June 20, 2001

GlaxoSmithKline

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Tel. 919 483 2100
www.gsk.com

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

Re: Docket No. 00N-1269
Proposed Rule on Prescription Drug Labeling

Dear Sir or Madam:

GlaxoSmithKline (GSK) applauds the agency's continued research into ways to improve product labeling for prescription drugs and biologics. These efforts over nearly a decade culminated in the recently published proposed rule, *Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics,* that delineates the agency's proposal for making prescription drug labeling easier to access, read, and use. Although GSK shares the agency's objective of enhancing the safe and effective use of prescription drug products, we cannot fully endorse all the elements of the proposed rule. Modifications such as reorganization of the comprehensive prescribing information and the addition of an index to improve access, use, and readability are particularly appealing, especially with the possibility of electronic access to prescribing information on the horizon; however, requirements for the addition of a "Highlights" section, revision of the definition of "adverse reaction," and increased font size are potentially problematic.

We appreciate the agency's willingness to accept comments on the proposed rule. Our position on major issues is provided below for your consideration, along with responses to specific questions posed by the agency.

HIGHLIGHTS OF PRESCRIBING INFORMATION

Whereas the proposal to create a section to highlight the most important information is conceptually appealing, the practical aspects of implementation counter the original intent. However well-intentioned, the proposal to require a "highlights" section[1] may be unnecessary and unwise, because it ultimately disserves the goal of effective communication of prescribing information, and would result in the imposition of unwarranted additional product liability risk on product sponsors. As the agency itself has implicitly recognized, by proposing a "limitation" statement that reads "[t]hese highlights do not include all the information needed to prescribe *(insert name of drug*

[1] *See* proposed § 201.57(a).

00N-1269

C46

product) safely and effectively,"[2] the entire premise of the "highlights" section is somewhat flawed: it is simply not possible to further condense prescribing information that should already have been distilled to its very essence in arriving at "comprehensive prescribing information." Further condensation into an artificially limited "highlights" space (be it ½ of a standard 8½" x 11" page[3] or otherwise) is possible only with the omission of information that could be critical to the best treatment decision for an individual patient. Because practitioners' time is necessarily limited, these omissions come at a potentially severe cost, because practitioners will predictably be lulled into a certain complacency about the need to consult beyond the initial (artificially limited) "highlights" section. Ultimately, the overall objective of supporting well informed prescribing decisions, in the best interest of patients, will suffer.

An example of this inevitable counter-productive impact is the proposed limitation to 20 lines of any boxed warning or contraindication, as it would appear in the "highlights" section.[4] If the full text of the warning or contraindication, as included in the "comprehensive" section of the label, exceeds 20 lines, the manufacturer is required to prepare a summary for the "highlights" section. Again, because of artificial space limitations, the proposal would force a reduction of what should already be irreducibly brief. Notwithstanding the proposed referral of a reader to the "full" text deeper in the label, busy practitioners who stop short may be mistakenly deterred, or inappropriately not deterred, from prescribing on the basis of an artificially limited initial statement.

Sub-optimal communication of prescribing information is not the only likely ill effect of mandating a "highlights" section. There are procedural costs as well. Given artificial space constraints on the section, and the consequent need for selectivity, labeling discussions between the agency and sponsors will be further complicated and burdened by the need to reach agreement on what to include. By no means will consensus be easy to reach (even possibly among agency reviewers) on what "aspects" of the information in the comprehensive "warnings/precautions" section[5] deserve mention in the "highlights," as evaluated on the proposed "*most* clinically significant" standard (emphasis added).[6] Resolving differences of opinion on such questions may substantially complicate the drug review and approval process. Inevitably, potential or apparent discrepancies will emerge among drugs within the same class or therapeutic area, and across FDA reviewing divisions, which will only compound the challenge of reaching consensus on what should be included in an individual case.

