Wyeth Research

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To: Dockets Management Branch (HFA-305) **Date:** October 10, 2003
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852
Docket No. 03N-0016

Subject: Docket No. 00N-1484: Comments on March 14, 2003 Federal Register: Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule. 68 Fed.Reg. 12406

Dear Sir/Madam:

Wyeth respectfully submits these comments on the Agency's proposed rule covering "Safety Reporting Requirements for Human Drugs and Biological Products" ("proposed rule"). Wyeth is one of the world's largest research-based pharmaceutical and healthcare products companies, and is a leading developer, manufacturer and marketer of prescription drugs, biological products and over-the-counter medications. As such, Wyeth is responsible for conforming to the safety reporting requirements of 21 C.F.R. parts 312 and 314 – the regulations the proposed rule seeks to substantially modify.

Wyeth applauds the Agency's stated purpose in the proposed rule – to improve the Agency's and industry's ability to monitor the safety of drug and biological products. Wyeth shares this goal and is committed to continuously enhancing its safety reporting systems to improve the quality of reports as well as pharmacovigilance. In addition, as a global company responsible for compliance with worldwide safety reporting regulations, Wyeth supports any effort to harmonize regulatory requirements between FDA and other regulatory authorities.

Unfortunately, however, certain of the proposed requirements would neither improve the ability to monitor product safety, nor further harmonization. Rather, these proposals would require substantial additional resources, not only from the pharmaceutical industry but from the health care sector as a whole, without a corresponding value for either the patients taking our products or FDA. The resources that would be expended in implementing these proposed requirements could otherwise be applied to other, more useful safety activities. Attached are Wyeth's detailed comments discussing the provisions of the proposed rule where Wyeth believes FDA should reconsider its proposals because they do not meet its stated goals. In these instances, Wyeth has also provided suggested alternative approaches. By way of summary, Wyeth believes that FDA should re-consider the following proposed requirements:

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- Active query: Wyeth believes that FDA has overestimated the effectiveness of active query and underestimated the burden to companies of performing active query on all of the categories of reports proposed by FDA. Wyeth's experience with active query indicates that it is not always the best mechanism to obtain complete follow-up information. Wyeth suggests that FDA allow companies the flexibility to choose the follow-up method and timing that is most likely to obtain the best results in a particular circumstance – whether that be a phone call or a letter. Further, Wyeth's experience indicates that many reporters would find the proposed approach unwelcome and intrusive, with a substantial potential to create the unintended effect of discouraging reporting by health care professionals. If FDA imposes any requirements for active query, Wyeth suggests that FDA adopt a risk-based approach and limit such a requirement to health care professional reporters who are reporting serious and unexpected reports for products on the market for less than three years.

- Definition of "relationship cannot be ruled out": Wyeth disagrees with FDA's interpretation of the "relationship cannot be ruled out" standard in the context of clinical trial events. Wyeth encourages FDA to adopt the ICH interpretation of this phrase – meaning that there are facts or evidence to suggest a causal relationship – as opposed to FDA's interpretation that deems an event "related" when it is temporally associated with drug administration. Wyeth believes that FDA's interpretation will result in a substantially greater number of reports to both FDA *and investigators* than FDA has predicted, with little chance of detecting a safety signal sooner than it would otherwise be detected. This increase in reports will have the unfortunate result of diverting FDA, investigator and company resources away from effective signal detection activities.

- Expedited reporting of medication errors: Wyeth believes that FDA's proposal will not reduce hospitalizations due to medication errors. FDA has not explained how its proposal to require expedited reporting of medication errors would result in a change in prescribers' behavior that would actually reduce medication errors. If reporting of medication errors is required as part of the proposed rule, Wyeth suggests that this reporting be limited to periodic reporting that allows companies to analyze the data to determine if there are any trends or any need for modifications to product labeling. Wyeth also suggests that if FDA requires reporting of medication errors as part of 21 C.F.R. 314.80, FDA delete the requirement to report medication errors as field alerts under 21 C.F.R. 314.81(b)(1)(i), as it would be redundant.

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- FDA specific requirements for Periodic Safety Update Reports (PSURs): Wyeth supports FDA's proposal to adopt submission of PSURs in lieu of FDA periodic reports. However, FDA's proposal to require the submission of numerous, detailed FDA-only appendices to the PSUR would undermine and would divert substantial time and resources, and would divert resources away from more valuable pharmacovigilance activities. The proposed FDA-only appendices are so extensive that, in practical terms, they amount to another separate report in scope and complexity. Thus companies would be forced to prepare both a PSUR for worldwide reporting and a US specific document (in the form of appendices) for FDA. Wyeth encourages FDA to adopt a requirement for PSURs consistent with the ICH E2C guidance that FDA has endorsed.

- Definition of contractor: FDA's proposal would permit reporting to FDA only by an NDA holder. Currently, companies engage in a wide variety of contractual license arrangements where both a license holder and a non-license holder may report to FDA or other worldwide authorities. Wyeth encourages FDA to adopt the approach taken by the EMEA to require companies who engage in license agreements to enter into detailed agreements outlining the exchange and reporting of safety information. The specifics of which company reports to which regulatory authority should be left to the license partners to determine. Failure to adopt such a flexible approach would require Wyeth and other companies to undertake extensive re-negotiation of our contractual business arrangements with several dozen license partners at great cost with no apparent benefit.

- 30-day and 45-day reports: Wyeth believes that FDA's proposal to add two new reports – the 30-day and the 45-day report – would place an additional significant compliance and economic burden on industry without any corresponding safety surveillance benefit. Additionally, these FDA-only reports are a clear example of FDA deviating from its stated goal of harmonization. Wyeth strongly encourages FDA not to promulgate additional compliance reporting requirements that divert FDA and industry resources away from more important pharmacovigilance activities.

Wyeth also believes that FDA has made many positive suggestions in the proposed rule – such as adopting MedDRA coding and codifying the definition of minimum data set. Wyeth supports these and other proposals that meet FDA's and industry's goals of increasing the ability to monitor product safety and

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promoting harmonization. Wyeth's detailed comments on these and other positive proposals are also contained in the attached comments.

Finally, Wyeth strongly suggests that the Agency publish a re-proposal of this rule once it has considered and incorporated comments and proposals for alternative approaches to the proposed requirements. In light of the sweeping scope of the proposed rule and the fundamental nature of the changes needed to align the contents of the proposal with its stated goals, for FDA to process directly to a final rule could deprive the affected parties of a full opportunity for notice and comment. In contrast, re-proposal would allow for a meaningful opportunity to review and comment on the changes and alternatives to the current proposed rule that are required to achieve FDA's stated goals without imposing unreasonable burdens on affected parties.

