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VIA ELECTRONIC MAIL
AND FEDERAL EXPRESS

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

Re: Docket No. 00N-1484
Request for Comment on Safety Reporting Requirements for Human Drug and Biological Products

Dear Sir or Madam:

Amgen Inc. (Amgen) is submitting the following comments on the Food and Drug Administration's (FDA's) proposed rule amending its regulations concerning the safety reporting requirements for human drug and biological products. 68 Fed. Reg. 12406 (March 14, 2003). Amgen is a pioneer in the development of biotechnology products. We manufacture and market many of the leading therapeutic protein products, including Epogen® (epoetin alfa), Neupogen® (filgrastim), Aranesp® (darbepoetin alfa), Neulasta® (pegfilgrastim), and Enbrel® (etanercept). Consequently, we have extensive experience with pre- and post-marketing safety reporting for human therapeutics.

Amgen supports FDA's efforts to improve the quality of safety reporting in the United States. We also support the goal of harmonizing domestic and international safety reporting requirements. In our view, however, certain aspects of the proposed rule may confound rather than advance these important objectives.

Our comments fall into two categories: legal and technical. From a legal perspective, we offer comments on the potential for mandatory safety reports to be misused in the context of product liability litigation. We do not believe the proposed rule provides a meaningful solution to this problem. We also are

concerned that certain provisions of the rule will exacerbate conflicts between federal reporting requirements and state privacy laws. Other proposed revisions, especially those involving reporting obligations for contractors, may lack a sound legal foundation.

From a technical perspective, we are concerned that the proposed definition of "suspected adverse drug reaction" (SADR) shifts the reporting and causation presumption in a manner that will reduce the pharmacovigilance value of the reported information. We believe certain other proposals, including "active query", may be impracticable and may yield little added useful information.

COMMENTS

Comment 1: Product Liability
FDA's current disclaimer language with respect to causation is inadequate and will not prevent the misuse of FDA-required safety reports in product liability litigation.

In the preamble to the proposed rule, FDA recognizes that adverse event reports may be misused in product liability litigation and expresses concern that such misuse "could imperil the credibility and functionality of this critical public health reporting system." *Id.* at 12418. FDA's current regulations attempt to address the issue by allowing for a "no causation" disclaimer. *See* 21 C.F.R. §§ 314.80(k) and 600.80(l). FDA asks for comment on whether such disclaimers are sufficient to protect manufacturers in product liability litigation, or whether further action is necessary to promote the submission of safety reports and guard against their misuse. *See* 68 Fed. Reg. at 12418-19.

Amgen believes that the current disclaimer is inadequate. We also believe that a disclaimer, in itself, is insufficient to address the rising tide of product liability litigation based on FDA-required safety reports and FDA-approved labeling. In a litigation context, the fact of an "official" adverse event report, along with the sheer volume of adverse event reports associated with a given product, to the extent admitted by the court, is likely to have a larger impact on jurors than is the disclaimer. The disclaimer itself is "defensive" in tone, to the extent it states that the report is not or "does not necessarily reflect a conclusion" that the drug caused the event. *See* 21 C.F.R. § 314.80(k). It has the potential to be used effectively in a litigation context to put the burden on the manufacturer to prove an absence of causation. Under the proposed rule, which is intended to increase the volume of safety reports, the prejudicial nature of FDA-required safety reports is likely to increase, despite the use of a disclaimer.

For that reason, Amgen supports adoption of a more prominent and definitive disclaimer. Further, we believe that the goal of increasing safety reporting must be married with an express regulatory preemption provision. The common law tort system is ill equipped to deal with the treatment population adverse event background rates and epidemiological issues raised by population level analysis of safety reports. Judgments from state courts may undermine FDA's risk-benefit determinations and may ultimately chill the flow of information on which establishing the product risk-benefit profile depends. In addition, increased safety reporting may lead to more frequent labeling changes which, in turn, will lead to yet more "failure-to-warn" suits. This predictable cascade must be addressed, with express recognition of the preemptive nature of FDA's approval and labeling decisions.1 We therefore believe the integrity of the reporting system would be best protected and advanced by an explicit preemption provision.