---

[2] *See* proposed § 201.57(a)(15).
[3] *See* proposed § 201.57(d)(8).
[4] *See* proposed § 201.57(a)(4).
[5] *See* proposed § 201.57(c)(6).
[6] *See* proposed § 201.57(a)(10).

That the content of a "highlights" section could have serious product liability ramifications only reinforces the importance, and potential difficulty, of decisions about what to include. As the agency has acknowledged[7], the existence of a "highlights" section that is explicitly intended to include "the most important information regarding drug-related risks"[8] sets up a convenient theory of liability for litigation-minded patients who experience an adverse drug reaction disclosed in the "comprehensive" portion of the label but not the "highlights": a theory that the warning was allegedly inadequate because it should and could have been more prominent, *i.e.*, have been placed in the "highlights" section. Because questions about the placement and prominence of warnings are typically central to product liability suits, the agency is unfairly dismissive in characterizing these concerns as "highly speculative,"[9] and somewhat naïve to think that the proposed "highlights limitation statement"[10] would serve as a fail-safe shield. If the agency persists, over industry objections, in mandating a "highlights" section that is artificially constrained in length, liability concerns will undoubtedly only add to the difficulty of agreeing upon what is "most important."

Given the unwarranted potential liability costs and counter-productive effects, GSK urges first and foremost that the agency dispense with a "highlights" section and instead focus formatting improvement efforts on the very positive proposals to reorganize the prescribing information and to orient readers with an index.

In any event, the agency should not proceed without curing the potential adverse liability impacts on manufacturers. To assure in no uncertain terms that product sponsors are not unfairly burdened by unwarranted additional liability risk, FDA should wait until necessary legislative and administrative action has been taken to assure *the preemption*, as a matter of federal law over state law, of any tort liability founded upon the placement of information outside the "highlights" section of the prescribing information. As a far inferior alternative measure, FDA should enhance the force and prominence of the proposed "highlights limitation statement,"[11] so that it would stand an improved chance of reliably shielding manufacturers from liability. At a minimum, the proposed second sentence of the statement should be strengthened considerably (*e.g.*, to read "Prescribers ***must*** review the entire comprehensive prescribing information provided below before prescribing *(insert name of drug product)*)," and the highlights limitation statement should be moved to the beginning of the section immediately following "HIGHLIGHTS OF PRESCRIBING INFORMATION" and preceding the product name. The font size

---

[7] *See* 65 *FR* 81082, 81087-88 (December 22, 2000).
[8] *See* 65 *FR* 81082, 81088 (December 22, 2000).
[9] *See* 65 *FR* 81082, 81087 (December 22, 2000).
[10] *See* proposed § 201.57(a)(15).
[11] *See* proposed § 201.57(a)(15).

should be equivalent to that of the subheaders (e.g. RECENT LABELING CHANGES, INDICATIONS AND USAGE, etc.).

DEFINITION OF "ADVERSE REACTION"

Just as adding a "highlights" section would likely burden the drug labeling review and approval process and serve unfairly to expose manufacturers to added product liability risk, without countervailing benefits, so too would changing the definition of "adverse reaction." More generally, this change would introduce inconsistency and potential confusion. The proposed change in definition should thus be abandoned.

The current definition in 21 C.F.R. § 201.57(g) is "an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." The proposed new definition, consistent with the definition of "adverse drug reaction" in the final ICH E2A guideline "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting," is "a noxious and unintended response to any dose of a drug product for which there is a reasonable possibility that the product caused the response (*i.e.*, the relationship cannot be ruled out)."[12]

The agency should appreciate the seeming lack of consistency in the thinking it has expressed about the import of the proposed change in definition, and the confusion that this can engender. In a "glossary" appended to a May 2000 draft guidance on the "adverse reactions" section of prescription drug labeling, FDA asserted that the ICH definition (the one that FDA has proposed to adopt as part of the revision of the prescription drug labeling regulations) "is considered to be consistent with the definition in [current] 201.57(g)."[13] However, in the preamble to the proposed regulations, FDA maintains that "adoption of the proposed definition of 'adverse reaction' will result in *a more focused 'Adverse Reactions' section*" (emphasis added)[14] by making changes of two kinds.