We hope the Agency finds these comments useful.

Sincerely,

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Wyeth Comments on FDA Proposed Safety Reporting Requirements for Human Drug and Biological Products
68 Fed.Reg. 12406 (March 14, 2003)

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Re-Proposal	Wyeth suggests that the Agency publish a re-proposal of this rule once they have considered and incorporated industries' comments and proposals for alternate approaches to the proposed requirements. Wyeth believes that re-proposal is necessary due to significant comments on a number of key sections to the proposed rule and, when promulgated, the proposed rule will result in substantial changes to the current safety reporting regulations. Re-proposal would allow industry to comment on FDA's changes to the rule and would allow both FDA and industry the opportunity to develop the best possible approach to meeting FDA's stated goals in revising these regulations.
Medical Device Reporting Regulations 21 C.F.R. part 803	The proposed rule addresses both drug and biological products pre and post marketing safety reporting requirements. However, FDA has not incorporated medical device reporting (MDR) requirements in this proposed rule. MDR definitions and reporting time frames are significantly different from those of drugs and biological products. For companies that market both products, these differences require companies to maintain two different reporting systems for their products. Moreover, some products considered devices in the US are considered drugs in other countries, which provides for inconsistencies in how events associated with these products are reported to worldwide regulatory authorities. Wyeth encourages FDA to consider harmonizing the definitions and requirements for Medical Device Reports with those of drugs and biological products in the proposed rule.
ICH VI Draft Guidance FR 12409 "An addendum to the ICH E2C guidance has been prepared..."	Wyeth supports the Agency's stated purpose of harmonizing FDA requirements with worldwide reporting requirements. Wyeth already has a process in place to prepare and submit periodic safety update reports (PSURs) to worldwide regulatory authorities that complies with the requirements of the ICH E2C guidance document. To truly meet FDA's stated goal of harmonizing worldwide reporting requirements, Wyeth encourages FDA to adopt the exact requirements as ICH E2C for FDA submission of PSURs.

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	FDA requested public comment on whether it should adopt the recommendation in the ICH V1 draft guidance (67 FR 79939, December 31, 2002) (permit use of summary bridging reports, include an executive summary in PSURs, permit use of different versions of reference safety information within a reporting interval or use of the version in effect at the end of the reporting interval). Wyeth is generally supportive of the ICH V1 draft guidance, but encourages FDA to take into account the comments made to that guidance before codifying any of those proposed provisions into the requirements of 21 CFR 314.80.
Tabulation of non-serious expected individual case safety reports (ICSRs) FR 12409-12410, "In the Federal Register of August 27, 1997..."	FDA is proposing to codify a requirement that non-serious, expected ICSRs be submitted in summary tabulations in periodic reports. Wyeth supports this proposal because, if codified, it would eliminate the need to request a waiver not to submit ICSRs for non-serious, expected adverse experiences (AEs).
Submission of PSURs FR 12412, "FDA believes the changes recommended by ICH and CIOMS..." 314.80(c)(3)(ii) and 600.80(c)(3)(ii). Periodic Safety Update Report. 314.80(c)(3)(ii)(K) and 600.80(c)(3)(ii). Periodic Safety Update Report. Appendices.	In an effort to harmonize, FDA is proposing to require submissions of PSURs rather than FDA periodic reports for certain products and permitting submission of PSURs for all products. FDA supports the ICH E2C guidance document by stating that "[t]he PSUR recommended for postmarketing periodic safety reporting in the ICH E2C guidance provides regulatory authorities with a comprehensive overview of the safety profile of a product along with other relevant information such as estimates of worldwide patient exposure and worldwide marketing status of the product." FDA also states that harmonization is helpful as it allows companies to use their resources to "focus on the safety profiles of their product and not on the different reporting requirements of different regions." Wyeth supports this effort to harmonize worldwide periodic safety reporting requirements to allow companies to focus resources on pharmacovigilance and agrees with FDA that following

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314.80(c)(3)(iii) and 600.80(c)(3)(iii). Interim Periodic Safety Report (IPSR).	the ICH E2C guidance provides regulators with PSURs containing valuable information. As a participant in ICH, FDA had input into the ICH E2C guidance and therefore FDA's endorsement of the guidance is not surprising. However, FDA is proposing to require the submission of numerous, detailed FDA-only appendices to the PSUR. Addition of these appendices undermines FDA's stated goal of harmonization and would detract resources away from company pharmacovigilance activities. That is, the proposed FDA-only appendices are so extensive that, in practical terms, they amount to another separate report in scope and complexity. Companies would still be in the position of preparing a PSUR for worldwide reporting and preparing a US specific document (in the form of appendices) for FDA. In addition, Wyeth, and most other pharmaceutical companies, process line-listings and summary tabulations using electronic drug safety computer systems. The FDA-only appendices would require extensive re-programming and re-validation of these drug safety computer systems – FDA does not appear to have factored in these re-programming costs as part of their estimated burden to companies in implementing the proposed rule. Wyeth also requests FDA provide additional clarification on how the US-only appendices meet FDA's stated goal of increasing FDA's and industry's ability to monitor drug safety. FDA is suggesting that companies include an appendix that assesses whether the frequency of lack of effect reports during the reporting period is greater than would be predicted by the premarketing clinical trials. Wyeth discourages FDA from adopting this requirement for two reasons. First, routine comparisons between the "frequency" of postmarketing reports to the "frequency" of clinical trial reports does not add value because of the biases inherent in spontaneous reporting systems. Second, FDA had removed any increased frequency analysis requirements from its last revision of the safety reporting. Wyeth questions FDA's rationale for re-introducing an increased frequency requirement. Analysis of spontaneous reports to detect increased frequency does not yield accurate results as the frequency of reports of any event with any product is sensitive to (1) the age of a product in the market, (2) the volume of market exposure, (3) the reporting rate,

