BIO
BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket No. 02N-0528; Risk Management; 68 Federal Register: Pgs 11120-11121

Dear Sir/Madam:

The following comments supplement those presented by the Biotechnology Industry Organization (BIO) at FDA's public meeting to discuss the Risk Management Concept Papers on April 9-11, 2003. BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the FDA concept paper #1: Premarketing Risk Assessments.

General Comments

BIO member companies develop innovative therapeutic products, many of which are for serious disorders, with substantial unmet medical needs. These include orphan and ultra orphan diseases. Given the range of indications and study treatments that BIO member companies are involved in, we wish to emphasize the importance of an empirical approach to risk assessment that tailors efforts to the specifics of each development program. Such a paradigm for risk assessment can best fulfill the shared goal of optimizing the benefit risk relation of new therapies, without causing unnecessary delays in access to effective new medicines.

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Each of the individual actions outlined in the series of concept papers has great value in specific situations. However, if used in settings in which they are not applicable they have the potential to increase the uncertainty and duration of clinical development without a corresponding benefit to patients. Thus the choice of tools for risk assessment, in all phases of development, should be carefully crafted and optimized for the specific circumstance.

Already the crescendo of scientific advances in molecular biology, immunology, pharmacogenomics, and other disciplines, is being transmuted into a myriad of new therapeutic targets and new biotherapeutic agents. Effective risk management strategies should facilitate the development of novel and effective products. Our obligation to understanding the risks associated with new therapies should not become an unintended obstacle to reaping the benefits of this new knowledge.

Particularly in the biotechnology industry, young and innovative companies make a special contribution to the translation of new science to new treatments. Clearly, the standards of efficacy and safety for a product must be the same regardless of the characteristics of the sponsor. However, risk assessment standards, if they increase the obstacles to approval without ensuring a better product can be especially problematic to such companies. Fitting the risk assessment strategy to the product under development addresses this concern.

The scope of the Concept Paper: "Premarketing Risk Assessment" includes premarketing development of both biologic products and drugs. As can be inferred from the concept paper, some of the most important safety concerns for drugs, such as QT prolongation, are not generally relevant to biologic products. On the other hand immunogenicity may need to be addressed for all biologics. Given such differences, one ought to be cautious about developing generic risk assessment strategies to be applied to all products. BIO recommends that that future guidance further define how differential risk assessment approaches may be developed for different types of products.

Throughout the documents discussed at the recent FDA workshop, the importance of evidence based approaches and the use of validated methods for risk management programs is emphasized. When designing pre-marketing risk assessment strategies, this same principle should apply. Whenever a tool for improved risk assessment is employed there should be good reason to believe that it will provide relevant, interpretable and pertinent information. Focused, differentiated approaches to risk assessment should be designed to delineate the risks of interest for the specific product and indication under development.

Risk assessment strategies are a means to an end and should be continually evaluated from that perspective. They reduce uncertainty about risks by providing relevant information. Well-designed risk assessment strategies can provide reassurance about the product's safety profile. Where clinically significant safety issues are identified, risk assessment provides the basis for designing a risk management strategy.

The premarketing risk assessment paper poses the question "What is an ideal safety database?" It affirms that "the composition of an appropriate safety database for a new product would be determined on a case by case basis." The subsequent discussion, however, of the ideal for what "all programs" would include, proposes three features of an ideal safety database. Each feature has the

potential to increase the number of patients included as well as the duration and complexity of clinical development. Some features may not be applicable all programs. It is important that these features not be seen to represent a *de facto* minimal standard for a product safety database. BIO suggests that the concept of an ideal safety database should be nested in the context of the specific program rather than be developed as an abstract, stand-alone notion.

Three suggestions regarding premarketing risk assessment deserve specific comment. Firstly, long term controlled safety studies are suggested. While the paradigm of the randomized clinical trial may be the ideal to address certain safety concerns, in practice this may not be possible for several reasons. Experience with patient recruitment and compliance has shown that such studies are difficult to conduct. It may not be possible to recruit and maintain a large enough patient population to address the issues of concern. Interpretation of such data is likely to be impaired by dropouts and missing data. In situations where there is a major unmet medical need and where efficacy has been demonstrated, ethical reservations may be raised. Should there be data driven concerns about a specific safety endpoint, an appropriate, targeted post-marketing risk management plan using pharmacoepidemiologic methods may be more feasible than an effort to generate long term controlled safety data prior to marketing.