One of the two proposed changes is of particular concern: substituting the phrase "for which there is a reasonable possibility that the product caused the response" for the phrase "reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence."

---

[12] *See* proposed § 201.57(c)(9).

[13] FDA draft "Guidance for Industry – Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (May 2000), p. 11, footnote 6. In footnote 6, the ICH definition is mistakenly attributed to the "ICH E8" guideline rather than the ICH E2A guideline; however the title of the relevant ICH guideline is recited correctly.

[14] *See* 65 *FR* 81082, 81094 (December 22, 2000).

According to the agency, this substitution would have the effect of excluding information that "is not meaningful to prescribers" because the current "reasonable association" standard "can be and in many cases has been interpreted as meaning that a reaction should be included merely if there is a temporal association, rather than a reasonable causal association, between a response and a drug."[15] Yet at the same time, the agency proposes to include a proviso, pertinent to "Warnings/precautions" only and virtually identical to existing language in current 21 C.F.R. § 201.57(e), that "labeling must be revised to include a warning as soon as there is *reasonable evidence of an association* of a clinically significant serious hazard with a drug; *a causal relationship need not have been definitively established* (emphases added)."[16] The agency thus appears uncertain itself whether "reasonable association" and "reasonable possibility of causation" are interchangeable or not, with one result being internal inconsistency within the proposed regulations.

GSK believes that the proposed "reasonable possibility of causation" standard is in fact distinct from the well-established "reasonable association" standard, and that the distinction can indeed make a difference. In fact, the difference can be extremely significant from a product liability standpoint. Plaintiffs' attorneys can be expected to argue strenuously that inclusion of any event in the "adverse reactions" section, on the proposed new "reasonable possibility of causation" standard, would be tantamount to an admission of causation, in satisfaction of one of the essential elements of a plaintiff's claim in a tort action. On the current "reasonable association" standard, in contrast, it could not so readily be argued that inclusion of an event in the "adverse reactions" section constitutes an implied admission of causation. Adoption of the proposed new standard may thus significantly compromise the position of manufacturers in individual product liability cases.

Because of those potential consequences, and more importantly, because expert medical opinions can honestly diverge on questions of possible causation, adoption of a "reasonable possibility of causation" standard may well have the unfortunate impact of delaying or deterring inclusion of potentially significant adverse reaction information in prescription drug labeling. Good faith disagreements can arise among concerned medical professionals, internally within the same organization or across organizational lines, about the degree of a potential causal relationship. This is all the more true given the well-understood limitations of spontaneously reported postmarketing adverse event information. Under the current "reasonable association" standard, the addition of potentially significant reported events to the "adverse reactions" section of a drug's labeling need not be delayed by internal or external debate over questions about the degree of a potential relationship, and need not be deterred, in the face of genuine

---

[15] *Id.*
[16] *See* proposed § 201.57(c)(6)(i).

uncertainty, by concerns about negative litigation consequences. Quite the contrary, inclusion in the label can take place at the earliest appropriate time, with prescribers and patients benefiting from inclusion of the most current available information about potentially significant reported events. The proposed new definition, in contrast, may well serve to delay or deter such updates.

Changing the definition has other practical disadvantages. Because of the need to reevaluate previously approved "adverse reactions" information against a new "higher" standard of inclusion, sponsors and agency medical experts may well bog down in reviewing and possibly debating a not inconsiderable number of previously listed events. Prescribers who consult prescription drug labels may certainly be confused in the transition to new standards. And as previously suggested, the proposed new definition cannot readily be reconciled with the long-standing policy that "warnings" be added as soon as "reasonable evidence of *an association*" emerges. All in all, the negative consequences of changing the definition clearly outweigh whatever positive benefit the agency asserts in terms of greater "focus."