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	and (4) publicity associated with that product or event. Those factors are constantly changing over time. Assessment of the potential impact of these factors on the number of reported events for a given time period is often difficult and adjustment for these factors is usually imprecise or impossible. Therefore, a routine analysis of increased frequency does not give meaningful results. FDA is also suggesting an appendix containing information on resistance to antimicrobial drug products intended to treat infectious diseases. Presumably, FDA is proposing this requirement in the hopes of using it as a signaling system regarding lack of effect with products used to treat infectious diseases. Wyeth discourages FDA from adopting this requirement as this information will not be an accurate signal of lack of effect with these types of products. The proposed rule also sets forth a schedule for FDA PSUR submission in conflict with worldwide requirements. That is, FDA is proposing an interim periodic safety report (IPSR) containing many of the same requirements as a PSUR be submitted at 7.5 years and 12.5 years after approval. Again, it is unclear why FDA has proposed this requirement as it directly conflicts with their stated goal to harmonize worldwide periodic reporting requirements. Rather than developing these US specific requirements, Wyeth encourages FDA to adopt the ICH E2C guidance as written. Any modifications to the PSUR content or schedule should be made via the ICH process, in which FDA is an active participant, in an effort to reach agreement with worldwide regulators so that companies can prepare one worldwide PSUR.
Active Query **30-day Follow-up Report** FR 12413, "Another amendment	**<u>Active Query</u>** FDA states its view that active follow-up is more successful than the "passive approach" of sending reporters a letter requesting additional information, which, in FDA's view "results in

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would require direct contact with the initial reporter..." FR 12420-21, "Active Query." FR 12429, "Determination of Outcome, Minimum Data Set, and Full Data Set." 314.80(a) and 600.80(a). Definitions. Active Query. 314.80(c)(1)(iv) and 600.80(c)(1)(iv). Full Data Set. 314.80(c)(1)(v) and 600.80(c)(1)(v). Serious SADRs not initially reported by a health care professional.	limited acquisition of new information." FDA states its belief that requiring "active query" follow-up will result in higher quality reports to FDA. Therefore, FDA is proposing to require "active query" – defined as direct verbal contact with an initial reporter – for seeking additional information on a number of different types of reports made to companies including all serious Suspected Adverse Drug Reactions (SADRs). FDA has stated that they believe active query will decrease follow-up time and has stated that they do not believe that it is sufficient for manufacturers to send a letter to reporters requesting follow-up. FDA has specifically requested comments on whether there may be situations where it would be appropriate for manufacturers to seek follow-up in writing (as set forth in the CIOMS V report). Wyeth supports FDA's stated purpose of seeking high quality, complete information for individual case safety reports (ICSRs). Wyeth has had procedures in place for approximately two years requiring telephone follow-up with health care professional (HCP) reporters for certain, select AEs and products. Wyeth established the criteria for telephone follow-up using a risk-based approach, that is, serious and unexpected AEs for newly approved products on the market for less than three years. Based on this practice, Wyeth has found that telephone calls, although time consuming and resource intensive, do not necessarily result in better quality or more complete follow-up information. The success of telephone follow-up seems to depend on the physician's practice and the type of product – telephone follow-up appears to be more successful for specialty products. In many cases, letters have provided more information than telephone calls. Requiring telephone calls for the broad category of reports proposed in the rule distracts HCPs away from the more important activity of proactively identifying and evaluating safety signals and it may not lead to the highest quality of information. As an alternative, Wyeth encourages FDA to allow companies the flexibility to select the follow-up method – a telephone call or letter or both – that is likely to result in better quality and more complete information depending on the type of report and the product at issue. Both methods of follow-up have unique advantages and should be used in conjunction – during a telephone call, company representatives

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314.80(c)(1) and 600.80(c)(1) Determination of outcome, minimum data set, and full data set – (i)(A) Initial determinations.	can ask the HCP reporter clarifying questions but, in response to a letter, the reporting HCP may examine documents (patient charts) to answer questions in more detail than they may be able to do on the phone (such as provide laboratory test values). Allowing flexibility in the method of follow-up used would better meet FDA's goal of ensuring high quality, complete ICSRs. This flexibility would also be consistent with the recently published ICH E2D guidance document setting forth standards for post approval safety reporting and would also promote FDA's goal of harmonization. 68 Fed.Reg. 53983 (September 15, 2003). If FDA does impose a requirement that companies pursue active query, Wyeth encourages FDA to either (1) limit the requirement to only serious and unexpected SADRs for products approved within the last three years, or (2) utilize active query as part of risk management plans and require it only for products thought to require additional surveillance as part of these plans. Given the resources required to perform active query, resources that would otherwise be utilized to perform other safety surveillance activities, it is critical that FDA adopt a risk-based approach to active query by requiring active query only for products or in cases where it is likely to lead to important safety information, such as information that might result in a change to prescribing information. Either of Wyeth's proposals would accomplish this objective while FDA's approach in the current rule goes well beyond this scope and may have limited value. Wyeth strongly discourages FDA from requiring active query to obtain information for other, ancillary types of reports. For example, the proposed rule would require that companies use active query to obtain the minimum data set for an ICSR if all four elements are not available in the initial report. Such a requirement would require substantial company resources with very little foreseeable pharmacovigilance benefit. FDA states that this change is being proposed to clarify that "timely acquisition of information is critical to determine whether an SADR must be submitted to FDA." However, FDA has stated that one of its goals is to adopt a risk-based approach to safety reporting. If an applicant has three elements of a report – such as reporter,

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	SADR, product – but not the fourth – such as patient – it is unclear why obtaining the patient information by telephone should be a priority in all cases. If the SADR that is identified is non-serious, or for an older product with a well established safety profile, then resources should not be allocated to tracking down additional information on this SADR. That is not to say that the information should not be sought, but given the resources needed to perform active query, this requirement might be taking resources away from performing more valuable pharmacovigilance functions. In addition to unduly restricting companies' ability to obtain complete and quality reports, FDA's approach raises several other issues. First, the FDA proposed rule appears to require manufacturers to use active query when contacting HCP and *consumer* reporters. It is likely that if consumers receive calls from company HCPs, they will ask those HCPs medical and treatment questions that are better left to a discussion between consumers and their own physician. The company representative would be placed in an uncomfortable position of seeking information from the consumer, while not being able to respond to these questions (any response might run afoul of state licensure laws). That is, it seems that if FDA requires HCPs to contact consumers, FDA might be interfering with the practice of medicine. Even if a telephone call to a consumer were limited to gathering contact information for the consumer's HCP, companies would have no documentation that the consumer has given them permission to gather follow-up information from their physician. Wyeth suggests that FDA limit any requirement for active query solely to HCP reporters. For consumer reports, companies can continue to use letters to ask consumers for contact information for their HCPs and to obtain releases for gathering additional information from their physicians. Second, it is not clear if FDA has fully considered the impact of active query on reporters, and consequently the health care system.

