Bonnie J. Goldmann, M.D.
Vice President
Regulatory Affairs

Merck & Co., Inc.
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2383
215 652 5000

March 2, 2001

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

MERCK
Research Laboratories

RE: [Docket No. 00D-1595]
Draft Guidance for Industry on Recommendations for Complying with the Pediatric Rule

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 Billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market, today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness, and safety of our so that important therapeutic advances reach patients without unnecessary or unusual delays.

In bringing our product candidates through developmental testing and clinical trials, Merck recognizes the importance of pediatric product development. Therefore, we are both interested in and well qualified to comment on the *Draft Guidance for Industry* (hereafter referred to as the Draft Guidance), *"Recommendations for Complying with the Pediatric Rule"* (21 CFR 314.55(a) and 601.27(a))" (hereafter referred to as the Rule).

We commend the FDA for its efforts to improve the availability of pediatric information in product labeling and, through the issuance of guidance documents, to clarify for industry the requirements for the study of products in pediatric populations. After reviewing this Draft Guidance, however, we submit the following comments and recommendations for your consideration:

Substantive issues

1. Page 2 – Footnote 5: Definition of meaningful therapeutic benefit over existing therapies (quoted from 314.55)

"The term meaningful therapeutic benefit is defined as a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population."

As defined in the regulation, "meaningful therapeutic benefit" is a comparative claim.

00D-1595

C 5

Recommendation: To the extent that pediatric claims are based on "evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction," or "documented enhancement of compliance," the guidance should confirm that the Agency will apply its current standards regarding inclusion of comparative claims in product labeling.

2. Page 3, Section II B – Generic Drugs Under 505(j)

The rule does not impose any pediatric study requirements on applications for generic copies of approved drugs (see section 505(j) of the Act). Applications for drugs that are not duplicates of already approved products are required to comply with the rule. This includes applications submitted under 505(j)(2)(C) suitability petitions for changes in dosage form, active ingredient, or route of administration. [emphasis added]

Section 505(j) requires ANDAs to demonstrate that their labeling is the same as that of the reference listed drug (RLD). In addition, applications that require studies to demonstrate safety or efficacy may not be submitted under 505(j). Section 505(j)(2)(C) allows a person to petition the FDA for permission to submit an application for a product that differs from the RLD in certain ways, including dosage form, active ingredient, and route of administration, as an ANDA with labeling that is the same as that of the RLD. Where a petitioner seeks permission to market a product that differs from the RLD in ways that would trigger the pediatric rule (new active ingredient, new dosage form, or new route of administration), according to FDA's interpretation in this Draft Guidance, the Rule would require the conduct of pediatric studies which, presumably, would lead to labeling different from that of the RLD. Therefore, FDA cannot conclude that the petitioner can submit an ANDA for such a product and would have to deny the petition. However, the applicant could submit its application under 505(b).

Recommendation: This section of the guidance should be revised to clarify that abbreviated applications that involve changes in dosage form, active ingredient, or route of administration can be submitted under 505(j)(2)(C) only if a waiver of the pediatric study requirement has also been granted. Otherwise, such an application would have to be submitted under 505(b).

3. Page 3, Section III. C.

"If a deferral has been granted, the pediatric assessment will be due by the date specified by the Agency." [emphasis added]

The regulation on deferrals only stipulates that a product may be approved in adults subject to the requirement that the applicant submit the required assessments within a specified time. The Draft Guidance, on the other hand, repeatedly calls for a specific date [See Page 6 (Section IV(A)(1) and Page 10-11 (Section V(D), and Attachment B, item 4].

Recommendation: Reference to a date for submission of deferred studies should be deleted. A specified time or time-frame, as envisioned by the regulation (such as "3rd Quarter, 2003" or "within 2 years") is sensible, practical, and realistic. A specified date will invariably require amendments when the specific but arbitrary date proves untenable.

4. Page 4, Section III D:

"Further, if extrapolation from adult effectiveness data is inappropriate, adequate and well-controlled efficacy studies in the pediatric population will need to be conducted (see section 505 of the Act; 21 CFR 314.55; 601.27)." [emphasis added]

If the findings from efficacy studies in adults cannot be extrapolated to pediatric patients without controlled pediatric efficacy studies the indication may not be the same in children and, therefore the Rule would not apply.

Recommendation: To the extent that inability to extrapolate adult efficacy data to the pediatric population may indicate a disease in children that is different from the disease in adults, the guidance should confirm that the Rule does not apply. If FDA believes there are indications that co-exist in adult and pediatric populations that would require, under the terms of the Rule, separate evidence from controlled pediatric clinical efficacy studies to support approval in the pediatric population, it should describe in the guidance the features that exemplify such conditions.