As with the proposed "highlights" section, GSK therefore suggests that the proposed new definition of "adverse reactions" be discarded as counter-productive, and unjustifiable given that the potential benefits gained by this change are unclear while the burdens imposed by this new regulation on manufacturers (including unfair adverse litigation consequences) and on the FDA will be large. Again, if the agency persists notwithstanding these compelling objections, it should mitigate the impact by assuring manufacturers, on the strength of necessary legislative and administrative action, that the inclusion of any information in the "adverse reactions" section may *not*, as a matter of federal preemption of state law, support a finding of causation in any tort action.

RESPONSES TO FDA QUESTIONS THAT ARE NOT ALREADY ADDRESSED ABOVE:

What different types of icons could be used to signal a boxed warning and what are their costs and benefits?
The agency has suggested including an "!" to signal a boxed warning. Since the "Warning" section is listed first in the index, an icon would appear not to be necessary for the index. Furthermore, inclusion of an icon in the boxed warning in the comprehensive prescribing information section of the labeling seems superfluous, as it does not increase the prominence of the warning.

Should there be a time limit by which the "Recent Labeling Changes" section must be removed?
Because implementation of the final rule on content and format of prescription drug labeling will involve substantial financial resources, sponsors should not have to incur additional expense by having to revise labeling if for no other reason that to meet an imposed revision date mandated by the final rule. Therefore, the regulation should require inclusion of "recent labeling changes" for a period of at least one year, but not dictate a removal date.

Should the information required under the "Indications and Usage" subsection in the proposed "Highlights of Prescribing Information" section be presented verbatim from the comprehensive labeling section or summarized in a bulleted format?
The final rule should encourage a bulleted format, while allowing the flexibility of verbatim provision in such cases where a bulleted format would not adequately or appropriately convey the indication or use.

Are standardized headings in the "Warnings/Precaution" section appropriate?
It would be difficult to determine a few standardized headers that would encompass the various topics that might fall into this section of the labeling. Sponsors should be given the flexibility to determine the need for headers and the specific language for such headers.

Is it necessary to include a contact number for reporting suspected serious adverse drug reactions in the proposed "Comprehensive Prescribing Information" section as well as the proposed "Highlights of Prescribing Information" section?
It should be sufficient to include a contact number for reporting suspected serious adverse drug reactions only once in the prescribing information.

Does the proposed requirement to bold certain information in proposed 201.56(d)(5) serve its intended purpose of ensuring the visual prominence of the bolded information or would different highlighting methods be more effective?
The requirement to bold certain information in proposed 201.56(d)(5) would serve its intended purpose of ensuring visual prominence of the bolded information.

Is the proposed one-half page limit on the "Highlights of Prescribing Information" section (not including boxed warning(s) or contraindication(s)) adequate or are there alternatives that would be more appropriate and under what circumstances should such alternatives be considered?
Please refer to the previous discussion on pages 1-3 of this letter.

What means (other than the vertical line proposed in 201.57(d)(9)) could be used to facilitate access to, and identification of, new labeling information in the proposed comprehensive prescribing information section?
It is difficult to implement a means of facilitating access to and identifying new labeling information without incurring the difficulties associated with graphic elements in the margin or without drawing inappropriate attention to particular sections of the label.

Is the proposed minimum 8-point font size for labeling sufficient or would a minimum 10-point font size be more appropriate?
Because of the amount and complexity of the data contained in prescribing information, locating information of interest is often difficult for the practitioner. Obviously, larger type is easier to read; however, provision of an index and standard formatting, along with highlighting techniques such as bolding, should lessen the need for enlarged type. Larger font size in commercial packages would not ensure practitioners easier access or enhanced readability, since as noted in the preamble to the proposed rule, the PDR is the most common source of labeling information. It seems reasonable to maintain current font sizes and reassess practitioner satisfaction with the revised content and format of prescribing information before implementing increased font size requirements.