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314.80(c)(2)(viii) and 600.80(c)(2)(viii). Supporting documentation.	➢ It is not clear that FDA had adequately accounted for concerns that reporters may have with compliance to the Health Insurance Portability and Accountability Act (HIPAA). Since the HIPAA has become effective, Wyeth has experienced some reluctance by HCPs to provide information on the phone based on concerns that doing so would run afoul of HIPAA requirements. While companies can and will explain to HCPs that HIPAA does not apply to information provided for regulatory reporting purposes, HCP's concerns may not be entirely assuaged, particularly in a phone conversation where they are unable to confirm the caller's identity. ➢ Before imposing any requirement for active query, Wyeth encourages FDA to seek input from HCPs on their perspective on the proposal. That is, it is not clear if FDA has considered the impact that requiring such a high volume active query will have on HCPs' willingness to continue to report safety data in the future. That is, the success of active query and the safety reporting system as a whole depends on HCP's cooperation and participation – cooperation FDA has no legal authority to require. As FDA is surely aware, HCPs are extremely busy and their first concern is not providing information to companies for FDA reporting. If HCPs receive a large influx of calls requesting additional information, they may be discouraged from future voluntary reporting to avoid follow-up calls. HCP time constraints underscore the need, as suggested above, for FDA to confine active query to cases where it is most likely to provide important information that might lead to prescribing information changes. If FDA imposes any obligation for companies to perform active query, Wyeth encourages FDA to take steps to improve the success of active query by actively voicing the importance of this policy, explaining HIPAA's scope, and encouraging HCP cooperation either through letters, conferences, and/or as public service announcements.

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	Third, FDA is proposing a requirement for companies to obtain hospital discharge summaries, autopsy reports or death certificates for serious SADRs. Wyeth strongly objects to this proposed requirement. Requesting this information raises significant privacy issues both in the US and ex-US. Obtaining this information is also extremely time consuming. It is not clear what safety information FDA hopes to obtain from these documents that wouldn't otherwise be available to counterbalance the issues associated with the proposed requirement. FDA is also proposing that for each expedited report companies start listing in the narrative of the report relevant documents maintained. The safety monitoring benefit of this enormous compliance burden is not evident. What does FDA plan to do with such a document list? If FDA plans to monitor compliance, all of the documents regarding ICSRs are already accessible to FDA via inspections. If FDA finds an issue with a company's follow-up procedures, document maintenance practices or any other safety reporting activities during an inspection, they have authority to take action against that non-compliant company. FDA should not impose an additional compliance burden on all of industry absent such a finding of non-compliance, as it will divert resources away from more important safety activities. This proposal also does not meet FDA's stated goal of harmonization – no other regulatory authority worldwide has requested this type of information or inclusion in any ICSR or aggregate safety report. Wyeth strongly discourages FDA from imposing this requirement that has no pharmacovigilance benefit and no benefit to the public health care system.
314.80(c)(2)(vi) and 600.80(c)(2)(vi). The 30-day follow-up report.	Finally, it is unclear if FDA has taken into account administrative difficulties with conducting telephone follow-up. For example, a telephone number may not always be available and, depending on the reporter's name, it may not be possible to track contact information. In certain countries, telephone follow-up by companies may be culturally unacceptable. Wyeth encourages FDA to adopt a requirement that a single, documented attempt to contact a reporter that provides the reporter with company contact information constitutes due diligence in pursuing active query.

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	Absent specific, detailed guidance this requirement is open to different interpretations by companies, FDA headquarters, and by FDA investigators who will audit companies' compliance to the requirement. **30-day Follow-up Report** FDA proposes that if a full data set does not become available via active query, the applicant must submit a 30-day report for serious and unexpected SADRs listing the reason why a full data set could not be obtained. FDA proposed that a 30-day report be submitted whether or not any new information has been received. It is not clear why FDA is contemplating imposing this new compliance burden as it does not meet any of their stated goals. Indeed, the proposal subverts FDA's goals as spending time writing a description of why obtaining a full data set was impossible, and diverts resources away from more important pharmacovigilance activities, such as obtaining complete reports. In addition, the requirement would result in an increased volume of reports that contain no new safety information. As such, requiring such reports would also take FDA resources away from more important activities. Furthermore, the proposal subverts FDA's harmonization goal as no other regulator, worldwide, requires such a report. And finally, as noted above, this type of information is already accessible to FDA via inspections. FDA should not impose additional burdens on all companies absent a finding of non-compliance.
Medication Error 314.80(a) and 600.80(a). Definitions. Actual Medication Error, Medication Error, Potential Medication Error.	The proposed rule has added definitions and reporting requirements for medication errors (actual and potential) not previously covered by the safety reporting regulations. FDA is proposing to require expedited reporting of actual and potential medication errors whether or not any SADRs were experienced or even whether any product was ingested. While Wyeth supports FDA's goal of reducing hospitalizations due to medication errors, Wyeth does not support the expedited reporting of medication errors in the absence of serious and unexpected SADRs. Wyeth does not believe that this reporting will result in meaningful enough data to actually reduce medication

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314.80(c)(2)(v) and 600.80(c)(2)(v). Medication error, Potential medication error. 314.80(c)(1)(iii)(B), (C) and 600.80(c)(1)(iii)(B), (C). Minimum Information for Reports of Actual Medication Errors that Do Not Result in an SADR/SAR and Minimum Information for Potential Medication Error Reports.	errors, much less hospitalizations due to medication errors. That is, FDA has not provided any link to how expedited reporting of medication errors would change the behavior of the medical communities. Nor has FDA provided any indication of how information reported to them will be communicated to the medical community in an attempt to reduce medication errors. FDA has also not provided any information on how it will encourage prescribers to report medication errors to pharmaceutical companies who will in turn report them to FDA. Based on FDA's own 2001 data, 42% of medication errors were caused by human factors such as knowledge deficit, performance deficit, miscalculation of dosage, transcription error, etc., yet FDA's proposal does nothing to reduce these human error factors. Unless FDA can provide a basis for how it believes reporting to FDA will change prescribers' behavior to reduce medication errors, it is not clear that FDA's proposal will have the desired positive impact. Moreover, since most medication errors are related to the practice and dispensing of medication, reporting and investigating medication errors should be the responsibility of health care providers and not the manufacturer. In addition to not meeting FDA's stated purpose, it is also unclear whether FDA has the statutory authority to include reporting of product complaints that do not involve actual identifiable patients (the proposed definition of a "potential medication error") within the context of the safety reporting rule. According to the definitions of medication errors as currently proposed, it appears FDA is requiring industry to monitor the prescribing practices of physicians, dispensing practices of pharmacists, and use/compliance of the patient taking the product. Requiring such monitoring is beyond FDA's statutory authority for the proposed rule. If reporting of medication errors is required as part of the proposed rule, Wyeth suggests that this reporting be limited to periodic reporting that allows companies to analyze the data to determine if there are any trends or any need for modifications to product labeling. Wyeth also suggests that

