that benefits both the manufacturer and FDA. It has been stated:

> "The adjustability of REMS—including the built-in assessment process that triggers opportunities to reconsider the balancing act inherent in the regulatory process—is one of its most powerful features, transforming FDA regulatory decisions from binary (you are on the market or you are off) into more tiered, nuanced controls."[37]

Figure 1-3. *FDAAA*-Mandated Advisory Commitee Meeting

Requires the agency, at least annually,

- to bring at least one drug with a REMS with elements to assure safe use (ETASU) to the Drug Safety and Risk Management Advisory Committee (DSaRM)
- solicit views of DSaRM on whether the elements
  - assure safe use of the drug
  - are not unduly burdensome on patient access to the drug
  - to the extent practicable, minimize the burden on the healthcare delivery system

FDAAA requires FDA to bring at least one REMS with elements to assure safe use (ETASU) each year for public discussion at FDA's Drug Safety and Risk Management Advisory Committee (see **Figure 1-3**). These meetings are intended to solicit the committee's view on the particular REMS' success in assuring the drug's safe use, ensuring the REMS is not unduly burdensome for patients who need the drug, and minimizing the burden on the healthcare delivery system. Although there have been criticisms that these meetings have not occurred annually (see Chapter 16), those that have occurred have involved extensive and critical evaluation of the REMS.

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Pharmaceutical Risk Management Plans Before REMS

Early Forms of Formal Risk Management: The Isotretinoin (Accutane) Example

Formal systems for drug product risk management developed gradually during the two decades leading up to the creation of REMS by *FDAAA*. A noteworthy example was the system developed for isotretinoin (originally sold under the brand name Accutane), a vitamin A analog indicated for the treatment of severe forms of acne. It had unequivocal benefit for many patients, but it also had the potential to cause severe birth defects if used during pregnancy. The risk was compounded by the fact that female patients who use isotretinoin often are at an age when sexual activity might occur and frequently are those whose self-perception of social rejection due to severe acne also might increase the likelihood of sexual activity and pregnancy. Throughout the 1980s and 1990s, FDA wrestled with how to maintain isotretinoin's availability for patients who needed it while trying to prevent its inadvertent use by girls and women who might become pregnant.[1,2] Hoffmann-LaRoche, the original product manufacturer (before the advent of generic isotretinoin products), worked cooperatively with FDA to try to balance the drug's availability by controlling its use.

Isotretinoin provided cosmetic benefits that helped end the social isolation and alienation of adolescents with severe acne. While it originally was labeled for use in cystic acne and now is labeled for severe recalcitrant nodular acne, it always was widely prescribed for any severe acne, "severe" being the prescribing physician's judgment. At one point in the 1980s, when isotretinoin was labeled for treatment of cystic acne, the number of prescriptions written in the US exceeded the number of patients with cystic acne by a factor of two. This "overprescribing" has continued throughout the years; at an FDA Advisory Committee Meeting in 2011,[3] it was stated that there were more than 4,000 patients with severe recalcitrant nodular acne in the US, but about 250,000 prescriptions for isotretinoin were being written each year. This discrepancy was largely