Comment 2: Privacy
The final rule should address the need to protect manufacturers and health care providers from liability under conflicting state privacy laws.

In the preamble to the proposed rule, FDA establishes that it is taking action to revise the safety reporting requirements in order to "strengthen its ability to monitor the safety of human drugs and biological products." 68 Fed. Reg. at 12406. Among other things, the proposed rules are intended to "increase the quality of safety reports." *Id.* In pursuit of this objective, the agency proposes to expand the types of information sought, the sources from which it is gathered, and the documentation required for each report, while stipulating the manner in which it is to be gathered.

Amgen recognizes that adverse event reports are a critical input to FDA's risk management and labeling decisions. But FDA is well aware that postmarket safety reporting is, in most cases, voluntary for physicians, other health care professionals, and entities engaged in health care delivery. Thus, with this proposed rule, it appears that FDA is attempting to leverage its authority over groups it directly regulates – applicants and manufacturers – to achieve its goal of increasing the quantity and quality of safety reports to "protect and promote public health." 68 Fed. Reg. at 12406.

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1 FDA has already recognized that its approval and labeling decisions preempt statue tort cases on the basis of implied preemption. We only ask in these comments that FDA incorporate into its regulations with express language that which the agency has said is implied in the statutory scheme applicable to prescription drugs and biological products. *See* Daniel E. Troy, FDA Involvement in Product Liability Lawsuits, FDLI Update (Jan./Fed. 2003) at 4 (discussing FDA's intervention in *Dowhal v. SmithKline Beecham Consumer Healthcare*, *Motus v. Pfizer Inc.*, and *In re PAXIL*).

This objective will be undermined without a more comprehensive preemption provision in the final rule to protect manufacturers, health care providers, and health care delivery organizations against liability from conflicting federal and state privacy laws. FDA's current regulations provide a limited preemption for any state law that would *permit or require* disclosure of the identity of a voluntary reporter or other person identified in a safety report. *See* 21 C.F.R. § 20.63(f)(2) (emphasis added). As the agency observed at the time it proposed the current provision preempting state law disclosure: some form of preemption was required "to maintain the agency's ability to collect information about safety risks of FDA-regulated products that is vital to protection of the public health." 59 Fed. Reg. 3944 (Jan. 27, 1994).

The provision noted above is not enough in light of the many strong state privacy laws enacted in recent years. It will not protect manufacturers or those submitting voluntary safety reports from liability under state privacy laws that *prohibit* disclosure of confidential medical information to third parties without consent of the patient. Indeed, FDA's proposed rule requiring manufacturers to "actively query" voluntary reporters and obtain from them a "data set" that may include confidential medical information may place manufacturers and voluntary reporters in conflict with state privacy laws.

In some states, healthcare providers are not exempt from state privacy laws even for reporting adverse events to federal authorities. For example, Florida's medical privacy statute has an exception that allows for reporting, without patient consent, for "statistical and scientific research," provided personal identifiers are removed from the report. *See* Fla. Stat. § 456.057. It does not, however, include an explicit exception for federal adverse event reporting or a general exception for public health-related functions. Illinois also has broad statutory and constitutional protection for patient privacy that does not include a public health or adverse event reporting exception. *See* Ill. Stat. Ch. 735 § 5/8-802; *Best v. Taylor Machine Works*, 689 N.E.2d 1057 (Ill. App. Ct. 1997) (ruling that the statutory waiver of privacy in case of litigation violated state constitutional privacy rights).

In addition, some states prohibit "*ex parte*" communications with a treating physician in tort cases. For example, Illinois law prohibits *ex parte* communications between defense counsel and plaintiff's treating physician. *See Petrillo v. Syntex Laboratories, Inc.*, 499 N.E.2d 952 (Ill. App. Ct. 1986). In such situations, physicians will be reluctant to respond to manufacturers' "active queries" or requests for additional information or documentation.

