Risk Management Prior to Approval for New Drugs

A summary of FDA’s Guidance for Industry: Premarketing Risk Assessment

“We’ve been served” are words that no one wants to hear, especially when it concerns a new product. There are steps, however, that can be taken prior to launch that may help alleviate some concern and mitigate some exposure. The United States Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (collectively referred to as “FDA”) published in March 2005 a Guidance for Industry: Premarketing Risk Assessment. In it, FDA sets out several nonbinding recommendations for assessing risks associated with new medicines. Although adherence is not required, it generally is quite helpful to be able to show a jury that you followed the practices recommended by FDA prior to submitting your New Drug Application (“NDA”).

1. Introduction

Risk management involves essentially two processes: risk assessment and risk minimization. Management of risk is an evolving function that continues throughout the lifecycle of the product but, naturally, should be initiated during development. It begins with evaluating the new medicine’s risk/benefit ratio. Once risks and benefits are separately identified, tools may be designed to lower the risks and preserve, or even elevate, the benefits. After implementing those tools, the sponsor must determine whether they are effective. In other words, the first step should be repeated: re-evaluate the risk/benefit ratio to determine any improvement. Finally, based on the follow-up evaluation, the sponsor should adjust the tools as appropriate (and, again, evaluate the ratio).
“We’ve been served” are words that no one wants to hear, especially when it concerns a new product. There are steps, however, that can be taken prior to launch that may help alleviate some concern and mitigate some exposure. The United States Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (collectively referred to as “FDA”) published in March 2005 a Guidance for Industry: Premarketing Risk Assessment. In it, FDA sets out several nonbinding recommendations for assessing risks associated with new medicines. Although adherence is not required, it generally is quite helpful to be able to show a jury that you followed the practices recommended by FDA prior to submitting your New Drug Application (“NDA”).

1. Introduction
Risk management involves essentially two processes: risk assessment and risk minimization. Management of risk is an evolving function that continues throughout the lifecycle of the product but, naturally, should be initiated during development. It begins with evaluating the new medicine’s risk/benefit ratio. Once risks and benefits are separately identified, tools may be designed to lower the risks and preserve, or even elevate, the benefits. After implementing those tools, the sponsor must determine whether they are effective. In other words, the first step should be repeated: re-evaluate the risk/benefit ratio to determine any improvement. Finally, based on the follow-up evaluation, the sponsor should adjust the tools as appropriate (and, again, evaluate the ratio).
While this process should be conducted prior to marketing the medicine in order to secure an acceptable risk/benefit ratio, it should continue after approval. New safety concerns always appear after approval — when larger and more diverse populations are exposed for longer periods of time. As such, the ratio may change, which in turn, may require the implementation of new risk management tools. Risk assessment and minimization is a never-ending process.

Sponsors are required by FDAs regulations to assess risk and attempt to minimize it during development and after approval. FDA pointed out in the Guidance, however, that these regulations “establish requirements for sponsors to assess the risk associated with risk minimization.” Perhaps due in part to recent withdrawals, FDA noted that the Guidance’s recommendations focus on the non-routine — the unusual type of risk or the unusual level of risk.

11. Risk Assessment

So, what is meant by “risk assessment,” and how is it accomplished? In a nutshell, “assessment” means “identification.” The sponsor must identify the nature of the risk associated with the medicine. What is the frequency of the risk? How often does the risk occur? When does it occur? In which populations does it occur? Additionally, part of the nature of the risk is its severity. Is it life-threatening, or will its effects be felt for life? Again, although this process must continue throughout the product’s lifecycle, an adequate premarketing assessment is crucial for at least two reasons: First, FDA requires it prior to approval. Second, a jury requires it prior to a defense verdict.

Deciding whether a risk assessment is “adequate” — specifically during Phase 3 studies — depends on the amount of information gathered, the information is presented and analyzed, and the nature of the information. Adequate risk assessment is a matter of quantity and quality. Adequate risk assessment is a matter of quantity and quality. Adequate risk assessment is a matter of quantity and quality.

A. POPULATION SIZE MATTERS

New safety concerns always arise after approval because the medicine generally is used by more people, for longer periods of time, with different medical histories, and with different concomitant drug use. Even the largest clinical trial simply cannot mimic real world use. However, the larger the pre-approval database and the more comprehensive the information in that database, the better. Certain factors might dictate when additional efforts should be made:

• The therapy is novel
• The effects of the proposed medicine are already safely available
• The proposed population is especially vulnerable
• The proposed duration of use is long-term

Generally, smaller safety databases may be appropriate when the disease being treated is life-threatening and there is no adequate alternative. In such situations, it is more acceptable to have less certainty concerning safety because the disease itself is so serious. The converse is true as well: Use larger data bases for non-serious illnesses. Additionally, safety signals gathered from preclinical data also may warrant a larger trial. If concerns are raised and no in-house consensus formed, FDA suggests discussing the matter with the appropriate review division. Although FDA does not offer much guidance with respect to the appropriate size of the safety database for new medicines developed for acute use, the agency specifically recommends 1,500 patients for products intended for use six months or longer (cumulative or continuous treatment). Three to six hundred should be exposed for six months, and at least one hundred should be exposed for a year. In addition to exposure duration, sponsors should design trials to include different dosing regimens, including doses above the amount sought for marketing.