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	if FDA requires reporting of medication errors as part of 21 C.F.R. 314.80, FDA delete the requirement to report medication errors as field alerts as part of 21 C.F.R. 314.81(b)(1)(i). In addition, the proposed rule provides three distinct definitions for medication errors. An actual medication error is one that involves an actual patient, whether or not a product was administered. A medication error is defined as a "preventable event" that may cause or lead to inappropriate medication use. A potential medication error is, essentially, a product complaint about the product name, labeling, or packaging similarities that does not involve a patient. The use of these various definitions is confusing, especially as FDA is proposing that all of the categories of medication errors be reported in the same way. Wyeth suggests that FDA provide one definition covering all of the concepts expressed, or limit the definitions to "actual medication errors" and "potential medication errors." The proposed rule also requires an applicant to "immediately determine" the minimum data set for actual and potential medication errors by using active query. As discussed above, Wyeth strongly objects to requiring active query for these ancillary types of reports. Wyeth also requests that FDA clarify what is meant by "immediately determine" and what would qualify as due diligence in gathering a minimum data set. Finally, FDA's proposal for reporting medication errors does not meet FDA's goal of harmonization. Wyeth suggests that FDA take the proposal through the ICH process in which FDA is a partner, to reach international consensus on how to address this issue globally.
Licensed Physicians Responsible for Report Content FR 12413, "Another amendment	FDA is proposing a requirement that licensed physicians be responsible for the content of safety reports, citing as its rationale that while certain companies already follow this practice, other companies have "postmarketing safety reports prepared and submitted by clerical personnel with no health care training." FDA's statement ignores common industry practice. Wyeth has

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would require that a licensed physician..." 314.80(c)(4)(iv) and 600.80(c)(4)(iv). Reporting Format.	physicians on staff responsible for the review of serious ICSRs; all Wyeth ICSRs are prepared and reviewed by health care professionals, ie, nurses and pharmacists. Wyeth encourages FDA to follow its stated goal of taking a risk based approach to safety reporting and limiting physician review to serious and unexpected or serious SADRs. In addition, Wyeth encourages FDA to replace the word "licensed" with the term "medically qualified." The term "license" is unique to the US and indicates the responsible physician would need to maintain licensure in one or more US states. Some physicians, while no longer maintaining an active medical license or active medical practice, may be medically qualified and have previously practiced before joining industry. No longer maintaining an active "license" does not reduce their ability to provide medical input into safety reports.
SADRs with Unknown Outcome FR 12414, "Unexpected SADRs with unknown outcome." 314.80(a) and 600.80(a). Definitions. SADR/SAR with unknown outcome. 314.80(c)(1)(ii) and 600.80(c)(1)(ii). SADRs/SARs with unknown outcome. 314.80(c)(2)(iii) and	FDA is proposing to require active query to obtain the outcome for all SADRs with an unknown outcome and proposing that applicants submit 45-day reports of SADRs with unknown outcomes if the attempts at active query were unsuccessful. Wyeth's comments on active query are summarized above. Again, Wyeth strongly discourages FDA from promulgating any requirement for active query on these types of ICSRs. Wyeth also objects to creating a new category of report and a new reporting time frame for cases that can be handled under existing definitions and regulations. That is, SADRs with unknown outcomes can be categorized as either serious or non-serious based on the usual outcome of the event. Imposing a requirement to submit these reports in 45 days would be an additional compliance burden on industry without any corresponding safety surveillance benefit. Creation of a new report type would require companies to re-program and re-validate their drug safety computer systems to accommodate such a reporting time frame. Furthermore, companies would have to develop additional monitoring systems to ensure timely submission of these reports. By contrast, Wyeth's proposal would meet FDA's goal of learning of potentially serious SADRs on

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600.80(c)(2)(iii). Unexpected SADR/SAR with unknown outcome.	an expedited basis without creating an unnecessary additional compliance burden for industry. Moreover, FDA's use of "outcome" in the section interchangeably with "seriousness" is confusing. By proposing that manufacturers and applicants use active query for SADRs with unknown outcomes and creating a new category of reports for these SADRs, FDA is, essentially, introducing another seriousness criteria. Such a requirement is contrary to FDA's stated goal of harmonization.
Always Expedited Reports FR 12414, "Always expedited reports..." FR 12432, "The proposal provides that the Agency could make a new SADR the subject of an always expedited report." 314(c)(iv) and 600.80(c)(iv). Always expedited reports.	FDA is proposing to require expedited reporting of certain types of SADRs whether or not the SADR is unexpected. It is not clear how submitting these SADRs, if expected, would result in improved safety information. FDA states that it needs to evaluate these reports on an expedited basis to determine if there is a qualitative or quantitative change in the nature of the reports. A single expected report cannot – even if submitted on an expedited basis – provide the data needed to determine whether a new study or a labeling change is warranted. Rather, companies are already required to evaluate in the overall safety evaluation section of a PSUR whether or not there has been a change in the characteristic of listed events (*see* proposed 314.80(c)(3)(ii)(I) at 12482). When the event is expected, an aggregate data review is much more likely to provide FDA with informative safety information than expedited ICSRs. As a result, Wyeth encourages FDA not to require "always expedited" reporting for these SADRs. Moreover, FDA can and has asked companies to submit certain types of AEs, whether expected or unexpected, for products on an expedited basis under special arrangement when FDA wants more information regarding the product and the AE in question. This tailored approach, used when an issue is raised, allows FDA to get information it needs without unduly burdening companies. By contrast, FDA's "always expedited" list is not tailored to a specific concern about a specific product and, as such, is overbroad. The list of conditions that trigger always expedited reports should be negotiated on a product-by-product basis as part of an overall approach to risk