A second proposed feature of an ideal database for all programs is diversity. A diverse safety database, it is pointed out, is likely to be more representative and more readily generalizable to the post-marketing population. While this is true, generating a diverse safety database has substantial implications for product development. Inclusion of a more diverse population in pivotal studies makes it more difficult to demonstrate efficacy: such groups have more confounding factors such as concomitant diseases and medications. They may also be less compliant, leading to more study dropouts and missing data. The consequence of each of these factors is to increase the number of patients to be studied in order to demonstrate efficacy, or its absence. A consequence is that patient exposure to an ineffective product might under some circumstances be increased.

By contrast, the resulting more "diverse" safety database may not always provide a better basis for assessing risks in the expanded population. The numbers of patients in each sub-group in the diverse population may well be too small to assess sub-group specific risks. Indeed, the risks detected would have to be high for them to be measurable in the premarketing setting. A further potential hazard to this approach is that the heterogeneous population might generate so much "noise" that real safety signals could be obscured. Thus a "diverse" safety database is not necessarily a characteristic of an ideal safety database for all products.

The third suggested characteristic of an ideal safety database is one that would allow comparison of safety profiles at different doses. Where the safety database generated by the clinical development program already includes patients treated at different doses, data analysis strategies exploiting that information can be very valuable. On the other hand, one would generally not design a clinical development program for the purpose of comparing the safety profile of different doses. Since the primary endpoint is efficacy, Phase III studies are neither designed nor powered to distinguish between "levels of risk" at different doses. Adding additional study arm(s) in Phase III increases the number of patients needed to demonstrate efficacy and correspondingly increases the duration of the studies and the required resources. The ability to recruit patients is commonly the limiting step in clinical development. In orphan indications this is an inherent constraint. Thus, while having patients

at different dose levels may be useful in a safety database, one should be very cautious about suggesting that this is an ideal to be achieved for all products.

The second part of the concept paper, section (G), on data analysis and presentation, offers creative strategies to identify and delineate specific safety issues. These suggestions open the way to better understand and utilize data collected during clinical development. This approach facilitates early identification of safety concerns. By prospectively defining safety issues during clinical development, available and accruing safety data can be organized and coded to cast light on specific issues. These are efficient and prudent approaches that are tailored to address specific problems. This approach also facilitates the early development of a problem-specific risk management strategy to be implemented post-approval.

In conclusion, BIO looks forward to additional guidance from the FDA on risk assessment based on a paradigm emphasizing empiricism, evidence-based strategies and the development of approaches that are crafted to the unique situation that each product development undertaking represents. This approach will help ensure that innovative, effective and safe biologic products continue to be developed to meet serious unmet medical needs. A more detailed set of comments are attached.

Sincerely,

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Vice President Science and Regulatory
Affairs

Specific Comments

I. INTRODUCTION *Lines 2-13*

In accordance with Section VIII of the PDUFA III Reauthorization Performance Goals and Procedures, the CDER/CBER Risk Assessment Working Group is drafting guidance for industry on good risk assessment practices during drug and biological product development... Specifically, this concept paper presents FDA's preliminary thoughts on:

- Important risk assessment concepts

- Generation and acquisition of safety data during product development

- Analysis and presentation of safety data in an application for approval

Comment

The scope of the Concept Paper: "Premarketing Risk Assessment" covers premarketing development of both biologic products and drugs. Some generic approaches are suggested for risk assessment strategies. However, these approaches are not necessarily relevant to biologic products. Some specific risk issues for biologic products are alluded to, but the guidance for addressing these issues is not articulated in these documents.

The paper includes several proposals about the generation and acquisition of safety data during product development, each of which is plausible in specific situations. However, if, as implied, these represent the "ideal" for drug development, it is anticipated that these proposals will systematically increase the duration and uncertainty of clinical development. It has not been demonstrated that proportionate improvement in risk assessment or risk reduction would be the automatic result. Taken together these suggestions have the potential to substantially change the current requirements for demonstrating the efficacy and safety of new products.