Even where a direct conflict does not exist, adverse event reporting is likely to decline. Health care providers and organizations have become sensitive to issues implicating medical privacy. Amgen is aware that concern about potential liability has led many health care providers and organizations to adopt a practice of not discussing or releasing confidential medical information beyond that provided in an initial voluntary report. Thus, if FDA expects manufacturers and health care providers to increase both the quality and quantity of adverse event reporting, it must provide clear and comprehensive preemption of conflicting state privacy laws in the final safety reporting rule.

Comment 3: Contractor Reporting Obligations
The proposed reporting requirements for contractors and oversight obligations for manufacturers are unclear, lack statutory authority, and will produce little useful information.

The proposed rule includes new reporting obligations for persons who enter into contracts with sponsors of drugs and biologics. 68 Fed. Reg. at 12435. The term "contractor" would include suppliers, packers, distributors, and sellers. *See, e.g.,* proposed 21 C.F.R. § 310.305(a). The rule is also broad enough to include contracts with sales representatives, pharmacy benefit managers, and managed care groups. In addition, it would make the manufacturer "responsible for ensuring that the contractors comply with these postmarketing safety reporting responsibilities." *Id.* The proposed rule would require that contracts between a manufacturer and a distributor include language to ensure that the distributor reports all adverse events to the manufacturer. *See, e.g.,* proposed 21 C.F.R. § 310.305(c)(2)(xi)(B).

These provisions substantially expand manufacturers' responsibilities and oversight concerning third party reporting of adverse events. We are concerned, though, that the scope and nature of these obligations is ill-defined and could create additional sources of potential liability for manufacturers. Moreover, FDA has offered no discussion or rationale for of its legal basis for expanding safety reporting to third party contractors. In general, both the form and substance of contracts between manufacturers and third parties has been the province of state law and private agreements.

Finally, the policy justification for these new reporting obligations is lacking. Third party contractors included in the scope of this rule are not likely to possess high-quality safety information, nor are they apt to add substantially to the quantity of safety information that is publicly available. We do not believe that perceived inadequacies in either the quantity or quality of reported safety information can be substantially attributed to the failure of third-party contractors

and subcontractors. As a result, we do not support the imposition of an additional indirect reporting stream to FDA.

Comment 4: SADRs and Always Expedited Reports
The proposed definitions of "suspected adverse drug reaction" (SADR) and "always expedited reports" are overly broad and will significantly increase the number of expedited reports, potentially diluting the value of such reports.

FDA's proposal requiring reporting of any "suspected adverse drug reaction" (SADR) is a significant shift in the agency's policy. *See* proposed 21 C.F.R. §§ 314.32 (c) and 314.80(c). Under current regulations, adverse events are reported if they are "associated with the use of the drug," which means "there is a *reasonable possibility* that the experience *may have been caused* by the drug." 21 C.F.R. §§ 314.32(a) and 314.80(a) (emphasis added).

Under FDA's proposal, an SADR occurs whenever "there is a reasonable possibility" that a product caused an adverse response. *See* proposed 21 C.F.R. §§ 314.32(a) and 314.80(a). FDA stipulates that a "reasonable possibility" transpires whenever a causal relationship "*cannot be ruled out.*" *Id.; see also* 68 Fed. Reg. at 12417 (emphasis added).

First, FDA has stated that one of its primary goals in proposing this rule is to bring the United States into greater agreement with the guidelines of the International Conference on Harmonization (ICH). *See* 68 Fed. Reg. at 12409. The agency's proposed definition for SADR, however, is too broadly drafted to foster the purposes of international harmonization in safety reporting. According to the most recent ICH guidance on the topic, "[a]ll noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions." *Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting*, ICH Harmonised Tripartite Guideline Draft, ICH Steering Committee (July 18, 2003)(ICH E2D ver 3.8). The ICH guidance explains that "a causal relationship between a medicinal product and an adverse event ... [should be] ...*at least a possibility*. *Id.* at 3/12 (emphasis added). FDA's proposal to adopt a standard based on finding "any possibility" of causation, no matter how "unlikely o remote," goes well beyond the more judicious standard established by ICH.