5. Page 5, Section III E – (last paragraph):

"In certain cases, the Agency recognizes that scientific and ethical considerations will determine that pediatric studies should not begin until after approval of the drug or biological product for use by adults. For example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic need is likely to be low, and the risks of exposing pediatric patients to the new product may not be justified until after the product's safety profile is well established in adults after initial marketing. To encourage use of properly labeled drugs in pediatric patients, the Agency may require that products carry labeling statements recommending preferential use in pediatric patients of products that are already adequately labeled." [emphasis added]

It is clear that there may be instances where pediatric studies need to be delayed for scientific or ethical considerations. The example, however, appears to refer specifically to products that represent new entries in a class for which a number of products are already approved. It suggests that the mere presence of some number of approved products in a class creates a scientific or ethical objection to conducting pediatric studies of the new member of the class. The implication is that at some point, a sponsor of a new product in an existing class of drugs will be denied the opportunity to conduct timely pediatric studies, not because of evidence

that the product poses new risks, but simply because of concern that there *may be* unidentified risks and an *expectation* of no benefit over existing products in the class.

In addition, according to the guidance, a sponsor denied the opportunity to generate pediatric data on the new product, may be required to label it with recommendations to use other products already adequately labeled. We believe that such labeling may be misleading by implying either a second line pediatric indication for the product bearing the statement, or the existence of known increased risk with the new product, or both. In contrast, the labeling statement presently required for products when the requirements for a pediatric use statement have not been met, *"Safety and effectiveness in pediatric patients below the age of (__) have not been established,"* accurately describes the status of such products with respect to pediatric use without these erroneous implications (21 CFR 201.57(f)(9)(v)). Further, we do not believe that the Rule authorizes the Agency to impose a statement in labeling recommending preferential use of other products. While the Rule requires that information appear in product labeling when a *waiver* has been granted on the basis of *evidence* that the product would be ineffective or unsafe in pediatric populations, it contains no similar labeling provision with respect to deferral of reports of studies on the basis of speculation about unidentified risk with a new product or, for that matter, for any other reason.

Recommendation: The Agency should revise the paragraph to delete the implication that sponsors of new products in a class may be denied the opportunity to conduct pediatric studies in the absence of an *identified* risk The statement *"To encourage use of properly labeled drugs in pediatric patients, the Agency may require that products carry labeling statements recommending preferential use in pediatric patients of products that are already adequately labeled,"* should be deleted. It should be replaced in the guidance by confirmation that the statement currently required under 21 CFR 201.57(f)(9)(v) for products that have not met the requirements for a pediatric use statement will be required in the event of deferral.

6. Page 5, Section IV(A)(1) – "Products Intended for Life-Threatening or Severely Debilitating Illnesses" -- second bullet

"For drugs for life-threatening diseases, the Agency will provide its best judgment at the end-of-phase 1 meetings whether pediatric studies will be required....

Here, and again in Attachment B, part (a), the Agency dropped reference to "serious" disease (or, as stated in its subheading to this section, "severely debilitating illnesses"). It is not clear whether the Agency intends to include or exclude serious diseases because of this inconsistency in the language in the Draft Guidance.

Recommendation: The Agency should use consistent language and either include or exclude serious (or severely debilitating) diseases (or illnesses) in both the heading and the explanatory text.

7. Page 6, Section IV(A)(2) – "Other Products"

The minutes of the meeting should indicate whether pediatric studies are likely to be required, waived, or deferred. If a deferral of studies is granted at the time of the meeting, a projected date for submission should be included. [emphasis added]

Pre-NDA or pre-BLA meetings should include a discussion of any major unresolved problems and whether ongoing or recommended studies are adequate to assess pediatric safety and effectiveness." [emphasis added]

Regarding the underlined sections of this part:

Recommendation 1: Because FDA apparently intends the minutes of the meeting to document conclusions regarding a sponsor's responsibility for pediatric studies, the Draft Guidance at this part should be revised to clearly state that the minutes WILL indicate whether a waiver or deferral has been granted and document other agreements on the pediatric program. This is stated correctly on page 9 (Section V(B)(4).

