Alcon

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March 21, 2001

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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20857

SUBJECT: Comments on Proposed Rules, 21 CFR Part 201, "Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics" (Federal Register, December 22, 2000, Docket No. 00N-1269)

Dear Sir or Madam:

In response to the FDA's request for written comments regarding the above proposed rules, Alcon Research, Ltd. is submitting the following information, concerns, and suggestions based upon dialogue within Alcon among the manufacturing/packaging, marketing, labeling, product safety, and regulatory communities.

Proposal for "Highlights" section and 8 point type

Because Alcon mostly markets small packages, we have consistently looked for ways to minimize insert sizes. In our opinion, Alcon has already removed duplications and statements found not to be sufficiently supported from our package inserts. Furthermore, Alcon has typically reduced text to 4 or 6 point type; thus, a required change to a minimum of 8 point type would have a significant negative impact upon our company, considering that the majority of our packages are small compared to those produced by the pharmaceutical industry "at-large."

To aid us in evaluating the impact of adding a "Highlights" section and increasing font size, our labeling group developed two "mock" inserts following the proposed regulations. We chose two of the larger inserts (Timolol Maleate Ophthalmic Solution USP and Betaxon™), since equipment and packages would have to be capable of handling the largest sizes. Since Timolol Maleate Ophthalmic Solution USP is an ANDA item, we changed only the font size, increasing it to 8 point type. However, since Betaxon™ is a recently approved product, we increased the type size as well as added a draft "Highlights" section at the beginning of the package insert. These changes result in package insert size increases (in inches) for Timolol Maleate Ophthalmic Solution USP and Betaxon™ from 9.75 x 7 .5 to 12.75 x 9.75, and from 10 x 5 to 10.75 x 9.75, respectively. Hence, these represent insert size increases of 169% and 209%, respectively. We estimate that 52% or more of Alcon's ASPEX facility production will be affected by these changes.

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Since our current insert-folding equipment cannot handle these new larger size inserts (particularly for Timolol Maleate Ophthalmic Solution USP), it appears Alcon would be forced to change from roll-feed inserts to prefolded inserts in order to maintain our current production rates and efficiencies. However, larger package inserts will be thicker when folded, and as such will require larger cartons and larger shippers to accommodate this increased thickness.
Based upon the above proposed changes to package inserts, one-time costs for Alcon would include equipment, installation and validation, and new art, film, proofs, and printing plates; Alcon's ongoing costs would include the added material and labor costs. Furthermore, costs for warehousing and shipping would be increased; however, these costs are not included in our estimate since they are difficult to capture.

Implementation of these changes would probably take 6-8 months. However, since not all lines can be shut down at one time to make the changes, these activities would have to be staggered by about 1-2 months, adding another 6-8 months to the transition time. Considering how great an impact these changes would have on our company, Alcon may be able to identify better and/or lower-cost alternatives if given additional time before implementation of any final rules is required.

Alcon's estimated cost impact for proposed changes to the package insert is based upon having approximately 23-2 4 products and approximately 60 to 80 SKU's that would be [initially] affected. The estimates listed below (A. and B.) include changes for five manufacturing lines in the ASPEX facility and the ophthalmic tube line in the FW North facility. Please note that these are rough estimates of the overall impact of these changes [as proposed in the Federal Register on December 22, 2000] upon Alcon's manufacturing, packaging, and labeling operations.

A. Start up costs to support proposed changes:

6 each prefolded inserters	$20,000. Ea	$120,000.
6 each cartoner modifications	$50,000. Ea	$300,000.
Installation and validation	$50,000. Ea	$300,000.
6 each barcode scanners	$15,000. Ea	$ 90,000.
Art changes	$ 800. Per product	$ 64,000.
Film and proofs	$ 600. Per product	$ 48,000
Plates	$ 900. Per product	$ 55,000.
Total non-reoccurring costs		$977,000.

B. Ongoing Annual Costs

Additional costs for enlarged cartons	---
Additional costs for enlarged shippers	$ 24,000.
Additional labor (3 lines 2 shifts)	$250,000.
Additional costs for prefolded inserts	$715,000.
Total annual costs	$989,000.

Additional concerns that Alcon has regarding the proposed "Highlights" section include (1) the impact that this would have on requirements for "comprehensive prescribing information" that is featured in conjunction with journal advertising for prescription products and (2) the requirement for a corporate telephone number for reporting of serious adverse reactions, since this number would be subject to change and would affect insert labeling for all products with a "highlights" section.

As an alternative to increasing the size of package inserts, we would like to suggest consideration of the "paperless insert" concept, since it solves most of the major issues for the physician, pharmacist, and pharmaceutical manufacturer. This could be accomplished by providing package insert labeling (a "Highlights" section along with comprehensive prescribing information) via the Internet and/or via an enlarged PDR. Text could be organized for all products, not simply those most recently approved, and it could be as extensive as needed without restriction. Type size could be as large as needed; in fact, on the Internet it could be adjusted to meet the reader's need. Inserts would be more readily available, as the physician may not have a package available when review of prescribing information is necessary. The Internet version could be updated more quickly if the need should occur, giving greater service to the physician and pharmacist. A synopsis insert, similar to the "Highlights" section proposed by the FDA, could still be required in the product package; a reference could be included in the "synopsis insert" explaining where to find the comprehensive prescribing information. We see this type of change as a major improvement over current package inserts because sizes would be significantly reduced. Since most medical professionals are on-line today, we believe this is a very viable alternative.

Additional proposed changes to package insert labeling

We would like to express our concern regarding the FDA's proposal that all package insert information (e.g. in vitro or animal pharmacology data), if not "sufficiently" supported by clinical studies, be removed from all product labeling. This concern is based upon the fact that Alcon is successfully able to differentiate our anti-infective products from others in the market based in part upon non-clinical data. Thus, this proposed rule directly impacts our ability to market products in this category.

Furthermore, we would like the FDA to clarify what is meant by additional "Medication Guides" and/or "Patient Information," in conjunction with the proposal to require this type of information to be added to the package insert.

In summary

Alcon hopes that this information is helpful to the FDA in assessing the potential impact of these proposed rules upon industry and appreciates the opportunity to provide these written comments. We also ask that our concerns and suggestions be seriously considered by the Agency, since these proposed rules could potentially have a significant economic impact upon our corporation.

Please contact me should you have any questions regarding these comments.

Best regards,

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Alcon Research, Ltd.

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