Second, we believe the proposed definition eliminates an important filter for the clinical trial reports received by manufacturers. By defining a "reasonable possibility" as one that "cannot be ruled out," FDA would seem to require that manufacturers serve more of a conduit function in collecting and forwarding reports to FDA. In clinical studies, investigators are required to report

all serous adverse events regardless of whether the event is deemed related to medication exposure. In oncology and critical care clinical trials, substantial volume of reports can be usefully triaged by highlighting those cases in which it is felt there is a reasonable possibility of causal association to therapy. Amgen has substantial and valuable expertise regarding the risks and benefits of approved and investigational products that can and should be utilized to evaluate safety data flowing from both clinical trials and commercial experience. We are confident that this experience is especially critical in the context of products typically administered to seriously ill patients. Where multiple diseases and perhaps multiple therapies – some of them of long duration – are at issue, careful analysis of both case level information and population level or aggregate safety data are appropriately employed for triage of adverse event reporting. We believe it is unproductive to segregate that analysis from the other investigative and monitoring functions sponsors are obliged to perform. For these reasons, we believe FDA should at the very least revise its definition of SADR to that currently recommended by ICH.

Finally, this proposed standard will significantly increase the number of premarket safety reports submitted to the agency, in part by including reports for SADRs where "the relationship to the drug is unlikely or remote." 68 Fed. Reg. at 12418. A retrospective analysis of data over a one-year period across all of Amgen's investigational products reveals that approximately 90 percent of serious adverse events were identified by investigators as *not* being reasonably associated with the study drug. Assuming a conservative 25 percent increase in submissions based on the proposed definition, it is possible that Amgen would be required to submit approximately 1,000 additional expedited reports per year. We believe that this projected increase in the flow of expedited safety reports will be burdensome for clinical investigators, the agency and industry. More importantly, these additional reports may actually decrease the value of information received by the agency by reducing the "signal to noise" against which the agency must discern safety signals. 3/

2/ For example, under the proposed rule, the number of reports we submit for vascular access thrombosis that occur in patients enrolled in an Aranesp (darbepoetin alfa) clinical study would increase substantially. Thrombosed vascular access is a common and well-documented occurrence in the dialysis population. As such, aggregate analysis and calculation of the rates of these events is necessary.

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Comment 5: Medication Errors
Extending manufacturers' reporting obligations to include virtually all types of medication errors intrudes on the practice of medicine and healthcare delivery, may exceed the agency's legal authority, and should only be required for those errors reasonably related to patient safety.

A key part of the proposed rule is expansion of the reporting system to include "actual" and "potential" medication errors. A "medication error" is defined to include "[a]ny preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer ..." *See, e.g.,* Proposed 21 C.F.R. § 310.305(a), 68 Fed. Reg. at 12472. Such events include those related to "professional practice" and healthcare "procedures and systems" ranging from prescribing and order communication, to dispensing, distribution, administration, monitoring and use. *Id.* An "actual medication error" involves an identifiable patient, while a "potential" error involves information or a complaint about the product name, packaging or labeling without the involvement of a patient. *Id.*

Amgen agrees that improved reporting of medication errors will help protect public health. However, the agency's proposed definition of "medication error" is extremely broad and may lead to a burdensome expansion of expedited reporting responsibilities without a corresponding increase in the quality of safety information available to the agency.

More significantly, we believe FDA's proposal intrudes on the practice of medicine and healthcare delivery. In essence, the agency is requiring manufacturers to monitor the prescribing practices of physicians, the dispensing practices of pharmacists, and the use and compliance of patients taking the manufacturer's drug or biologic product. It is simply not realistic to expect healthcare professionals, health care delivery organizations, and consumers to *voluntarily* report medication errors to a *manufacturer* when they have been reluctant or unwilling to voluntarily report this type of information directly to the FDA in the past.