As always, certain signals may exist that should prompt sponsors to propose larger trials. These may include: indications that the medicine is associated with adverse events that develop later or that increase in frequency or severity; serious adverse events may have been observed in earlier trials; an alternative treatment may be available; the overall benefit achieved from the medicine is small; or the condition sought to be treated has a high rate of mortality or morbidity. A larger database may be necessary to distinguish between the baseline rate and that seen with the medicine. Larger databases likewise may be appropriate when the intended population is healthy (i.e., vaccines).

B. DESIGN MATTERS

Once the sponsor determines the size of the safety database, several other considerations come into play. Oftentimes, the total database is comprised of multiple clinical trials. In such situations, it is imperative to coordinate terminology (so that investigators from each trial describe the same events similarly and the statistical rates of adverse events are not masked by differing lingo) and methods of assessment (so that investigators from each trial actually record similar events).

Sponsors also must ensure that they test the medicine in a sufficiently diverse, yet adequately representative, population. The safety database, to the extent feasible and ethical, should mimic real-world use. A wide population spectrum allows for safety information to be developed from individuals like the elderly, those with concomitant disease states, or persons ingesting concomitant drugs.

14 Pro Ti: Solvita

15 Pro Ti: Solvita

Sponsors also must ensure that they test the medicine in a sufficiently diverse, yet adequately representative, population. The safety database, to the extent feasible and ethical, should mimic real-world use. A wide population spectrum allows for safety information to be developed from individuals like the elderly, those with concomitant disease states, or persons ingesting concomitant drugs.
While this process should be conducted prior to marketing the medicine in order to secure an adequate risk/benefit ratio, it should continue after approval. New safety concerns always appear after approval — when larger and more diverse populations are exposed for longer periods of time. As such, the ratio may change, which in turn, may require the implementation of new risk management tools. Risk assessment and minimization is a never-ending process.

Sponsors are required by FDAs regulations to assess risk and attempt to minimize it during development and after approval. FDA pointed out in the Guidance, however, that these regulations “establish requirements for risk management and risk minimization.” Perhaps due in part to recent withdrawals, FDA noted that the Guidance’s recommendations focus on the non-routine — the unusual type of risk or the unusual level of risk.

11. Risk Assessment
So, what is meant by “risk assessment,” and how is it accomplished? In a nutshell, “assessment” means “identification.” The sponsor must identify the nature of the risk associated with the medicine. What is the frequency of the risk? How often does the risk occur? What does it do? In which populations does it occur? Additionally, part of the nature of the risk is its severity. Is it life-threatening, or will its effects be felt for life? Again, although this process must continue throughout the product’s lifecycle, an adequate premarketing assessment is crucial for at least two reasons: First, FDA requires it prior to approval. Second, a jury requires it prior to a defense verdict. Deciding whether a risk assessment is “adequate” — specifically during the Phase 3 studies — depends on the amount of information gathered, how the information is presented and analyzed, and the nature of the information. Adequate risk assessment is a matter of quantity and quality. Adequate risk assessment is a matter of quantity and quality. While this process should be conducted prior to marketing the medicine in order to secure an adequate risk/benefit ratio, it should continue after approval. New safety concerns always appear after approval — when larger and more diverse populations are exposed for longer periods of time. As such, the ratio may change, which in turn, may require the implementation of new risk management tools. Risk assessment and minimization is a never-ending process.

Sponsors are required by FDAs regulations to assess risk and attempt to minimize it during development and after approval. FDA pointed out in the Guidance, however, that these regulations “establish requirements for risk management and risk minimization.” Perhaps due in part to recent withdrawals, FDA noted that the Guidance’s recommendations focus on the non-routine — the unusual type of risk or the unusual level of risk.