The Concept papers as a whole quite appropriately emphasize the need for validated tools in risk assessment and risk management plans. The use of validated tools seems appropriate when considering the tools used for premarketing risk assessment. New safety assessment approaches are best applied selectively and in settings in which their utility has been validated. Risk assessment strategies that are focused and discriminating are likely to be most efficient and effective. Thus, it is important that the innovative approaches proposed by the FDA in this concept paper be evaluated and where applicable, validated in appropriate settings prior to being adopted in premarketing risk assessment.

Recommendation: Agreement on product/indication-specific methods applicable to various settings in clinical development will be more helpful to sponsors than a general discussion of safety assessment concepts. The proposals in the marketing risk assessment document are most advantageous when applied in specific settings with a well defined goal. Evidence- based standards should be used to validate new approaches to risk assessment that are likely to have

an impact on product development. This will help to better characterize the risks associated with a given product candidate.

II. IMPORTANT RISK ASSESSMENT CONCEPTS L 15-49

L15...This process (Ed., I.e. risk assessment) entails ensuring that the body of evidence generated by the clinical trials not only defines the product's effectiveness, but also comprehensively describes its safety (as required by the Food, Drug and Cosmetic Act, which calls for the conduct of all tests reasonably applicable to evaluate a drug's safety).

Comment:

The Federal Food, Drug and Cosmetics Act requires a marketing application to include adequate tests by all methods reasonably applicable to show whether or not a drug is safe under the conditions prescribed, recommended, or suggested in the proposed labeling. Consequently, we believe it is important for agency officials and sponsor representatives to work closely together to identify the tests needed to satisfy the definition of adequate and reasonable, thereby meeting the "to show" standard during the course of product development. We recommend that care be taken to preclude additional onerous safety assessments that delay development and do not enhance a sponsor's ability to characterize the product safety profile.

This Concept paper may lead to an across-the-board expansion of the notion of "all tests reasonably applicable to evaluate a drug's safety". The standard for determining what is "reasonably applicable" is not further defined. We recommend that the concept of "reasonably applicable" require that the additional efforts are feasible, generally accepted by the medical and/or scientific community and that there is reason to believe that they will lead to a commensurate improvement in the ability to evaluate a drug's safety.

It is stated (L41) that this paper "focuses solely on risk assessment based on safety data generated during product development". However, by redefining the makeup of the safety database, the process of product development (for efficacy as well as for safety) is substantially altered.

Recommendation: Add the following definition to the concept of "reasonably applicable".

Tests in the premarketing environment that are deemed "reasonably applicable" to evaluate a drug's safety must be feasible to perform and generally accepted by the medical and/or scientific community. They must have a reasonable likelihood of providing specific information needed to characterize potential risks attributable to the product or improving the management of recognized risks.

III. Important considerations in generating risk information during clinical trials L51-60

(L 58- 59) "(T)his concept document presents FDA's thoughts on selected issues as they apply to optimal risk assessment. "

Comment:

Risk assessment is a process that cannot be optimized in isolation. Efforts to do so will be at the expense of "optimized product development". Indeed, several of the suggestions for "optimizing" risk assessment presented in section lll of this concept paper might be at the expense of demonstrating efficacy and might increase the risk and duration of the clinical development program.

Recommendation: Alter the text to read "(T)his concept document presents FDA's thoughts on selected issues that may assist sponsors in developing appropriate risk assessment plans."

III A. What is the appropriate size of the premarketing safety database? **L 61 –137**

"The FDA would be interested in input on what general guidance could be provided on appropriate sizes of databases for products intended only for acute use and/or for serious and life-threatening conditions." L79-80

Comment on acute use:

Acute use is a special situation and the duration of follow-up should depend on the duration of exposure to the effects of the agent. This would be determined by the agent's pharmacokinetics or, in some cases, by the duration of its pharmacodynamic effects. Assessment of risk is easier for products with acute uses since the temporal relationships are often clearer between treatment and attendant risks. Depending on the specific circumstances, it should be possible that some of these patients would be accrued after the drug is marketed. Should there be a specific safety signal, an alternate strategy should be considered that would target the specific safety concern.

Recommendation on acute use: For products intended to treat orphan indications, regardless whether for acute use or chronic treatment, we recommend the number of patients targeted for the safety database take into account the actual population likely to be treated. The number of patients in the safety database for such products may need to be less than that recommended in the ICH guidance. We also recommend it take into account the number of patients in the pivotal studies. It may not be possible to exclude the occurrence of uncommon adverse drug reactions, prior to approval. We hope the FDA will consider developing specific post marketing observational cohorts to complement the

premarketing safety database in specific circumstances or, where possible, to track validated surrogate safety markers.