Amgen is concerned that such an expansion requires reconsideration of the scope of the FDA's statutory authority for safety reporting requirements, an issue not discussed in the preamble to the proposed rule. FDA's legal authority to require reporting of adverse events is expressly tied to the standards under section 505(e) of the FDCA for withdrawal of approved drugs. *See* 21 U.S.C. § 355(k). Consequently, FDA can only require reports on matters directly related to determining whether the approved product continues to be safe and effective when

used according to the labeling recommended or suggested by the sponsor. *See* 21 U.S.C. § 355(e). The foray into the use of the product within the context of healthcare delivery and the practice of medicine is a questionable extension of that authority. *See APhA v. Mathews*, 530 F.2d 1054 (D.C. Cir. 1976) (FDA is confined to considering the safety of a drug within the approved labeling; were it otherwise, "[t]here would be almost no limit to the FDA's authority ...").

Amgen also believes that there is no reasonable justification for requiring manufacturers to submit expedited reports for medication errors that are not reasonably related to patient safety and for which no SADR has occurred. Under proposed section 310.305(c)(2)(v)-(vi), for example, expedited reports are required for both actual medication errors and potential medication errors. *See, e.g.*, 68 Fed. Reg. at 12474. Such errors include, among others, pharmacy errors unrelated to potential product deficiencies. Just as Amgen believes that manufacturers should not be charged with policing the practice of medicine, so we believe that manufacturers should not be charged with policing pharmacy practices such as "compounding and dispensing." *Id.* We are also concerned that the definitions of medication errors and potential medication errors are so broad that they would incorporate numerous product, product naming, product labeling, and product packaging complaints that are not plausibly related to product safety. We do not believe that such complaints reasonably justify expedited reporting.

Finally, we find the tripartite definitions of "medication errors," "actual medication errors," and "potential medication errors" to be needlessly confusing while serving no distinct regulatory purpose. Consistent with our view that only medication errors resulting in serious adverse events merit expedited reporting, we recommend that the category of "potential medication errors" be deleted.

Comment 6: Active Query
The definition of "active query" should be modified to allow for written queries that, in many instances, will improve both the quality and the quantity of safety reporting.

FDA's proposed rule requires that manufacturers investigate safety reports using "active query," defined as "direct verbal contact with the initial reporter of a ...SADR or medication error by a health care professional ...representing the manufacturer." 4/ *See, e.g.*, proposed 21 C.F.R. § 310.305(a). Active query involves, "at a minimum, a focused line of questioning designed to capture clinically relevant information ... including but not limited to, information

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4/ Amgen has for some time employed health care professionals in this context and we intend to continue this practice whether or not it is mandated by the final rule.

such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results." *Id.* FDA speculates that use of active query during initial contact with reporters "could eliminate or decrease followup time expended by manufacturers, applicants, and the agency." 68 Fed. Reg. at 12421. We respectfully disagree and are concerned that requiring direct verbal contact in every instance may actually prove damaging to the agency's goals of improving safety reporting.

Postmarket safety reporting is, in most cases, voluntary for healthcare professionals and organizations. Amgen has found that both the quantity and quality of follow-up information we receive is optimized when we are able to individualize queries to the needs and expectations of the reporting individual or entity. In particular, we have learned that physicians – and other health care professionals – prefer to provide written feedback to manufacturer queries at their convenience, usually after office hours. Based on our experience, Amgen is concerned that to insist on verbal contact, as required by the proposed rule, would be perceived by some practitioners as unacceptably intrusive and inconvenient. At stake in such circumstances is not just the quality of an individual safety report, but the manufacturer's relationship with a reporting health care professional whose participation in the reporting system is entirely voluntary. In addition, we have found that the quality of safety report follow-up information is often improved when written queries succeed in eliciting written responses, especially when those responses incorporate portions of the written patient record.