Increased font size would also pose packaging challenges. Some complex, larger package inserts could be increased by 70% using 8-point type. Problems with printing and folding the larger inserts are anticipated. It is important to note that prescribing information for commercial packs is not printed on 8 ½" x 11" pages, but rather paper of various sizes including some as narrow as 2 ¾".

Larger prescribing information leaflets affect other aspects of packaging. Products that are packaged in bottles with "outserts" (labeling attached to the bottle itself rather than in a carton) would require larger bottles to accommodate the increased size of the prescribing information leaflets. When larger bottles cannot be accommodated, products may have to be packaged in cartons using inserts rather than outserts. Substantial capital expenditure would be required to implement and maintain such packaging changes.

Should the revised format be applied to drug products with an NDA, BLA, or efficacy supplement that is pending at the effective date of the final rule, submitted on or after the effective date of the final rule, or that has been approved from 0 up to and including 5 years prior to the effective date of the final rule, or should alternative application criteria be used?
The effective date of the final rule should not negatively impact the review of any application. The most practical method of implementation would be to apply the revised format to those products submitted on or after the effective date of the final rule. This

would eliminate problems associated with having to reanalyze data in previously approved applications.

ADDITIONAL COMMENTS/QUESTIONS

1. Patient Counseling Information:
Proposed 201.57(c)(17) would retitle the "Information for Patients" subsection of the Precautions section of the labeling as "Patient Counseling Information" and move this section to a separate section at the end of the comprehensive prescribing information. According to the proposal, this would ensure that patient counseling information would immediately precede any approved patient labeling or Medication Guide. Further, the proposed change would clarify that the information under this section is not intended to be distributed to patients, but is intended to facilitate practitioner counseling of patients. Please clarify whether a reference to patient information approved as part of the labeling would be sufficient in the "Patient Counseling Information" section of the labeling or whether the agency would expect redundancy with a summary of the important patient information in this section in addition to the full text of the approved patient information printed immediately following this section of the labeling.

2. Recent labeling changes
Proposed section 201.57(a)(5) would provide a section of the labeling for recent FDA approved or authorized substantive labeling changes. The agency should clarify the definition of "substantive" to avoid potential misunderstandings. A sponsor might wish to highlight the addition of a new indication or clinical study, when the agency may interpret "substantive" more narrowly, in a way that would restrict "recent changes" to safety related issues. In addition, to aid the reader, the agency may wish to consider associating a date (month/year) with each change.

3. References
The conditions for citing a reference in prescription drug labeling have not changed in proposed 201.57(c)(16)(i) and (ii); however, the agency should be aware that currently there are substantial differences in the way these regulations are applied across reviewing divisions.

4. Changes to labeling required to be made within 1 year of the Final Rule
FDA is requiring changes to the labeling for both older and newer applications related to evidentiary support for indications implying or suggesting unapproved uses or dosing regimens, discussion of clinical studies, and use of *in vitro* and animal data. Although these required changes can be implemented via a "Changes Being Effected (CBE)" supplement, it is unrealistic to think all sponsors and reviewing divisions would independently agree on the information that falls under this requirement. Therefore, CBE

supplements might need to be resubmitted as prior approval supplements, if the agency were to disagree with the sponsor's conclusions. Furthermore, sponsors could elect to take advantage of the waiver provision to possibly avoid making any changes to the labeling. Given these scenarios, it is difficult to envision how this part of the rule could be implemented for all products within 1 year of publication of the final rule, necessarily disadvantaging some products.