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	management activities. In addition, the terms on FDA's always expedited list are of varying specificity. Some of the events listed are very general (seizure) or are subject to interpretation ("acute" liver failure). This issue will be exacerbated as the list is translated into other languages. If any form of an always expedited list is adopted, Wyeth requests that FDA provide more guidance on the scope of the events listed to clarify exactly what events FDA is seeking to be reported on an expedited basis. Wyeth suggests that expedited reporting for this list be based on the verbatim term used by the reporter. That is, if a reporter reports "acute liver failure," the SADR would fall under the scope of the always expedited list, but if the reporter reports "serious liver failure," the SADR would not fall under the scope of the always expedited list. As an alternative, Wyeth suggests that FDA use the actual MedDRA term for the medical conditions they want expedited. FDA's proposal for an always expedited list does not meet its stated goal of harmonization, as other worldwide regulators have not adopted similar requirement. Finally, the preamble suggests that FDA might add additional SADRs to the always expedited report list via a guidance document. Wyeth objects to adding a substantive requirement – that is, a new type of always expedited report – in the absence of notice and comment rule making. FDA's own good guidance practice regulations state that "guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA." 21 C.F.R. 10.115(d)(1). Yet, FDA is proposing a requirement contrary to these regulations by suggesting that it can add reporting "responsibilities" via a guidance document. Wyeth suggests that FDA not permit additions to the always expedited list in a manner that is inconsistent with its own regulations.
Relationship Cannot be Ruled	FDA is proposing to replace the definition of the term AE with the term SADR. An SADR is

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Out FR at 12417-18, "The phrase 'the relationship cannot be ruled out' clarifies..." 312.32(a). Definitions. Suspected Adverse Drug Reaction.	defined as "a noxious and unintended response to any dose of a drug (or biological) product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out." FDA explains that the proposed rule would require manufacturers to consider an event "related" (ie, defined as an SADR) if it is classified as "remotely related" or "unlikely related" because these terms indicate that a causal relationship between the product and the event cannot be ruled out. FDA has acknowledged that this will result in certain events that are most likely attributable to a patient's underlying disease state being considered a "related" event though the event is unlikely to be due to use of the drug. As an example, FDA cites death from cancer of a patient in a clinical trial studying cancer treatments. FDA states that this definition is consistent with the ICH E2A guidance. FDA has specifically requested comments on whether: • Its interpretation of the ICH E2A phrase "relationship cannot be ruled out" as set forth in the proposed rule is the same as manufacturers' interpretation of that phrase; • The proposed definitional change will result in an increase in reporting beyond that identified by the Agency in the proposed rule; • There are alternate reporting mechanisms that will minimize over-reporting while assuring that SADR reporting is not compromised (ie, propose noting in the study protocol those events that would not be subject to expedited reporting because they are known consequences of the disease being studied). Wyeth has several comments on FDA's new definition and the above questions. First, Wyeth does not agree with FDA's interpretation of the ICH E2A phrase "relationship cannot be ruled out." FDA has taken one line from the ICH definition and in doing so has taken the line out of context. The phrase "the relationship cannot be ruled out" is taken from the ICH definition of the term adverse drug reaction (ADR). ICH E2A defines an ADR as "all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

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	The phrase 'responses to medicinal products' means that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out." 60 Fed. Reg. 11284, 11285 (March 1, 1995). FDA's example of "cannot be ruled out" as disease progression – ie, "[i]n some cases an adverse event may most probably have occurred as a result of the patient's underlying disease and not as a result of the drug, but since it cannot usually be said with certainty that the product did not cause the adverse event, it should be considered an SADR" – indicates that under the proposed rule almost all serious AEs from clinical trials will have to be considered as related. This is not a balanced representation of the ICH concept of relatedness for clinical trial events. ICH E2A clarifies that the phrase a "reasonable causal relationship" means that "there are facts (evidence) or arguments to suggest a causal relationship." 60 Fed.Reg. at 11286. FDA's example of disease progression is exactly the type of events that would not, in most instances, be considered related under ICH E2A because the disease progression is evidence that suggests that there is not a causal relationship. If FDA's rule is implemented as drafted with a causal relationship existing if "the relationship cannot be ruled out," then the consequence would be that any AE that has a temporal relationship to administration of a drug should be regarded as an ADR, given that a temporal relationship inevitably means that the role of the investigational product in the causation of an AE cannot be totally excluded. In practice, this would mean that virtually all reported AEs would then be regarded as ADRs, thereby completely negating the distinction drawn by ICH between the two terms. First, this interpretation of "relationship cannot be ruled out" is a critical issue if the FDA wants to meet its stated purpose of harmonizing global reporting requirements. Indeed, not only is FDA's interpretation inconsistent with ICH, but it also conflicts with the EU Clinical Trials Directive 2001/20/EC Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use

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	(April 2003) that adopts ICH terminology and indicates that the expression "reasonable causal relationship" means that there is evidence or arguments to suggest a causal relationship. *See Annex* 1. This proposed conflict between the FDA and worldwide safety requirements, especially in terms of basic definitions and interpretations in causality, will impede the ability of companies to manage the safety of their products on a worldwide basis. The confusion resulting from these differences could lead to delay in identification of important safety signals and ultimately to a diminished ability of the organization to protect patients. Wyeth suggests that the FDA adopt the definition of ADR set forth in ICH E2A and suggests FDA adopt the ICH E2A concept that there is a "reasonable possibility" of a causal relationship if there are positive reasons for such a judgment rather than on the basis of simply being unable to totally exclude a product's role. Second, FDA's interpretation of "reasonable possibility" would result in almost all serious and unexpected AEs from clinical trials being reported and unblinded not only to FDA but also to participating investigators. This will adversely impact the ability of investigators to conduct clinical research, as their already strained resources will be overwhelmed dealing with the administrative burden of this increased volume, with relatively little, if any, added value in terms of protecting subject safety. Wyeth believes that this increased reporting goes beyond that anticipated by FDA in the proposed rule. By Wyeth's estimate the proposed requirement would result in, at a minimum, a doubling of expedited clinical trial reports. Wyeth questions whether FDA has the resources to process and analyze these additional SADRs or if the requirement is imposing a compliance burden without a corresponding safety surveillance benefit. Wyeth encourages FDA to modify the companies' reporting responsibilities pertaining to participating investigators. Wyeth suggests that instead of individual investigator letters, companies be permitted to provide periodic reports of line-listings to investigators and investigators be permitted to provide these periodic reports (rather than ICSRs) to their Institutional Review Boards.

