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



RE: [Docket No. 00N-1663, RIN 0910-AA61] Investigational New Drugs: Export Requirements for Unapproved New Drug Products

Merck & Co., Inc., is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the most important pharmaceutical products on the market, today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading global biomedical research organizations. MRL tests many compounds or potential drug candidates in human clinical trials, conducted in most countries around world. Merck physicians and professional staff regularly submit written requests to FDA in order to secure authorization to export clinical supplies (unapproved investigational new drug products) to the sites of our clinical studies being conducted outside the United States (ex-US). This is to comply with requirements in 21 CFR Part 312 (known as the *312 program*) of the *Federal Food Drug and Cosmetic Act*, hereafter referred to as *The Act*. Therefore, we are very interested in and well qualified to comment on this *Proposed Rule* pertaining to the *Export Requirements for Unapproved New Drug Products*, hereafter referred to as the *Proposed Rule*.

General Comment

Merck's experience with FDA's export waiver request process is extensive¹. Most of Merck's written requests will benefit from changes under the 4th mechanism listed in this *Proposed Rule* in the provisions of § 312.110 (b)(4), pertaining to

“...unapproved new drugs exported to any country for investigational use without an IND, although the agency anticipates that the provision would be used by persons who intend to export a drug for investigational use to countries that are not *listed* under section 802 of *The Act* and proposed §312.110(b)(2).”²

It is important to note that almost all Merck's investigational new drugs studied in foreign countries are also studied in the US under an IND and these US INDs are referenced in all export requests submitted to FDA. There will be rare cases, when an investigational product

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¹ On average, Merck submits 15 export requests, each year; each includes all the information required to secure FDA permission to export one product to 8 – 10 countries where multi-site clinical investigations on that one product will be conducted.

² Federal Register Vol. 67, No. 118, page 41644, col. 2, para 1

will be studied for markets outside the US, e.g., for tropical diseases, and, therefore, there may not be a US IND to reference in an export request.

Comments Specific to § 312.110(b)(4)

Merck enthusiastically supports FDA's initiative to strategically streamline the process for exporting investigational materials, as noted under § 312.110 (b)(4) or the 4th mechanism of the *Proposed Rule*. Changing the requirement from *FDA prior authorization* to *sponsor certification* is a bold but considered move, that should be supported by all affected parties.

For a variety of valid reasons, the time has come to move this process from *prior authorization* to *sponsor certification*, in order to expedite export of investigational materials. These include:

1. The *prior authorization* process has become unnecessarily complicated and time-consuming, with little practical benefit for patients or sponsors, but with significant disadvantages for sponsors. *Prior authorization* has increasingly delayed shipments of time-sensitive materials, resulting in delay of study start dates, loss of investigators and, ultimately delayed marketing of products in underserved markets.

2. Despite the thoroughness of the *prior authorization* process, FDA experience indicates that there has not been the expected public health benefit resulting from these efforts. FDA concludes the following:

“...because the agency's experience with the 312 program indicates that very few investigational new drug exports under the existing programs raise any safety, quality or other public health concerns, the certification [process] would eliminate the requirement of prior FDA authorization of a request to export a drug for investigational use.”³

3. Obligations imposed legally on sponsors through this *sponsor certification* process are significant. Documentation, recordkeeping and other regulatory obligations of the new *sponsor certification* system remain essentially the same as under the *prior authorization* process. The only real change in the process is whether or not the system actively requires FDA authorization to ship materials in advance of export or passively allows foreign clinical study logistics to proceed while FDA reviews relevant data. Since sponsors will continue to legally assure FDA that all pertinent foreign laws will be followed and that US quality standards for materials will supplement foreign requirements, *sponsor certification*, together with oversight by local health authorities, will ensure that the objectives of this regulation will be satisfied.

4. The *Proposed Rule* will bring FDA's procedures for review and approval of clinical research plans for foreign studies in line with its procedures for review of US clinical research plans. In this proposal, FDA notes that the purpose of the written request is to “...provide sufficient information about the drug to satisfy FDA that the drug is appropriate for investigational use in humans...”⁴ which mimics the intent of the US IND regulations. However, the process for reviewing export requests has become more cumbersome and time-

³ Federal Register, Vol. 67, No. 116, page 41644 (col. 3, para. 2)

⁴ Federal Register, Vol. 67, No. 116, page 41642 (col. 2, para. 4)

consuming than that for reviews of US INDs, even though less information is submitted. For example, information required in a US IND is clearly outlined in the regulations and FDA routinely completes review of a complete IND within 30 days. In contrast, information required for an export request is a subset of that in a US IND; additional information is routinely provided *on demand*. FDA's review of export requests should be completed within 60 days, but actual reviews have ranged from 34-67 days, according to some recently published statistics.⁵ Therefore, the *Proposed Rule* will attempt to harmonize these discrepancies and certain other differences in related regulations, thereby removing the perception of a double standard for US vs. foreign clinical research.

Conclusions

FDA is to be commended for recognizing the responsibility of industry sponsors, foreign government officials and local ethical review professionals, in maintaining safeguards over foreign clinical research by streamlining its administrative review of export requests. The *Proposed Rule* harmonizes requirements for foreign clinical research with those for clinical studies conducted in the US. Its most significant impact will be to reduce the administrative burden on FDA and on sponsors for exporting investigational products to foreign countries, by allowing FDA more time to review these requests and allowing sponsors to meet their operational obligations more efficiently. No significant obligations are waived or will be lost in the new *sponsor certification* process.

In the interest of advancing global clinical research, FDA should move swiftly to finalize and implement these changes to these important regulations. Since different Centers and functions within the Office of the Commissioner will need to cooperate to ensure efficient implementation of this *Proposed Rule*, the agency should outline a plan for transition to the new procedures when this regulation is finalized.

We appreciate the opportunity to comment on this important matter.

Sincerely,



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⁵ Fisher, Travis S. & Copmann, Thomas L. *Aggregate Analysis of the Export petition and Waiver Process: A Pharmaceutical Industry Perspective* Drug Information Journal, Volume 36, Number 2, 2002 pp343-348.

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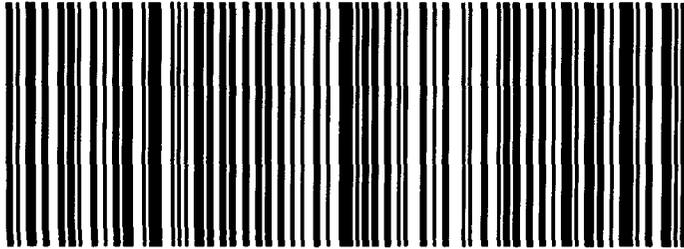
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