Holland & Knight

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This petition is submitted on behalf of a manufacturer/distributor of research materials sold purely for non-human research use ("Research Materials") pursuant to 21 C.F.R. § 10.30 to ask the Commissioner of Food and Drugs to clarify FDA regulations and policies with respect to Risk Evaluation and Mitigation Strategies ("REMS") implemented and enforced by the FDA and whether such regulations and policies have any applicability to Research Materials.

I. ACTIONS REQUESTED

We request that the Commissioner (1) clarify FDA regulations and policies with respect to REMS implemented and enforced by the FDA and, to the extent REMS are not applicable to Research Materials, (2) agree to take no enforcement actions against the manufacturers and sellers of such Research Materials pertaining to such REMS.

II. STATEMENT OF GROUNDS

A. REMS Programs Are Designed To Ensure The Safe Use Of An Approved New Drug

The FDA is tasked by Congress with, among other responsibilities, assuring the safety of new drugs. Pursuant to the Federal Food, Drug, and Cosmetic Act ("FDCA") including the FDA Amendments Act (enacted Sept. 27, 2007) (the "FDAAA"), the FDA has the authority to require that new drugs be distributed in accordance with a REMS "to ensure that the benefits of a drug product outweigh its risks." FDC Act § 505-1(a)(1) and (2). Under the FDCA, the FDA may require that a REMS program "include such elements as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness." FDCA § 505-1(f)(1). These elements may include restricted distribution, dispensing, prescribing and patient enrollment requirements. Accordingly, a new drug approved with a REMS program may be subject to restrictions that limit the availability of the approved new drug.

Celgene Corporation's ("Celgene") REVLIMID, for which the active pharmaceutical ingredient is lenalidomide, is approved for distribution with a REMS program that Celgene has branded "RevAssist"®. Lenalidomide is a known mouse teratogen with close structural and pharmacological similarity to a known human teratogen and the RevAssist REMS program is apparently required to protect users of the prescription drug REVLIMID against the risk of human fetal exposure. Under the RevAssist REMS program, Celgene must assure that REVLIMID is only (i) prescribed by prescribers certified in the RevAssist program, (ii) dispensed

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by pharmacies certified in the RevAssist program, and (*iii*) received by patients enrolled in the RevAssist program. REVLIMID samples are not provided to physicians and wholesalers do not distribute REVLIMID.

B. The Need For Regulatory Clarification

1. Celgene Has Challenged Non-Clinical Research Use Only Sales Of Lenalidomide As Unlawful Because They Do Not Flow Through The RevAssist REMS Program

Seventeen non-clinical Research Material supply companies are selling lenalidomide as a Research Material, labeled to varying extents to make clear such materials are intended only for research use and explicitly not for human, medical, veterinary, or household use. Though these sales of lenalidomide powder are not intended for human, medical or veterinary use and are not in finished drug product form, Celgene has alleged that sales of lenalidomide are prohibited by or otherwise unauthorized because of the RevAssist REMS requirements for REVLIMID.

2. REMS Programs Apply Only To A Particular Approved New Drug, and Do Not Apply to Research Materials Not Intended For Clinical Research Use and Not Intended for Human, Medical or Veterinary Use.

Under the FDC Act, a REMS program governs the distribution, dispensing, prescribing and patient use of the new drug identified in the relevant new drug application:

FDCA § 505-1:

> (a) Submission of proposed strategy.
>
> ...
>
> (2) Post-approval requirement.
>
> (A) In general. If the Secretary has approved a covered application (including an application approved before the effective date of this section) and did not when approving the application require a risk evaluation and mitigation strategy under paragraph (1), the Secretary, in consultation with the offices described in paragraph (1), may subsequently require such a strategy for the drug involved (including when acting on a supplemental application seeking approval of a new indication for use of the drug) if the Secretary becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug.

> (B) Submission of proposed strategy. Not later than 120 days after the Secretary notifies the holder of an approved covered application that the Secretary has made a determination under subparagraph (A) with respect to the drug involved, or within such other reasonable time as the Secretary requires to protect the public health, the holder shall submit to the Secretary a proposed risk evaluation and mitigation strategy.
>
> (b) Definitions. For purposes of this section:
>
> (2) Covered application. The term "covered application" means an application referred to in section 505(p)(1)(A).

FDC Act § 505(p):

> (p) Risk evaluation and mitigation strategy.
>
> (1) In general. A person may not introduce or deliver for introduction into interstate commerce a new drug if--
>
> (A) (i) the application for such drug is approved under subsection (b) or (j) and is subject to section 503(b) [21 USC § 353(b)]; or
>
> (ii) the application for such drug is approved under section 351 of the Public Health Service Act [42 USC § 262]

Thus, it is only the composite drug product intended for human consumption, identified and approved pursuant to a new drug application (such as REVLIMID) -- and not a pure, Research Material that is not intended for human, medical or veterinary use -- that is subject to a REMS program like RevAssist.

REMS programs are designed to ensure patient safety. REMS programs are not intended to interfere with the research and development of new drugs. FDC Act § 505-1(f). Specifically, FDC Act § 505-1(f)(8) states:

> No holder of an approved covered application shall use any element to assure safe use required by the Secretary under this subsection to block or delay approval of an application under section 505(b)(2) or (j) or to prevent application of such element under subsection (i)(1)(B) to a drug that is the subject of an abbreviated new drug application.

Sales of Research Materials, explicitly sold for non-human, non-veterinary research use only and involving material not eligible to be a drug substance, do not put patient

health at risk. To the contrary, if competing drug companies cannot obtain Research Materials for research into the non-clinical development of new drug products, research into new drugs that might benefit patient health would be chilled.[1]

C. Requested Actions

We ask the FDA to issue guidance clarifying its position regarding whether interstate distribution of drugs intended for research use only, and not intended for human, medical, or veterinary use are prohibited if the drug is the active ingredient for a new drug approved subject to a REMS program and to promulgate regulations embodying this position. To the extent REMS are not applicable to the sale of Research Materials, FDA should make clear in such regulations that Research Materials are excluded from the scope of the REMS provisions and no enforcement actions will be taken against the manufacturers and sellers of Research Materials.

D. Conclusion

A significant industry exists for the purpose of manufacturing and selling Research Materials. Confusion exists regarding whether REMS programs are applicable to the sale of Research Materials intended for non-human, non-veterinary research use only, where the Research Material involved happens to be the active ingredient for a new drug approved subject to a REMS program. Both the pharmaceutical companies that sell drug products for clinical human use and the Research Material supply companies that sell Research Materials for non-human use rely heavily on the FDA's statutory interpretations to guide them.

We ask FDA to establish comprehensive, clear guidance to industry in the matters discussed herein.

III. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

V. CERTIFICATION

[1] Dr. Reddy's Laboratories, Inc. has submitted a Citizens Petition to the FDA seeking guidance and enforcement to prevent REMS programs from being used to block generic competition.

The undersigned certify that, to the best of their knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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