Comment on serious and life-threatening conditions:

We believe the assessment of risk for treatments aimed at serious and life-threatening conditions (L81) should focus on the risk of excess deaths in the treated population. In this setting, the question should be whether any comparably severe event (e.g., irreversible coma) is induced by treatment at a greater/equal frequency to the outcome which is being averted (i.e. the benefit).

Recommendation on serious and life-threatening outcomes: We recommend that power of the combined phase III studies to identify an excess risk in the worse outcome (e.g. death or severe brain injury) between the two groups should be estimated. If the results are sufficient to rule out important excess in the treated group, this may provide the critical safety information needed to assess benefit/risk. In such a setting, pooling of data across studies (L 458) may be appropriate. In such circumstances, the information derived from the safety database may not contribute substantially to such assessments.

> "FDA is also interested in input on the proposals below, related to safety assessments of chronically administered drugs for non-life threatening conditions." (L81-83)

Comment on chronically administered drugs for non-life threatening conditions

We recommend the nature of the indication be taken into account in defining the appropriate safety assessment for non-life threatening conditions requiring chronic treatment. Chronic, serious and disabling diseases, not necessarily immediately life threatening, may be associated with major unmet medical needs. The expected safety profile for many biological products is likely to be determined by the molecular target of the therapy and by potential allergic reactions to the therapeutic agent.

The actual target population may be relatively small, even when the indication is not an orphan disease. It is possible that as patient specific pathogenic mechanisms can be better defined in individual patients (e.g. personalized medicine), the target populations for new products will become smaller and the benefits to that target group, greater. Such evolution has the potential to alter the benefit/risk relationship for these chronic diseases. Fewer individuals who are unlikely to benefit from the product would be exposed to its risks, either in development or on the market.

It may be difficult to accrue patients in clinical studies because of a variety of factors, including selection criteria, competing experimental therapies and dropouts. We

recommend that in such situations, the size of the safety database depend on the size of the clinical trials required to demonstrate efficacy and the size of the population expected to be treated in the first year on the market. An arbitrary number, such as 1500, in the premarketing database may not be appropriate. Should additional safety information be needed, this may be sought in the context of a post marketing surveillance cohort.

When the therapeutic agent is a biological product, large safety databases designed to detect rare cases of QT prolongation, hepatotoxicity or blood dyscrasias are not necessary or appropriate. Again, we recommend that in such settings the safety database be designed to identify manifestations of hypersensitivity, and to identify those adverse effects which may be anticipated based on the products effect on its specific target.

Recommendation: The size of the safety database for severe and disabling conditions might be determined by the phase III study population size, and the size of the population which will likely be treated in the year following approval. For biological agents, the safety database might be designed to identify specific safety issues related to the biology of the target, as well as to immunologic concerns, rather than identifying events such as QT prolongation which are unlikely to be safety concerns for the product.

Lines 128-137 "(O)ther reasons why a larger database could be appropriate include:...2. A very safe alternative to the investigative product is already available."

Comment:

We believe this is appropriate for situations in which therapeutic equivalence is being demonstrated. In this setting, it would be appropriate to demonstrate that safety is comparable, and therefore, might require a larger safety database. On the other hand, if superior efficacy is demonstrated, we recommend the safety of the alternative product be evaluated in light of the additional benefit. We hope the FDA will take into account the benefit/risk relationship and the nature of the indication.

Recommendation: Amend (L128-137) statement to read "2. A very safe alternative to the investigative product is already available and the investigative product has demonstrated equivalent efficacy rather than superiority to the established product.

III B. **What are some characteristics of an ideal safety database?**

The composition of an appropriate safety database for a new product would be determined on a case-by-case basis. Ideally, however all programs would include:

Comment: See general remarks above.

Recommendation: Suggest that this statement be changed to read:

III B. What are some characteristics of an ideal safety database? The composition of an appropriate safety database for a new product would be determined on a case-by-case basis and may include some or all of the following features: ~~Ideally, however all programs would include:~~

Long-term controlled safety studies"

... In most cases it would be preferable to have controlled safety data including long-term safety data, to allow for comparisons of event rates and for accurate attribution of adverse events. Control groups could be given a placebo or active control depending on the disease being treated. " (L146-150)

Comment:

While there may be difficulties in interpreting the experience of a single arm safety extension cohort, the proposal to have long term controlled safety data as an ideal implies a new minimal standard for clinical development. This would have significant impact on the design of the clinical investigation program with substantial impact on size, complexity, timelines and costs. We believe that, in many settings, this new standard might not achieve commensurate improvements in risk assessment.