Recommendation 2: The Agency should clarify the statement on Pre-NDA/pre-BLA meetings. It should be made clear that agreements on the appropriateness of pediatric studies reached at end-of-phase 2 (or earlier) meetings will not be rescinded by FDA except in rare instances, and then only when there is clear scientific and medical justification, based on new information that was not available at the time of the original discussion. In cases where there has been no prior discussion or previous agreement on pediatric studies (at an end-of-phase 2 meeting, for example), it is appropriate for the Pre-NDA/pre-BLA meeting to be the forum for discussion of the adequacy of any ongoing studies or studies proposed by the sponsor. When there has been prior discussion and agreement, however, it is inappropriate to suggest that FDA may reverse its prior conclusions on the adequacy of ongoing or recommended studies. As a blanket statement without qualification, this suggests that applicants should not rely on agreements reached with the Agency on pediatric studies earlier than the Pre-NDA/pre-BLA meeting.

8. Page 6, Section IV(C) –

"Under the Pediatric Rule you may be required to produce a pediatric formulation if one is necessary, particularly in cases where a new drug or biological product provides a meaningful therapeutic benefit over existing treatments and the required pediatric studies are to be conducted in the age groups needing the pediatric formulation." [emphasis added]

Careful reading of the preamble to the Pediatric Rule and the Rule itself suggests that a pediatric formulation is *required* only when the drug product is expected to provide a meaningful therapeutic benefit (See 314.55(a)). The rule does not stipulate that studies must be carried out using an appropriate formulation in the absence of anticipated meaningful therapeutic benefit.

Recommendation: The guidance should clearly establish that a pediatric formulation is required only when the product is expected to provide meaningful therapeutic benefit over existing therapies to pediatric patients.

9. Page 7, Section IV(C), second to last sentence

"In certain cases the Agency may also take to an appropriate advisory committee or other external expert body questions about whether a waiver should be granted in light of the technical difficulties in producing pediatric formulations."

Recommendation 1: The Agency should include language in the guidance acknowledging the trade secret status of information related to formulation development and should include a discussion of how it intends to protect such information in the event that it becomes necessary to take formulation issues to an Advisory Committee "or other external expert body."

Recommendation 2: The guidance should provide further information, perhaps by including examples, regarding what it means by "other external expert body."

10. Page 7, Section V(B)(1) – "Full Waiver"
"A full waiver may be granted if an applicant provides evidence that the drug product does not represent a meaningful therapeutic benefit over existing treatments...," [emphasis added] and

Page 9, Section V(B)(2) – "Partial Waiver"
"A partial waiver can be granted for a specific age group if the applicant provides evidence that...." [emphasis added]

The Rule requires applications to include the results of a pediatric assessment for *all* new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration, regardless of either expected meaningful therapeutic benefit or whether the drug is expected to be used in a substantial number of patients unless the requirement is deferred or waived. "Meaningful therapeutic benefit" over existing therapies functions in the Rule as a basis for (1) empowering the FDA to require pediatric studies of marketed products under 21 CFR 201.23, (2) triggering the requirement for development of a pediatric formulation for certain products, and (3) as a basis (in addition to "substantial number") upon which an applicant may seek a waiver from the default requirements for a pediatric assessment. In keeping with the prospective purpose of "meaningful therapeutic benefit", the Rule does not require an applicant to *provide evidence* that a product does not represent a meaningful therapeutic benefit in applying for a waiver. The Rule requires only that a sponsor certify that the product does not represent a meaningful therapeutic benefit and provide "adequate justification" for the waiver. The Draft Guidance, on the other hand, states that a full or partial waiver may be granted if the applicant "*provides evidence....*" As proposed, therefore, the Draft Guidance could be interpreted as establishing a substantially stricter

standard for waiver than envisioned by the Rule and one under which a sponsor may have to first conduct pediatric studies in order to qualify to have them waived.

Recommendation: The language in the guidance should be revised to retain the standard for waiver established in the Rule.

11. Page 9, Section V(B)(4), "Waiver Decision", paragraph 2:

"Decisions to waive the requirement for pediatric studies that are made early in the pre-approval development period (e.g., end-of-phase 1 or end-of-phase 2 meetings) reflect the Agency's best judgment at that time. If, prior to approval, the Agency becomes aware of new or additional scientific information that affects the criteria on which the waiver decision was based, the Agency may reconsider its earlier decision."

The FDA encourages applicants to discuss pediatric issues early in the drug development process. The Rule gives the agency 3 choices regarding the requirement for pediatric studies. It can waive the requirement entirely; defer the conduct of studies and the submission of reports; or require pediatric studies be submitted in the application without waiver or deferral.

Recommendation: A waiver, once granted, should not be open for reconsideration except, perhaps, in rare instances. In rare instances where a waiver decision is reversed, the guidance should state that the applicant will automatically be granted a deferral to allow development of a pediatric plan without delaying approval of the product for adults.