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	Third, FDA has stated that the proposed SADR definition is intended "to minimize situations in which an adverse event that proves ultimately to be due to a drug or biological product is not reported as soon as possible to the agency because the etiology of the adverse event is attributed to the patient's underlying disease (ie, a patient's hepatic deterioration is judged to be related to the patient's viral hepatitis and not to the hepatotoxicity of the drug the patient received)." 68 Fed.Reg. at 12418. In short, FDA wants to improve signal detection. This is the same concern that FDA expressed in its 1994 proposed rule where FDA suggested modifications to its IND reporting regulations based on recommendations made by an FDA task force convened to analyze whether deaths and serious injuries that occurred with the compound FIAU might have been prevented. See 59 Fed.Reg. 54046 (October 27, 1994). The task force found that "an overview of the data, in which deaths and serious adverse experiences were analyzed cumulatively, and with the hypothesis that the events were drug related, was not produced and thus was not available for use by the sponsors, the principle investigators, or FDA reviewers. Rather, the analysis performed focused on each individual event and determined a plausible explanation, other than drug toxicity, for each occurrence. The task force recommended that, to detect similar patterns of events reflecting toxicity in future studies, sponsors should conduct cumulative analysis with a systematic consideration of the possibility that the adverse events are caused by the investigational drug." *Id.* FDA's current proposal is contrary to the recommendation of its task force and will not address FDA's concern of improving signal detection, rather, FDA's proposal may detract from signal detection as companies focus resources and attention on individual case processing. Wyeth recommends FDA (1) as stated above, adopt the ICH E2A interpretation of "a reasonable possibility," (2) follow the recommendations of the FIAU task force and require that companies

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	have processes and procedures in place to periodically review safety data to detect "signals," and (3) if needed, based on the specific trial and disease entity being treated, specify in the respective protocols any events that should be submitted in an expedited fashion regardless of causality. The latter decision should be made with consultation between FDA and the sponsor. Fourth, FDA's proposal minimizes the investigator's role in the study as the individual at the patient's bedside with the facts and clinical medical judgment to determine whether or not an AE is related to the administration of an investigational drug product. That is, if FDA promulgates a safety rule that, in practice, results in every serious AE being related, there is no point in having the investigator provide their opinion on drug relationship. And, as such, investigators' responsibilities in a clinical trial are substantially diminished as is a company's ability to use their expertise to determine the safety profile of their drugs. Fifth, FDA's proposal is particularly difficult to defend, from a safety standpoint, for studies with marketed products. The safety profile of a marketed product is better established than an investigational compound. Therefore, Wyeth questions the benefit of assuming the vast majority of serious SADRs in postmarketing studies are related. In the current regulations, FDA requires expedited submission of a smaller category of cases from postmarketing studies than spontaneous reports generally – ie, FDA only wants cases that are thought to be related. Under the proposal, this distinction would no longer exist and, as a practical matter, FDA is requesting all serious and unexpected spontaneous and postmarketing study reports be expedited. FDA has not cited any rationale or basis for eliminating this distinction. Finally, Wyeth questions why FDA is proposing a new term and acronym rather than adopting the term adverse drug reaction (ADR) already used by ICH E2A. To promote consistency between pre and post approval safety reporting terms, ADR was also the term used by ICH in the recently issued ICH E2D document providing definitions and standards for post approval

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	reporting. It is not clear what value in terms of case quality or improved safety surveillance the new term adds, and use of the new term does not promote FDA's stated purpose of harmonization. Therefore, Wyeth encourages FDA to adopt the ICH term ADR.
Disclaimer FR 12418, "Some members of the public have maintained..." 314.80(i) and 600.80(j). Disclaimer.	FDA has specifically requested comment on whether its current disclaimers are sufficient to protect reporters from use of SADR reports in product liability actions, or whether additional safeguards against misuse should be implemented. FDA has asked whether it should consider prohibiting use of SADRs reported to FDA in product liability actions. The current MedWatch disclaimers are insufficient to protect reporters from use of SADRs in product liability actions. ICSRs routinely form the focal point of plaintiffs' lawyers' arguments in these cases; the disclaimer is not an effective defense against this use. Wyeth encourages FDA to include a requirement prohibiting use of ICSRs as evidence in product liability actions.
Minimum Data Set FR 12420, "Minimum data set." 21 CFR 312.32(a), 314.80(a) and 600.80(a). Minimum data set.	In the proposed rule, FDA codifies the requirement that a minimum data set (identifiable patient, reporter, SADR and product) must exist prior to submitting an ICSR to FDA. Wyeth supports FDA's codification of this requirement. Wyeth requests that FDA provide additional clarification on what constitutes an identifiable patient in hearsay situations and a literature context. Wyeth proposes that an identifiable patient is defined as a specific patient on which a company can perform follow-up, ie, the details of a hearsay report or a literature report must be sufficient so that companies are able to tie a specific event to a specific patient that can be identified in requests to reporters for follow-up information.
Unblinding ICSRs from Clinical Trials FR 12420, "As noted previously,	As discussed above, FDA's definition of "reasonable possibility" would result in a significant increase in the number of expedited clinical trial ICSRs being submitted to FDA. The preamble states that FDA would expect any ICSRs submitted to FDA be unblinded, unless specific alternative arrangements have been made with FDA. This would result in companies being

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for each ICSR a suspect product would be required to be identified. Reports from blinded clinical studies..."	required to unblind a significantly higher number of clinical study ICSRs and this proposed practice could have a negative impact on the evaluation of study outcomes. This is particularly true in studies where the target population has significant underlying and/or fatal diseases. FDA states that its position is consistent with the ICH E2A guidance. However, since the FDA proposed rule would result in a greater number of "related cases" than under the ICH guidance, the number of cases subject to unblinding is also greater than that contemplated by the ICH guidance. As noted above, Wyeth suggests that FDA harmonize its interpretation of "reasonable possibility" with ICH, which would make excessive unblinding no longer an issue. FDA specifically requested suggestions on alternate unblinding mechanisms. If FDA maintains the proposed interpretation of "reasonable possibility," then FDA should not require unblinding of ICSRs. If the sponsor or FDA detects a trend, then FDA could ask for the ICSRs to be unblinded.
Spontaneous Report 314.80(a) and 600.80(a). Definitions. Spontaneous Report.	Wyeth supports FDA's proposal to define the term "spontaneous report" as unsolicited information. FDA states that it believes that reports from class action law suits are most likely duplicate information and should not be treated as either study or spontaneous reports. Nonetheless, FDA is proposing to require that summary information from these reports be submitted as an appendix to the PSUR. To prepare this "class action law suit" appendix, companies will still be required to enter this information into their databases. This data entry will take time and resources that would be better spent focusing on other reports and safety surveillance activities. Wyeth suggests that FDA not require submission or databasing of this information in any format. At the very least, FDA should not require submission or databasing of this information for products withdrawn from marketing (even if the application has not been withdrawn or withdrawn and not published in the federal register), as submission is unlikely to provide any important new safety information.