A major motivation for patients to enter a placebo controlled clinical trial is the possibility of access to a new therapeutic modality. Rollover provisions in the protocol ensure that placebo patients will have access to the new treatment at the end of the study, or, if they fail on placebo. However, we believe that under the proposal for long term controlled safety studies, this would not be possible.

While the duration of "long-term studies" is not specified, we believe it would be questionable to maintain patients on an inferior treatment for the purposes of expanding the safety observation time. For example, comparison of death rates with Alzheimer disease suggests extended follow-up, which would continue long after a typical endpoint (cognitive or functional improvement) was successfully demonstrated. The study would not have been powered to assess this safety endpoint. What would be the duration of observation needed to rule out a given excess in mortality in the safety database? Even with a control safety group, it might not be feasible to identify meaningful differences in

mortality. Observational post marketing studies would be more likely to provide interpretable information.

For these reasons, long term controlled safety studies extending beyond demonstration of efficacy are rarely appropriate. We recommend this not be part of the standard for "all programs". Should there be data driven concerns about a safety endpoint, it is important that an appropriate study be designed.

Recommendation: Revised text: In ~~most~~ rare cases it would be preferable and feasible to have controlled safety data including long-term safety data, to allow for comparisons of event rates and for accurate attribution of specific adverse events. Control groups could be given a placebo or active control depending on the disease being treated.

II B 2. A diverse safety database L-159-168

> "Ideally, a safety database (and, indeed, the efficacy database) would include a diverse population in phase 3 studies, and only patients with obvious contraindications would be excluded from study entry. .... Broadening the inclusion criteria in the studies could enhance the sponsor's ability to generalize findings in the population likely to use the product in the post-marketing period."

Comment:

We believe this proposal has the potential to substantially alter the standards for demonstrating efficacy in the name of creating a "representative or generalizable" safety database. Indeed, the proposal explicitly states that the standard for demonstrating efficacy would be altered, in that the study population would be designed to mirror the post marketing target population.

Early identification of safety signals in such populations is made more difficult by the presence of confounders. For example, if patients on immunosuppressive drugs are included, it will be more difficult to identify immunosuppressive effects of the drug under study. Such diverse populations may have so much "noise" that real safety signals are obscured.

A diverse study population is likely to make demonstration of efficacy more difficult by increasing variability (e.g. confounding medications and medical conditions, compliance issues leading to dropouts). What is the evidence that it would provide usable data for assessing risks in the expanded population? The risks in those sub-populations would have to be quite high for them to be measurable in premarketing setting. If one increases the number of patients over 80 for example, there will be additional problems in study conduct which may have an impact on determination of efficacy. Nonetheless, the number of patients in this age group may be too small to make inferences about the product's safety in the geriatric age group.

Thus, a "diverse" safety database may not be a characteristic of an ideal safety database for all products. Increasing diversity of the database has the potential unintended effect of increasing the exposure of patients to an ineffective product, since it increases sample sizes needed to demonstrate efficacy or its likely absence. We recommend the issues raised about differential safety profiles be addressed in the context of post marketing surveillance.

During product development, a clearly defined target population (or set of similar patient populations) is evaluated and prescribing information is constructed for safe product use under specific conditions. We believe broadening inclusion criteria for clinical studies during late stage development limits a sponsor's ability to create clear and specific product use instructions for intended patients.

Recommendation: Alter the above text to read: "~~Ideally,~~ In special cases, a safety database (and, indeed, the efficacy database) would include a diverse population in phase 3 studies, and only patients with obvious contraindications would be excluded from study entry. .... Broadening the inclusion criteria in the studies could enhance the sponsor's ability to generalize findings in the population likely to use the product in the post-marketing period. Such circumstances include:

> "When the Sponsor is seeking use of the product as a preventative in asymptomatic individuals.
> " When the Sponsor is seeking use of the product for symptomatic relief of common conditions *(define).*

L 170-181 Development of safety (and effectiveness) data over a range of doses (and plasma levels) throughout the clinical program.

