

**General Correspondence
Comments on FDA's Proposed Rule**



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October 17, 2003

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

RE: Novo Nordisk® Pharmaceuticals, Inc. Response to the FDA Proposed Rule on the Safety Reporting Requirements for Human Drug and Biological Products, Federal Register, Vol. 68, No. 50 (March 14, 2003): Docket No. 00N-1484

Dear Sir/Madam:

Herein are provided comments on behalf of Novo Nordisk® Pharmaceuticals, Inc. on the FDA Proposed Rule referenced above.

Novo Nordisk fully supports FDA's initiative to improve safety reporting for all drugs and biological products. We also support the Agency's intention of promoting global consistency and quality in the collection of safety information and submission of safety reports, as well as the stated objective in the proposed rule to harmonize with other international pharmacovigilance initiatives such as CIOMS and ICH. We strongly believe that it is important to help reduce the number of people who are injured or suffer serious harm as a result of medical errors and medical product use. However, we have reservations that this initiative will not effectively address the program's objectives.

We welcome the opportunity to provide comments on the referenced proposed rule and have summarized these comments below. Our four major concerns are presented below.

Definition of a Suspected Adverse Drug Reaction (SADR)

SADR, defined as a noxious and unintended response to any dose of a drug product for which the relationship between the product and response to the product cannot be ruled out, is not fully consistent with ICH definition and thereby contradicts the intent of the proposed changes. In practice, this change in definition will not only substantially increase the number of reports submitted but will negate any value in the distinction between an adverse experience and an

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adverse drug reaction. Based on Novo Nordisk's safety surveillance experience, the number of reports will potentially increase more than tenfold. The increased reporting will reflect any and all experiences and will result in an over reporting of minor and unrelated events with no significant benefit. For example, Novo Nordisk anticipates the increase will predominantly impact our reporting on experiences of individuals with diabetes. In contrast, we do not anticipate a significant increase in reporting to those events reported among other product lines which are already adequately monitored by the scientific community due to the inherent risk associated with these products. The increased reporting will obfuscate the ability to discern epidemiologic findings particularly in the latter scenario and potentially delay the ability to identify true safety concerns. This issue is more problematic in the conduct of clinical studies, wherein nearly all serious adverse events will need to be reported within 15 days. Because all serious adverse events from clinical trials are reported to the Agency under current regulations, this change in definition will increase the burden not only on the pharmaceutical industry but on FDA as well. In addition, the increase in expedited reports will not impact safety surveillance efforts conducted by the sponsor as all serious adverse events are typically adjudicated upon receipt. Therefore, the ability to detect a new safety signal will not be impacted by this definitional change.

For postmarketing events where the SADR has an unknown outcome, industry needs clarification on which classification of SADR needs to be reported (serious, non-serious, listed or unlisted). The Agency needs to clarify the requirement; otherwise every adverse event without a full data set would result in a 15-day report. Again, this potential over reporting does not facilitate the ability to quickly and adequately discern safety trends.

Active Follow-Up

The requirement for follow up by a company health care professional needs to be expanded to permit current employees with relevant experience who may not have a health care licensure or specific professional degree to continue serving safety surveillance efforts. The requirement for a health care professional is negated by the fact that the FDA proposed regulation will require no differentiation of medical adverse events. Therefore, the need for medical evaluation is now deemed irrelevant. We request that this discrepancy be reviewed by the Agency.

Reporting health care professionals may not be adequately resourced to provide the requested follow-up information. Pursuit of follow-up information may also cause health care professionals to refrain from future reporting. Novo Nordisk's concern that the requirement for the expanded follow-up information may result in an underreporting or failure to report thus negating FDA's intent for more complete information. Such information is often not readily available given the extent, duration and complexity of the adverse event which is confounded by numerous health care professionals involved with a given patient. The line of reporting responsibility and duration in which a patient is followed is often unclear.