11. Risk Assessment
So, what is meant by “risk assessment,” and how is it accomplished? In a nutshell, “assessment” means “identification.” The sponsor must identify the nature of the risk associated with the medicine. What is the frequency of the risk? How often does the risk occur? What does it do? In which populations does it occur? Additionally, part of the nature of the risk is its severity. Is it life-threatening, or will its effects be felt for life? Again, although this process must continue throughout the product’s lifecycle, an adequate premarketing assessment is crucial for at least two reasons: First, FDA requires it prior to approval. Second, a jury requires it prior to a defense verdict. Deciding whether a risk assessment is “adequate” — specifically during

Phase 3 studies — depends on the amount of information gathered, how the information is presented and analyzed, and the nature of the information. Adequate risk assessment is a matter of quantity and quality.

A. Population Size Matters

New safety concerns always arise after approval because the medicine generally is used by more people, for longer periods of time, with different medical histories, and with different concomitant drug use. Even the largest clinical trial simply cannot mimic real-world use. However, the larger the pre-approval database and the more comprehensive the information in that database, the better. Certain factors might dictate when additional efforts should be made:

• The therapy is novel
• The effects of the proposed medicine are already safely available
• The proposed population is especially vulnerable
• The proposed duration of use is long-term

Generally, smaller safety databases may be appropriate when the disease being treated is life-threatening and there is no adequate alternative. In such situations, it is more acceptable to have less certainty concerning safety because the disease itself is so serious. In other words, the specific drug will dictate the necessary contents of the safety database. Prior to approval, FDA considers known risks and unanswered questions versus demonstrated benefits. Thus, in addition to gathering information about efficacy, it behooves sponsors to design clinical trials so as to maximize the amount of safety information. For instance, if preclinical data suggest a potential problem, a trial should be designed to target that problem. Or, if related drugs already on the market have generated suspicious post-market safety information, a trial to address those suspicions should be designed. FDA addresses four main areas to guide sponsors with respect to developing an adequate safety database.

1. Risk Assessment

So, what is meant by “risk assessment,” and how is it accomplished? In a nutshell, “assessment” means “identification.” The sponsor must identify the nature of the risk associated with the medicine. What is the frequency of the risk? How often does the risk occur? What does it do? In which populations does it occur? Additionally, part of the nature of the risk is its severity. Is it life-threatening, or will its effects be felt for life? Again, although this process must continue throughout the product’s lifecycle, an adequate premarketing assessment is crucial for at least two reasons: First, FDA requires it prior to approval. Second, a jury requires it prior to a defense verdict. Deciding whether a risk assessment is “adequate” — specifically during the Phase 3 studies — depends on the amount of information gathered, how the information is presented and analyzed, and the nature of the information. Adequate risk assessment is a matter of quantity and quality.

A. Population Size Matters

New safety concerns always arise after approval because the medicine generally is used by more people, for longer periods of time, with different medical histories, and with different concomitant drug use. Even the largest clinical trial simply cannot mimic real-world use. However, the larger the pre-approval database and the more comprehensive the information in that database, the better. Certain factors might dictate when additional efforts should be made:

• The therapy is novel
• The effects of the proposed medicine are already safely available
• The proposed population is especially vulnerable
• The proposed duration of use is long-term

Generally, smaller safety databases may be appropriate when the disease being treated is life-threatening and there is no adequate alternative. In such situations, it is more acceptable to have less certainty concerning safety because the disease itself is so serious. In other words, the specific drug will dictate the necessary contents of the safety database. Prior to approval, FDA considers known risks and unanswered questions versus demonstrated benefits. Thus, in addition to gathering information about efficacy, it behooves sponsors to design clinical trials so as to maximize the amount of safety information. For instance, if preclinical data suggest a potential problem, a trial should be designed to target that problem. Or, if related drugs already on the market have generated suspicious post-market safety information, a trial to address those suspicions should be designed. FDA addresses four main areas to guide sponsors with respect to developing an adequate safety database.

1. Risk Assessment

So, what is meant by “risk assessment,” and how is it accomplished? In a nutshell, “assessment” means “identification.” The sponsor must identify the nature of the risk associated with the medicine. What is the frequency of the risk? How often does the risk occur? What does it do? In which populations does it occur? Additionally, part of the nature of the risk is its severity. Is it life-threatening, or will its effects be felt for life? Again, although this process must continue throughout the product’s lifecycle, an adequate premarketing assessment is crucial for at least two reasons: First, FDA requires it prior to approval. Second, a jury requires it prior to a defense verdict. Deciding whether a risk assessment is “adequate” — specifically during the Phase 3 studies — depends on the amount of information gathered, how the information is presented and analyzed, and the nature of the information. Adequate risk assessment is a matter of quantity and quality.
FD&A presents several recommendations to sponsors concerning steps that should be taken to make an adequate premarketing risk assessment and how to present that assessment in the NDA. Abiding by FD&A’s recommendations or creating an approval letter but also in obtaining a defense verdict. What states have statutory limitations on damages in personal injury or wrongful death actions? Which states have placed limits on either non-economic damages, the total amount recoverable against a healthcare provider or institution, or punitive damages in personal injury or wrongful death actions?