"Using a range of doses in phase 3 trials would better characterize the relationship between exposure and the resulting clinical benefit and risk, allowing provision of the best dosing advice. (Labeling for doses in excess of what is needed for effectiveness resulting from inadequate dose exploration increases risk with no potential for gain.) In addition, exposure-response data from clinical trials could provide critical information on the need for dose-adjustments in special populations. Finally, demonstrating a dose-response relationship in late phase clinical trials also could add important information to the assessment of efficacy.

Comment:

It is proposed that several doses of a product be included in an ideal safety database and that this proposal would be appropriate for all programs. As in the previous proposals for defining an ideal safety base, we believe the suggestion for improving risk assessment may result in major revisions to the standards and usual practices of clinical development. Here, dose-ranging activities are moved from Phase 2 into Phase 3 of clinical development. Adding one or more additional study arms will substantially increase the number of patients needed to demonstrate efficacy and correspondingly increase the time

and cost of introduction of a new product. This is without attempting to power the study to distinguish between ill-defined "levels of risk" and trying to make benefit/risk comparisons between dose levels.

The ability to recruit patients is commonly the limiting step in clinical development. In orphan indications this is the major constraint in development. We recommend that, while additional attention should be given to the criteria for dose selection in clinical development, the place for those efforts is not as a component of the safety database.

Furthermore, the patients treated at doses lower than the ultimately recommended clinical dose might not (see L92-94) be considered as part of the safety database, thus, further enhancing the standard number of exposed patients in the safety database.

The FDA's suggestion of evaluating a range of doses in Phase 3 is reminiscent of the concentration-controlled clinical trials concept considered in the early 1990's. While advantageous in certain circumstances (e.g., narrow therapeutic window), we believe most product candidates do not benefit from this type of evaluation since simplified dosing is more desirable in clinical practice and in the post marketing setting. We suggest that a more accurate safety profile could be constructed for a product candidate using results from one or more confirmation-directed Phase 3 trials evaluating doses identified in smaller Phase 2 studies

Recommendation: "Under certain circumstances, using a range of doses in phase 3 trials might help characterize the relationship between exposure and the resulting clinical benefit and risk, allowing provision of the best dosing advice. ~~(Labeling for doses in excess of what is needed for effectiveness resulting from inadequate dose exploration increases risk with no potential for gain.)~~ This approach is most likely to provide clinically reasonable results if there is reason to believe that the dose response curve for efficacy is likely to flatten at higher doses. In this setting, additional exposure is unlikely to result in a corresponding increase in efficacy. Finally, demonstrating a dose-response relationship in late phase clinical trials could also add important information to the assessment of efficacy.

L 183-184 III C. How can unanticipated interactions be detected as part of a safety assessment.

BIO notes that drug interaction issues (e.g. cytochrome oxidase system mediated drug-drug interactions, product-food interactions) are less likely to be of concern with biological products.

The recommendations in this section have, under some circumstances, the potential to result in a major expansion in the nature of premarketing research required to demonstrate

the efficacy and safety of a product. While these may be important issues in specific settings and may need to be addressed, we recommend they ought not to be viewed as part of a generic clinical development program. Issues which are raised in the course of the premarketing risk assessment process may need to be further evaluated. Should this be appropriate, a specific risk management plan might be proposed, possibly involving a risk management program in the post marketing setting. It is important to avoid studies in the premarketing arena which unnecessarily expose additional patients to products for which the efficacy has not yet been evaluated.

It is probably advantageous to focus on identifying and confirming anticipated reactions rather than unanticipated reactions. Anticipated reactions can be the basis of testable hypotheses which may be assessed using Phase 3 data. Moreover, there is a need to characterize reactions which have been identified as theoretically possible, in terms of their nature, severity, and frequency. It is likely that the greatest benefit is to be achieved by better understanding such potential reactions.

It is possible that Phase 3 data may suggest hypotheses about previously unanticipated interactions (e.g. an association between specific adverse events and specific concomitant medications). We recommend such explorations be limited to serious reactions whose character might alter the benefit/risk relation for some patients.

For the most part, we recommend assessment of unanticipated drug interactions be conducted in a post marketing setting to prevent delayed access of an otherwise beneficial medication to patients predicted to have a typical therapeutic experience.