12. Page 11-12 – Section VI

"If a manufacturer fails to conduct required pediatric studies, FDA can bring issues related to progress of the pediatric studies before a panel of experts, and can use other forms of publicity to provide the public with information about the status of required pediatric studies, in addition to the enforcement actions discussed above."

Merck respectfully disagrees with the Agency's position that it can publicly disclose the status of pediatric studies, as such disclosure could potentially result in the release of confidential and highly sensitive commercial information. The disclosure of such information would be contrary to the Freedom of Information Act that specifically exempts confidential commercial information from public disclosure. 5 U.S.C. § 522(b)(4). Nothing in the pediatric regulations creates a separate right of disclosure.

Recommendation: The language in the guidance should be deleted.

<u>Editorial and other minor comments</u>

1. Title: Specific reference to 21 CFR 314.55(a) and 601.27(a) only in the title is misleading because the proposed guidance addresses other parts of the regulation in addition to 314.55(a)

and 601.27(a). For example, the guidance includes information related to deferrals (314.55(b)), waivers (314.55(c)), post-marketing reporting (314.81), and meetings (312.47, 312.82).

Recommendation: Revise the title to include all parts of the pediatric rule included in the guidance or delete specific reference to the CFR from the title.

2. Page 2, Section II. B., "Postmarketing Requirements"

"Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, adolescents) must be provided, including dosage form (21 CFR 314.81 for NDAs and 601.27 for BLAs)." [emphasis added]

This language is taken directly from the pediatric rule. However, it is not clear what "including dosage form" means in the context of post-marketing reports of exposure to the pediatric population. Postmarketing reports are "application-specific" and, in general, separate applications exist for each dosage form of a particular drug.

Recommendation: The guidance should clarify that reference to the pediatric population need only include specific dosage form information when there is more than one dosage form included in the NDA or BLA.

3. Section numbering: Both the "Introduction" and the "Background" sections are numbered "I."

Recommendation: Either re-number the document starting with "I" for the "Introduction" and "II" for "Background" or delete the number from the "Introduction" section and begin with "I. Background." Make corresponding changes to the table of contents and any reference to section numbers in the text.

4. Page 2 - Incorrect reference to later section: "II. Overview—WHAT AM I REQUIRED TO DO UNDER THE PEDIATRIC RULE?" – Subsection A. – General Requirements - Reference to section IV.B. appears to be intended to lead to further information on deferral or waiver. Instead, it references "What ages should I cover" (in my pediatric plan).

Recommendation: Change reference to "see section V."

5. Page 4, Section III D – Subtitle, "What Types of Studies Should I Submit as *Part* of My Pediatric Assessment?" [emphasis added]

Recommendation: Delete the word "Part" from the subtitle because it suggests that there is more to submit than is described in the Draft Guidance.

6. Page 7, Section V(B) - *"Discussions with FDA should occur early in the drug development process, as described in section V.A."*

Recommendation: Correct the reference to section IV. A.

7. Page 8 "Disease-Specific Waivers"

The preamble to the Rule includes the following statement directly preceding the list of diseases identified by FDA as having limited applicability to pediatric patients:

"FDA may add to or revise this list in the future by issuing guidance documents."

Recommendation: The same statement that preceded the list in the preamble should be added to the guidance to make it clear that the current list is not intended to be all inclusive and to describe in an easily accessible document the way FDA plans to revise the list in the future.

8. Page 10, Section V(D)(1), "How do I get a Deferral?" – 6th bullet:
"Evidence that planned or ongoing studies are proceeding."

Recommendation: This should be revised to read, "Evidence that studies are planned or that ongoing studies are proceeding." As written, it requires planned studies to be proceeding when, in fact, later planned studies may depend on the outcome of earlier trials.

9. Page 11, Section V(D)(2), last paragraph.

"Ordinarily, a discussion of deferral of pediatric studies should take place at the end-of-phase 2 or pre-NDA/pre-BLA meetings, and this discussion should be reflected in the minutes of the meeting. If this did not occur, and a sponsor wishes to obtain a deferral, the deferral request should be submitted to the Agency at least 60 days prior to the application submission."

Recommendation 1: FDA should state a usual time frame within which it intends to respond to these written deferral requests. It should also clarify whether its decision on a deferral request submitted 60 days prior to the planned application submission will be communicated in the form of a letter or other means.