With respect to active query directed at patients, Amgen believes that follow-up of serious adverse events is predictably more fruitful if the sponsor communicates with the patient to clarify the contact information for the treating physician, who is then contacted to confirm the event initially described by the patient. In this way, greater depth of perspective can be accessed regarding comorbidities, additional medications, and event causality.

Finally, as discussed earlier, Amgen is concerned that telephone queries may be especially unacceptable to some practitioners in the context of changing and growing federal and state protections for the privacy of medical records and information. Many physicians may be concerned that conversations regarding patient cases may unwittingly intrude upon patient privacy; written queries, on the other hand, can be treated in a more deliberate fashion. As FDA is aware, the FDCA requires that reporting rules "shall have due regard for the professional ethics of the medical professional and the interests of patients" and Amgen is concerned both that the safety reporting system respect that statutory requirement, and that the system avoid creating – in physicians and other health care professionals who are voluntary reporters – any impression to the contrary. 21 U.S.C. § 355(k)(1).

Comment 7: Follow-up Reports
The proposed requirement to document and submit reports of all attempts to obtain a "full data set" is not productive and should be eliminated.

Amgen recognizes the importance of obtaining complete safety information whenever serious adverse events are reasonably related to an approved product. In our experience, however, good faith follow-up inquiries often fail to elicit from spontaneous reporters the range of information required for a "full data set" as defined in the proposed rule. *See, e.g.* proposed 21 C.F.R. § 310.305(a).

Amgen believes that it is inefficient and uninformative to require detailed chronological accounts of such unsuccessful attempts to complete data sets in 30-day follow-up reports. Although we support the requirement of appropriate follow-up efforts when suspected serious adverse events do not yield full data sets, we believe that a detailed manufacturer accounting of efforts to achieve such data sets in each individual case can be stored in individual adverse event report files, and be available for review during inspections.

Comment 8: PSRs/PSURs
FDA should accept either the MedWatch or CIOMS periodic reporting form and harmonize the information required with that suggested by ICH guidelines.

Amgen appreciates FDA's efforts to harmonize international safety reporting. *See, e.g.*, 68 Fed. Reg. at 12409, 12480. We agree with the agency that streamlined and consistent international safety reporting will increase the available, usable body of safety data even as it eases record-keeping and reporting burdens on manufacturers. To that end, Amgen suggests that FDA accept either MedWatch or CIOMS reporting forms for periodic safety reporting purposes and we recommend that the requirements for traditional Periodic Safety Reports (PSRs), Periodic Safety Update Reports (PSURs), and Interim Periodic Safety Reports in proposed sections 314.80(c)(3) and 600.80(c)(3) be modified accordingly.

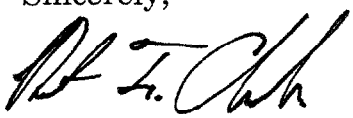
In addition, Amgen is concerned that these sections of the proposed rule require substantially greater information to be submitted than that suggested by any of the relevant ICH guidance documents. Such extra information includes United States-only appendices regarding non-serious, expected SADRs and reports from class action lawsuits. *Compare* 68 Fed. Reg. at 12481, *with* ICH Harmonised Tripartite Guideline, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, E2C (Nov. 6, 1996); *compare also* ICH Harmonised Tripartite Guideline, Addendum, *with* ICH E2C, Clinical Safety Data Management:

Periodic Safety Update Reports for Marketed Drugs (Feb. 6, 2003). As a result, we request that the requirements of the final rule be brought into accord with the ICH guidance.

Conclusion

Amgen appreciates the opportunity to submit these comments and looks forward to working with the agency on this important initiative to improve pharmacovigilance and the safety reporting system.

Sincerely,



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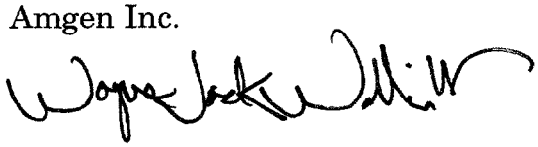

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