L 228—251 III .D. When would comparative safety data be useful?

Comment

The use of an active treatment arm is generally driven by the ethical imperative that patients in clinical studies not be deprived of appropriate treatment. This issue, which is addressed in point 4 below (rather than the experimental considerations that are listed as points 1-3 and 5) drives the decision to incorporate a well-characterized agent, in addition to the test product in the study design. Thus, the question becomes, "Are there any situations in which an active comparison arm, which is not standard of care, might be preferable to placebo because of the ability to generate comparative safety data?" Phrased in this way, it is apparent that this strategy would only be appropriate in the premarketing setting in exceptional circumstances. We believe the use of an active comparative arm introduces many problems into study design. Issues of blinding and bias arise, which apply to both the assessment of efficacy and safety.

With regard to the specific points enumerated:

Line 235-236 1. When there is a need to characterize background rates of certain adverse events in order to adequately assess the product.

Comment:

It is not clear why this need leads to the use of an active comparator.

Recommendation: Remove this point as a basis for recommending an active comparator.

Line 238-240. 2. When there is a well-established, well characterized product with minimal toxicity to treat the condition of interest. This examination would be intended to show that the novel therapy has a comparably benign safety profile.

Lines 242-244. 3. Where there is a well established related therapy. This examination could show whether the toxicity profile for the established therapy holds for the novel therapy of whether imported differences exist.

Comment:

Comparison of efficacy or safety of a new product to current marketed products is not currently a part of the standard for approval for a new product. These points suggest that under certain circumstances, the Agency might effectively be determining whether there is a need for a new agent in the market.

Recommendation: Delete points 2. and 3 as a basis for recommending an active comparator.

L 246-247. Where there is a well-established related treatment with an effect on survival or irreversible morbidity.

Comment:

This circumstance would almost always require the use of an active comparator.

L 249-251 5. Where the sponsor hopes to claim superiority. In this case, it would normally be expected that such comparative superiority claims would be based on more than one controlled study.

Comment

We believe that if a trial is designed to demonstrate therapeutic equivalence to a product which is standard of care, it would seem appropriate that the new product should also demonstrate a similar benefit/risk relationship. However, we recommend that when therapeutic superiority is demonstrated by the new product, the overall benefit/risk balance of the new product should also be evaluated.

The stipulation that comparative superiority claims be based on more than one study does not seem to be inherent to this point.

Recommendation: Revise : Where the sponsor hopes to claim superiority or therapeutic equivalency, the overall benefit/risk of the two products must also be assessable. ~~In this case, it would normally be expected that such comparative superiority claims would be based on more than one controlled study~~

L253. E. What are some special considerations for optimal risk assessment during product development?

Comment to this section:

We recommend premarketing risk assessment focus on the evaluation of defined risks in special situations. We believe it is important that specific clinical strategies aim to exclude, define, or characterize specific risks through a carefully conceived plan. This section presents some such situations under examples, 1-4.

Lines 260-264. 1. If a product is chronically-used (and particularly when it has a very long half-life) or has dose-related toxicities, an examination of whether a maintenance dose lower than the initial dose or decreases in dosing frequency from the initial recommended schedule would be appropriate.

The standard for approval requires demonstration of safety for the identified indication under the conditions specified in the label. Over the course of time on market, many changes in the usage of a product occur. The label evolves to reflect developing knowledge. We recommend these changes not be construed as automatically implying that the initial decision to make a drug commercially available was not appropriate. Most studies relating to optimizing dose administration and frequency might best be undertaken in the post marketing setting after safety and efficacy of the product in its initial form and dosage are established. The comments on the issue of dose selection discussed above (re L 170-181) are relevant to this issue. We recommend that this point generally not be part of the premarketing assessment unless the initial dose or methods of administration do not meet the standard for a safe and effective product.

Recommendation: Revise: Lines 260-264. 1. If a product has unacceptable risks or tolerability during the course of clinical development ~~is chronically used (and particularly when it has a very long half-life) or has dose-related toxicities,~~ an examination of whether a maintenance dose lower than the initial dose or decreases in dosing frequency from the initial recommended schedule would be appropriate.

L 279-298 In certain circumstances a large, simple, safety study (LSSS) would be conducted prior to approval.