In addition, although adverse event reporting is exempt from HIPAA, reporting health care professionals are citing HIPAA as their rationale for not providing follow-up information (full

data set) about adverse events. Based on Novo Nordisk's experience, HIPAA is not fully understood by many reporting health care professionals. As such, HIPAA requirements will negatively impact adverse event reporting. Novo Nordisk has recently experienced a situation in which the company requested follow-up information and the reporting health care professional repeatedly refused to provide any information on the serious adverse event reported by his patient citing HIPAA violations. This situation clearly exemplifies the ability of the manufacturer to adequately address potential safety concerns. Therefore, it behooves the Agency to collaborate with Health and Human Services to ensure that reporting health care professionals are adequately informed and trained with regards to patient privacy issues and safety reporting needs. This issue is further complicated by the fact that reporting health care professionals are not obligated by law to report adverse events.

Medication Errors

FDA is requiring expedited reporting of medication errors by manufacturers.. However, reporting health care professionals do not typically report such errors to the manufacturer. Medication error reporting does occur at an institutional level. Moreover, there are numerous existing resources to capture medication errors at a national level. For example, the Institute for Safe Medical Practice (ISMP) and the United States Pharmacopoeia (USP) Medication Errors Reporting Program (MERP) are systems already in place for health care professionals to report medication errors, both actual and potential.

Therefore, Novo Nordisk questions how a requirement for expedited reporting will identify safety concerns when the reporting body (i.e. health care professionals) is not required to do so. Novo Nordisk believes the FDA has a unique opportunity to impact the reduction and risk of medication errors through other means, such as with the naming of drugs. One of Novo Nordisk's recently approved products was a subject of a naming controversy between the Agency and Novo Nordisk. The Agency recently advocated the use of family name in lieu of a brand name despite knowing of a similar product name that could result in medication error. Novo Nordisk has noted potential medication errors which have since occurred as reported to the company. While Novo Nordisk recognizes the Agency's efforts in systematically evaluating product name development, we recommend that the Agency be more receptive to dialogue concerning names suggested by industry during the NDA process.

Periodic Safety Update Reports (PSURs)

In the proposed regulation FDA advocates consistency with ICH regulations. However, the proposed regulation on PSURs is not consistent with most current ICH E2B, specifically with regard to content (appendices) and timing of interim reports. The impact of this discrepancy has significant bearing on the ability to assess global safety trends which are of critical importance with regards to orphan drugs and other therapeutic moieties in limited patient populations as well as rare disease occurrences that will trigger safety signals.

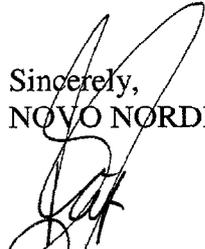
In addition, other discrepancies regarding PSURs warrant reconsideration, namely the designation of international birthdates for reporting. Under the proposed rule, it is possible that the first international approval may be years before the US approval yielding different reporting review periods. Novo Nordisk recommends the use of a uniform reporting period.

Conclusion

Novo Nordisk respectfully contends that the proposed changes to the reporting and submission requirements will not lessen the burden (time and economic) on companies. Rather, this approach contradicts the Least Burdensome provision set forth by the Agency as Novo Nordisk will require considerable additional resources to address the increase in reporting and to comply with the proposed rule. Moreover, Novo Nordisk is concerned that the proposed rule may lead to increased health care costs because of the increased reporting burden on industry and the health care professionals. The Agency will also need additional resources to handle the number of reports anticipated at an increased cost to US taxpayers.

Although the Agency through the proposed rule advocates it will be able to identify safety concerns in a timelier manner, the ability to do so and improve patient safety remains questionable given the notable discrepancies and concerns stated above. It is Novo Nordisk's understanding that part of the impetus for the proposed rules was the fact that a number of companies routinely failed to comply with current reporting regulations thereby placing patients on their products at potential risk. The Agency should look to ways to address the deficiencies in these companies rather than impacting the industry as a whole. If a company cannot comply with the current regulation, it is difficult to understand how the increased reporting requirements will be adhered to. In summary, Novo Nordisk supports FDA's efforts to improve patient safety but has reservations as to its ability to do so under the proposed rule.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.



Barry Reit, PhD
Vice President, Regulatory Affairs and Quality Assurance