Alaska: Alaska. Stat. §09.55.549 (2007) limits non-economic damages to $250,000. This cap has been interpreted to extend to past and future non-economic damages reduced to a lump sum. Salgado v. County of Los Angeles, 967 P.2d 585 (1999).


Georgia: Ga. Comp. Ann. §§51-12-1-5 (2007) limits punitive damages to $250,000 except in cases where the defendant asserts intentionally or under the influence of drugs or alcohol, and here no limitations on punitive damages exist. Under §51-13-1, non-economic damages are limited to $350,000 per medical provider or a single medical facility; if there is more than one medical facility, the total damages against multiple facilities may not exceed $700,000.


Idaho: Idaho Code Ann. §6-1605 (2007) places a maximum $250,000 limitation on non-economic damages (adjusted for inflation). Under §6-1604, punitive damages are limited to the greater of $250,000 or three times the amount of compensatory damages awarded.

Indiana: Ind. Code §34-18-14-3 (2007) limits the total recovery of damages in wrongful death actions to $1.25 million and the total portion of damages recoverable from a healthcare provider to $250,000 if the act of malpractice occurs after June 30, 1999. Under Ind. Code §34-51-3-4 (2007), the plaintiff may recover maximum punitive damages of the greater of three times the amount of compensatory damages or $50,000.


Maryland: Md. Code Ann. Tit. 11, §10-107 (1997) limits non-economic damages for any personal injury cause of action for medical malpractice to $710,000 increasing to $1,050,000 October 1, 2013. The statute applies to wrongful death cases as well as personal injury, with the total damages recovered by all beneficiaries limited to 75% of the cap.

Massachusetts: Mass. Gen. Laws Ch. 231, §60H (2007) limits punitive damages to $500,000 for certain crimes, including permanent bodily loss or impairment or substantial disfigurement.

Michigan: Mich. Comp. Laws §600.1485 (2007) caps non-economic damages recoverable in a medical malpractice action at $280,000 for all the plaintiffs unless a specific situation is present (brain or spinal injury, permanent cognitive impairment).


Montana: Mont. Code Ann. §§25-5-411 (2007) caps non-economic damages per plaintiff at $250,000 based on a single incident of malpractice against one or more healthcare providers. Mont. Code Ann. §§27-1-220 (2007) limits punitive damages to $10 million or 3% of the defendant’s net worth; whichever is less; however, this limitation does not apply in class action lawsuits.

Nevada: Nev. Rev. Stat. §41A.035 (2007) caps non-economic damages at $350,000 on injury or wrongful death actions against a healthcare provider. Nev. Rev. Stat. §42.045 (2007) limits exemplary and punitive damages to three times the amount of recovered compensatory damages if those damages are greater than $100,000, or if the compensatory damages are less than $100,000, the exemplary and punitive damages awarded is capped at $300,000.

New Jersey: N.J. Stat. Ann. §2A:15-14 (2007) limits the amount of punitive damages recoverable to either five times the amount of awarded compensatory damages or $350,000, whichever is greater.

New Mexico: N.M. Stat. §§41-5-6 (2007) limits the aggregate recoverable amount for all persons incurred in injury or death as a result of malpractice to $600,000. This amount, however, does not include punitive damages and medical care and related benefits. An individual healthcare provider’s liability is limited to $200,000.

North Carolina: N.C. Gen. Stat. §S1D-25 (2007) caps punitive damages at the greater of $250,000 or three times the amount of compensatory damages.

One way to ensure accurate identification of adverse events consistent with coding conventions should be avoided introduction, subsequent versions of dictionaries and coding conventions should be avoided. Additionally, sponsors should perform audits prior to analysis of the safety database to determine the extent of any variability with respect to coding. Acknowledging that product development may be years in duration, if the single trial is superior in design or if it considered a distinct population, it may be worthwhile for the sponsor to separately report the findings. Factors to consider when deciding whether to pool data include any differences in duration or dose and distinct differences in population groups. FD&A specifically recommends “when there is clinical heterogeneity among trials with regard to the safety outcome of interest […] sponsors should present risk information that details the range of results observed in the individual studies, rather than producing a summary value from a pooled analysis.”

FD&A presents several recommendations to sponsors concerning steps that should be taken to make an adequate premarketing risk assessment and how to present that assessment in the NDA. Abiding by FD&A’s recommendations or creating a thorough audit trail otherwise generally will be helpful in not only obtaining an approval letter but also in obtaining a defense verdict.

A thorough audit trail otherwise generally will be helpful in not only obtaining an approval letter but also in obtaining a defense verdict.