Comment

For biological products, large, simple safety studies are seldom appropriate; both because of the nature of the conditions for which they are indicated, and because of the size of most targeted populations, even for non-orphan indications. The expense and usual modes of administration of these products makes it difficult to treat large numbers of patients in the premarketing setting. Where there is no alternative therapy, the prospect of delaying the availability of efficacious medications to better characterize the associated risks, is frequently unacceptable to patients.

Before undertaking such studies, we recommend there be a clear understanding about how the results will be used in determining the availability of a product. In addition, we believe it important that the LSSS only be instituted in the premarketing setting if the objective is clear and achievable.

More generally, since only very large sample sizes are able to detect infrequent events, it may be impossible to study such events in the premarketing setting. We recommend that efforts to do so take into account the indication under study and the corresponding size of the target patient population, the rate of the specific AE of interest, and the strength of the evidence supporting the concerns AE, and whether the resulting size of the required database could reasonably be attained.

Recommendation: The LSSS should only be instituted in the premarketing setting if the objective is clear and achievable. Such studies should be used only when the results are essential to making the drug available in the post marketing setting- i.e. in their absence the benefit/risk balance is not adequately defined, or in situations in which the available information does not support the commercialization of the product.

337-338 G. Are there safety aspects of products that should be addressed in all development programs?
We recommend that the potential for the following serious safety effects be assessed as a part of all new drug development programs:

1. QTc prolongation,
2. Liver toxicity
3. Drug-Drug interactions,

4. Polymorphic metabolism

For new biological products, we recommend that the following serious safety effects be assessed:

1) Therapeutic products- Immunogenicity, neutralizing antibodies.
2) Biologic products that are live agents – virulence, transmissibility, genetic stability
3) Transplantation therapies-survival, function, host immunocompetence

Comment:

This section is important in that it clarifies that it is not necessary to evaluate biological products for the issues defined as essential to all drug development programs. We recommend this be made explicit.

Regarding the biological products, it should be possible to determine that the safety concerns addressed may not be relevant to specific types of biological products in those groups. In these circumstances, it would not be necessary to evaluate them clinically. For example, studies of autologous cell therapies may not need to demonstrate effects on host immune competence.

Recommendation: Revise L 340-351 We recommend that the potential for the following serious safety effects be assessed as a part of all new drug development programs (but not for all biological therapies):

1. QTc prolongation,
2. Liver toxicity
3. Drug-Drug interactions,
4. Polymorphic metabolism

For new biological products, we recommend that the following serious safety effects be assessed, if they are relevant to the product under study:

1. Therapeutic products- Immunogenicity, neutralizing antibodies.
2. Biologic products that are live agents – virulence, transmissibility, genetic stability
3. Transplantation therapies-survival, function, host immunocompetence

IV.L 353-354 IMPORTANT CONSIDERATIONS FOR DATA ANALYSIS AND PRESENTATION.

364-365 A. How can adverse events be described to best ensure that safety signals are identified.

Comment:

We recommend that for Phase 3 studies, if potential safety signals have been identified, prospective grouping of relevant adverse event terms be undertaken to establish a functional "case definition" for the purposes of data analysis. Post-hoc definitions can be done in numerous ways and increase the potential for bias. We suggest this approach be limited to early exploratory data analysis or hypothesis generating approaches.

L395-396 When do temporal associations between adverse events and product exposure merit analysis?

Comment:

Time-to-event analyses can be very useful, but we recommend it be limited in number so as not to complicate interpretation of results (note that these are secondary analyses to begin with), and that it focus on AEs (or groups of AEs) of specific interest. In addition, such analysis would only be appropriate for events of interest that occur with some minimum frequency (e.g. 10%, 15%, 25%) to allow for adequate estimation of parameters.

L458 D. What is the role of data pooling in risk assessment?

Comment:

Data pooling may give more power to detect lower-frequency AEs ("relatively rare"). Nonetheless, lack of power may remain an issue. It may help to define the maximum frequency of an event (Rule of 3). However, it still will not help with truly rare AEs; for that the sheer numbers of postmarketing exposure are needed. In general, it should be informative to compare AE rates across trials. One should be careful, however, not to obscure rates seen only in specific studies and/or subgroups that appear to have some merit.

L 475. What are appropriate methods for data pooling in risk assessment?

Comment

We recommend patient populations in the pooled analysis be homogeneous. One would want to be careful not to mask certain safety signals by inappropriately combining groups of patients.