5. Inverted Black Triangle

GSK questions the appropriateness of including such a symbol in prescribing information. In principal, use of a symbol creates a two-tiered catalog of prescription drugs ("new" versus "old"), absent any legal or regulatory basis for FDA to make such a distinction. In addition, use of the symbol carries the implicit assumption that "new" drugs merit this "alert" symbol since there is less experience with them and they are inherently less safe. In fact, the data suggest that "old" drugs are still associated with lethal medication errors and adverse reactions (e.g., errors with potassium for parenteral administration).

6. Index

By associating numbers with particular sections, it appears the intent of the proposed regulations is to maintain consistency of the index numbering system across products. To avoid confusion when a number/data is omitted from the index, FDA should consider maintaining a standard index for recurring headings and using N/A or "not applicable" to indicate when data are not available for a particular section.

7. Comprehensive Prescribing Information

The third sentence in proposed 201.57(c)(7)(i), should be revised to read, "...pertaining to clinical use of the drug in humans," since many drug interaction studies are performed in healthy volunteers, not "patients."

8. *In vitro* data

The proposed change to existing 201.57(b)(2) regarding excluding *in vitro* data for anti-infective products should be reconsidered. Clinicians need to be informed of the full spectrum of activity for antimicrobial agents so that when choosing an antimicrobial, they have an understanding of which products have a broad spectrum of activity and which are narrow in their spectrum. Consideration should be given to maintaining *in vitro* data with the inclusion of appropriate caveats. For example: "The clinical relevance of the *in vitro* activity of Product X against these microorganisms is not known. These data were generated in a controlled trial setting and they do not necessarily represent the current body of knowledge for Product X in each clinical setting."

9. Dose-ranging studies

Proposed 201.57(c)(15)(i) states that studies in this section should not imply dosage regimens which are not proven safe and effective. This proposal should not preclude the inclusion of a dose ranging study that serves as a basis for approval and includes dosage regimens that are not approved for use.

10. Most Common Adverse Reactions

It would be misleading and inappropriate to subsume the most common adverse reactions under the "WARNINGS/PRECAUTIONS" section in the HIGHLIGHTS of PRESCRIBING INFORMATION. The "Most Common Adverse Reactions" section should be moved below the telephone numbers for reporting suspected serious ADRs and given a separate identifying header.

* * * * * * *

GlaxoSmithKline wishes to thank the Agency for the opportunity to offer these comments on the proposed revisions to the content and format of labeling for human prescription drugs and biologics. This proposed rule and the many constructive comments and suggestions it will engender represent an important step in enhancing the safe and effective use of prescription drug products. We look forward to subsequent interactions with the Agency on this topic.

Sincerely,

Michele M Hardy

Michele M. Hardy
Director, Strategic Product Labeling Development
Regulatory Affairs

To Open Envelope, Pull Tab Slowly from Either Side

PLEASE TYPE OR PRINT

FOR SHIPMENTS WITHIN U.S. ONLY

FROM

GLAXO WELLCOME
CTRL SHIPPING DOORS 13-15
2312 S TRICENTER BLVD

DURHAM NC 27713

Michele M. Hardy 919-990-6961

TO

Dockets Mgmt Branch, HFA-305
FDA, Rm. 1061, 5630 Fishers Lane
Rockville, MD 20852

5393991385

001 (9/98)M-06
PACKAGE LABEL

Preprint Format No. 2922-0500 R0U

Origin

Airbill Number 5393991385

Method of Payment
- Bill Sender
- Bill Receiver
- Bill 3rd Party
- Paid in Advance

Assumed sender unless otherwise noted

AIRBORNE EXPRESS.

EXP (Letter - 150 lbs)

NAS (Letter - 5 lbs)

SDS (Letter - 150 lbs)

Billing Reference will appear on invoice

Cost Code: 8150

No. of Pkgs	Weight(LBS)	One box must be checked: Letter Express	Express Pack	Other Packaging
1	1			X

Special Instructions
- SAT
- HAA
- LAB

539 399 1385

MLDA - 4X

but not limited to loss of profits or
as defined in the current Airborne Express Servic
to change without notice). Copies are available u