Recommendation 2: The section on deferrals, like the section on waivers, should describe whether an applicant is expected to document the deferral decision in its application. In the waivers section, it states *"Full or partial waiver documentation should be submitted in an NDA or BLA in the Pediatric Use part of item 8 of the Clinical data Section of the application (form FDA-356h), and also under item 20, Other."* No similar advice is given with respect to deferrals. The guidance should describe the documentation required.

c) ***Recommendation 3:*** The language of this section should be revised to state that any early discussion at an end-of-phase 2 meeting or pre-NDA/pre-BLA "**must**" or "**will**" be reflected in the minutes of the meeting (not "should"- see Page 5, Comment #7, Recommendation 1).

10. Attachment B

Recommendation 1: Section (a): If FDA intends to consider "serious" diseases as well as "life-threatening" conditions, it should include both in the language on this template.

Recommendation 2: Item 4. FDA should change "deferred date for submission of studies" to "specified time-frame for submission of studies (see Page 2, Comment #3).

Conclusion

The Draft "*Guidance for Industry: Recommendations for Complying with the Pediatric Rule (21 CFR 314.55(a) and 601.27(a))*" provides a concise and thorough summary that should assist applicants in fulfilling the requirements of the Pediatric Rule. Certain issues, identified above, are raised by the Draft Guidance which need to be taken into consideration before a final guidance is issued.

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

Sincerely,

Bonnie J. Goldmann, M.D.
Vice President
Regulatory Affairs

SPH32

FedEx USA Airbill

FedEx Tracking Number 810495663830

Form I.D. No. 0210

Recipient's Copy

From

3/2/01

Your Name: Bonnie J. Goldmann, M.D. Phone: (610) 397-2383

Company: MERCK SHARP & DOHME

Address: 5 SENTRY PKWY WEST BLA-20 Dept./Floor/Suite/Room

City: BLUE BELL State: PA ZIP: 19422

2 Your Internal Billing Reference Information

3 To

Recipient's Name: Dockets Mgmt Branch Phone: ( )

Company: Food and Drug Administration

Address: 5630 Fishers Lane Room 1061 Dept./Floor/Suite/Room

(To "HOLD" at FedEx location, print FedEx address here)

☐ Check here if residence (Extra charge applies for FedEx Express Saver)

City: Rockville State: MD ZIP: 20852

For HOLD at FedEx Location check here

☐ Hold Weekday (Not available with FedEx First Overnight)

☐ Hold Saturday (Not available at all locations) (Available for FedEx Priority Overnight and FedEx 2Day only)

For WEEKEND Delivery check here (Extra Charge. Not available at all locations)

☐ Saturday Delivery (Available for FedEx Priority Overnight and FedEx 2Day only)

☐ NEW Sunday Delivery (Available for FedEx Priority Overnight only)

8 1 0 4 9 5 6 6 3 8 3 0

4a Express Package Service *Packages under 150 lbs.* Delivery commitment may be later in some areas.

☐ FedEx Priority Overnight (Next business morning)
XX ☐ FedEx Standard Overnight (Next business afternoon)
☐ FedEx First Overnight (Earliest next business morning delivery to select locations) (Higher rates apply)
☐ FedEx 2Day (Second business day)
☐ FedEx Express Saver (Third business day)
FedEx Letter Rate not available. Minimum charge: One pound rate.

4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.

☐ FedEx Overnight Freight (Next business day)
☐ FedEx 2Day Freight (Second business day)
☐ FedEx Express Saver Freight (Up to 3 business days)

(Call for delivery schedule. See back for detailed descriptions of freight services.)

5 Packaging

☐ FedEx Letter XX Declared value limit $500
☐ FedEx Pak
☐ FedEx Box
☐ FedEx Tube
☐ Other Pkg.

6 Special Handling (One box must be checked)

Does this shipment contain dangerous goods?* ☐ No ☐ Yes (As per attached Shipper's Declaration) ☐ Yes (Shipper's Declaration not required)

☐ Dry Ice Dry Ice, 9, UN 1845 ____ x ____ kg.

☐ Cargo Aircraft Only

*Dangerous Goods cannot be shipped in FedEx packaging.

7 Payment

☐ Obtain Recipient FedEx Account No.

Bill to: ☐ Sender (Account No. in 510 will be billed) ☐ Recipient ☐ Third Party ☐ Credit Card ☐ Cash/Check

(Enter FedEx Account No. or Credit Card No. below)

Total Packages	Total Weight	Total Declared Value*	Total Charges
		$ .00	$

* When declaring a value higher than $100 per shipment, you pay an additional charge. See SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY section for further information.

Credit Card Auth.

8 Release Signature

Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

321

Questions?
Call 1·800·Go·FedEx® (800)463-3339

WCSL 1293
Rev. Date 7/98
Part #153023os
©1994-98 FedEx
PRINTED IN U.S.A.

00855470&1