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November 20, 2001

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



RE: Docket No. 01N-0400

Agency Information Collection Activities; Proposed Collection; Comment Request; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients

Merck & Co., Inc. is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations.

In the course of bringing our product candidates through developmental testing, clinical trials, and product approval, we continue to recognize and support the need to develop reliable pediatric information about our products and to provide the information to the Food and Drug Administration (FDA) for inclusion in approved labeling. Indeed, the labeling of many of our products already contains instructions for their proper use in the pediatric population based on information from Merck studies, and our commitment to the pediatric population continues with a number of pediatric product development programs underway. Therefore, we are both interested in and qualified to respond to FDA's announcement of opportunity for public comment on the agency's proposed extension of information collection activities related to the regulatory requirements for pediatric assessment in drug development, hereafter referred to as "the pediatric rule"¹ [66 FR 49389, September 27, 2001].

FDA invited public comment on, among other things, the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used.

General comments

FDA's estimated annual reporting burden appears to underestimate significantly the resources required to satisfy the collection of information. The notice, however, did not include a discussion of the assumptions and methodology used to develop the published estimates other

¹ "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients," 63 FR 66632, December 2, 1998

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than the statement that the estimates were “based on the number of submissions the agency has received as a result of the December 2, 1998 final rule.” It is not clear from this statement, however, whether the numbers in Table 1 represent totals of all submissions since December 2, 1998, or whether they represent an annualized number based on the total received. It is also unclear how past volume of submissions was used to estimate the level of future collection activity. While we do not disagree with the need to collect adequate information to carry out the pediatric rule, we believe that the public record must provide a realistic estimate of the burden imposed.

The following examples illustrate the basis for our concern that the estimated burden significantly understates the resources necessary to comply with the pediatric rule:

1. The burden for a response under 21 CFR 201.23(a) is estimated at 48 hours per response. Under 201.23(a), FDA may require the holder of an approved application for a marketed product to submit a supplemental application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. In addition, a sponsor may be required to develop a pediatric formulation under this provision, which, if successful, would require the submission of a New Drug Application (NDA). Clearly, the burden of responding to a collection of information² under 201.23(a) is dependent on how one defines “response.” If the response to a 201.23(a) request is a supplemental application or a New Drug Application for a pediatric formulation, the resource commitment would involve hundreds of hours of development time and a variety of scientific specialties.

On the other hand, FDA may have divided the burden of submitting a pediatric application in response to 201.23(a) among the various other regulatory provisions cited in Table 1. The development of data for a supplement or an NDA likely would involve development of a plan (21 CFR 312.47(b)(1)(iv)), a possible “pre-NDA” meeting (312.47(b)(2)), data collection, and preparation and submission of a pediatric application (314.50(d)(7)) and 314.55(a)/601.27(a). In this case, the burden of response to a 201.23(a) request would be limited to the sponsor’s “opportunity for a written response and a meeting, which may include an advisory committee meeting” as described under 201.23(b). Even a meeting with the Agency to discuss a 201.23(a) request, however, would involve more than 48 hours in travel and attendance time alone for most sponsors, not counting the resources for pre-meeting preparations. An advisory committee meeting would require an even larger burden. Thus, the estimated 48 hour burden for response under 201.23(a) appears to be unrealistic in the absence of an explanation of the assumptions on which it was based.

² The definition of “collection of information” (5 CFR 1320.3(c) includes “the obtaining,” or “causing to be obtained” of information.

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2. The agency-estimated burden for compliance with the collection of information under 314.55(a) [new drugs] and 601.27(a) [biological products] is also 48 hours. Sections 314.55(a) and 601.27(a) are the requirements for each new drug application and biologics license application and certain supplements to contain data adequate to assess the safety and effectiveness of the drug product in the pediatric population for its claimed indication. Because the collection, analysis, and reporting of data adequate to support pediatric use of a new drug or biological product under 314.55(a) and 601.27(a) respectively involves extensive resources of a multi-disciplinary team to plan and execute the necessary clinical development program, we believe the 48 hour estimate for this collection understates significantly the burden involved.

3. FDA estimates 73 total annual responses @ 50 hours per response under 314.50(d)(7), which outlines the requirements for the pediatric use section of a supplemental application or NDA as follows:

“...a section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information...that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full description of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under 314.55” (emphasis added).

Because 314.50(d)(7) requires the pediatric section of an application to include “information submitted under 314.55,” it is unclear why the number of responses expected under 314.50(d)(7) is not equal to the total number of annual responses under 314.55. The table shows 25 annual responses under 314.55(a) [actual pediatric submissions]³ and 73 responses under 314.50(d)(7).

4. Full reports of any pediatric studies conducted in response to the pediatric rule are required to be submitted in an application under 314.50(d)(3) [human pharmacokinetics section] and 314.50(d)(5) [clinical data section]. No estimate of the burden under these sections is provided, and no explanation for its omission is offered.

5. FDA estimates 100 respondents annually under 314.81(b)(2)(i), 314.81(b)(2)(vi)(c), and 314.81(b)(2)(vii). Section 314.81(b)(2) is the requirement for *every holder of an approved NDA* to submit an annual report. FDA’s *Orange Book* [Approved Drug

³ Table 1 also shows 65 responses under 314.55(b) [deferrals] and 90 responses under 314.55(c) [waivers] but one would not expect an application for which pediatric studies had been deferred or waived to include a pediatric section under 314.50(d)(7).

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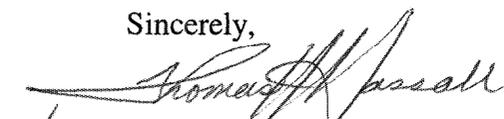
Products with Therapeutic Equivalence Evaluations] includes, in its "prescription drug products" section, approximately 3000 NDAs (not counting abbreviated new drug applications, discontinued products that are still approved, or products approved under 505 that are managed by the Center for Biologics Evaluation and Research). Given the requirement for the holders of each of these applications to submit, at least annually, a report under 314.81(b)(2) and to comply with subsections (i), (vi)(c), and (vii), it would follow that FDA might expect approximately 3000 responses annually not including responses from holders of approved Biological License Applications (BLAs) under 601.28.

Conclusion

Merck recognizes the need for reliable pediatric information in the approved labeling of products that are prescribed for children or are likely to be prescribed for children. To achieve this end, in accordance with the provisions of the pediatric rule, the collection of information is necessary. It is essential, however, that estimates of the reporting burden imposed by the collection of this information be both realistic and comprehensible. The estimated annual reporting burden published in the above referenced notice appears to substantially underestimate the actual burden of compliance as shown in the examples cited herein.

We welcome the opportunity to comment on this notice and, if appropriate, to meet with you to discuss these issues.

Sincerely,



for Bonnie J. Goldmann, MD
Vice President
Regulatory Affairs, Domestic

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