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Company Core Data Sheet FR 12422, "Company core data sheet..."	Wyeth requests FDA clarify whether it is requiring core data sheets or core safety information for each drug product. Wyeth suggests that any such requirement be limited to chemical entities regardless of dosage form or indication, rather than drug products. Wyeth also requests that when setting an implementation date for this requirement, FDA allow companies sufficient time to ensure that they have core data sheets for all products.
Determining Expectedness FR 12423, "SADRS that are mentioned in the US labeling (investigator's brochure for proposed 312.32(a)) as occurring with a class of drugs..."	Wyeth requests FDA clarify what they mean by occurring with a class of drugs. That is, if FDA requires that specific events are listed in a product's label as associated with the product because those events have been seen with other products of the same class, that FDA does not intend to make those events unexpected. For example, "as with other drugs of this class, drug X may cause Y" – if a company received a report of Y with drug X, Y would be considered an expected event for that drug. By contrast, "class X drugs may cause Y" – if a company received a report of Y for drug X, Y would be considered unexpected for that drug. Please clarify if these examples correctly reflect FDA's intent with this proposal.
Cross Reporting FR 12425, "Current IND safety reporting regulations at 312.32(c)(4) state that a sponsor of a clinical study..."	FDA appears to be clarifying that for drugs marketed in the US, reports are submitted under the IND reporting regulations (312.32) and then to the IND reviewing division only if the study is conducted under an IND. For other postmarketing studies, applicants would only be responsible for following the requirements in 314.80 and 600.80. Wyeth supports this clarification. Wyeth further encourages FDA not to require investigator letters for marketed products even if conducted under an IND, unless the investigation is for a different patient population or different indication than that approved. In the alternative, Wyeth suggests FDA allow periodic line-listings be sent to investigators rather than individual letters. For marketed products, any significant new safety information will be evaluated by companies as part of their signal detection process and if need be, will be incorporated in the product label. As such, the requirement for notifying participating investigators on a case-by-case basis of serious, unexpected, related events occurring

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	in that postmarketing trial does not provide them with valuable new safety information as they do not have the data to put the individual report in perspective and cannot perform meaningful signal detection. Wyeth also requests FDA clarify their expectations for cross reporting to investigators participating in different trials under the same IND or different INDs with the same active moiety.
Review of Internet Materials FR 12426, "FDA is proposing to add electronic communications..."	The FDA preamble clarifies that companies are only responsible for reviewing internet sites that the applicant sponsors for possible AE information. Applicants are not responsible for reviewing internet sites it does not sponsor. However, the preamble goes on to state that if an applicant "becomes aware of safety information on an Internet site that it does not sponsor, the applicant would be responsible for reviewing the information." Wyeth requests guidance on what would constitute an identifiable reporter and patient for AEs encountered via all internet sites. Please confirm that a chat room "nickname" would not constitute identification of a valid patient or reporter. Wyeth strongly encourages FDA not to require reporting of information from "chat rooms" as there is no way to conduct confidential follow-up.
Incomplete ICSRs FR 12430, "In some cases, the agency has received incomplete safety reports for serious SADRs, making interpretation of their significance difficult."	Wyeth agrees that some ICSRs are incomplete, that this is unfortunate, and that it also makes interpretation difficult. Wyeth supports FDA's goal of improving the completeness and quality of ICSRs. However, the completeness of ICSRs is not entirely within a company's control. Often, despite best efforts including active query, companies are unable to obtain complete data from reporters. Reporters may refuse to provide that information or simply be unavailable or too busy to give additional information. In drafting the final rule, FDA should take into account these realities of seeking follow-up information. FDA should not impose new, overreaching substantive information gathering and reporting requirements that may result in taking resources

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	away from the very safety surveillance activities FDA and most applicants are striving to improve.
Lack of Efficacy FR 12431, "Lack of efficacy reports."	FDA's proposed rule would no longer require submission of individual lack of efficacy reports. Rather, it would require expedited submission of information sufficient to consider product administration changes, which the preamble appears to imply includes reports of lack of efficacy with a drug/biological product used to treat a life-threatening disease. In addition, the proposed rule would require an analysis of lack of effect reports in the PSUR. FDA should clarify whether it expects reporting of lack of effect reports that result in serious outcomes. These would currently be reported as ICSRs containing serious AEs (on an expedited basis if also unexpected). The European Union's guidance on Pharmacovigilance, Volume 9, supports this approach. Volume 9 states "in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes. Judgment should be used in reporting." Wyeth requests FDA clarify whether it intends to harmonize with this requirement.
Contractors FR 12434-35, "Contractors and Shared Manufacturers." 314.80(c)(2)(x). Submission of safety reports by contractors. 600.80(c)(2)(x). Submission of safety reports by contractors and shared manufacturers.	FDA has proposed a new definition of contractor to include any license partner of the applicant. FDA has then proposed a requirement that contractors submit SADR information to the applicant within five business days. If implemented, this requirement would impose an enormous, unnecessary burden on industry and unwanted results for FDA because it precludes companies entering into arrangements where one company reports on the other's behalf unless the reporter is also the NDA holder. This is a change from current practice where individuals in license agreements (who's name appears on a product label) may report either to the NDA holder in 5 days or to FDA in 15 days. Currently, companies engage in all manner of license agreements. One company may hold the NDA, while another company holds marketing authorizations worldwide. In this case, one

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	company may report worldwide and maintain the global database, even if they are not the NDA holder. Another example is a larger company entering into a licensing arrangement with a smaller company that holds the NDA. Again, in this case, it may make more sense for the company who is not the NDA holder to report to FDA as they have the resources, systems and processes in place to ensure reporting and safety surveillance. Presumably, FDA has two goals in proposing the new requirement (1) ensuring that all companies involved with a particular product (whether NDA holder, a license partner, or a company appearing on a product label as a manufacturer, packager or distributor) have responsibility for collecting and reporting SADR information, and (2) that companies engaged in licensing agreements discuss and document how worldwide information will be collected, processed, and reported to FDA. As such, FDA should adopt the approach set forth in European Union's Pharmacovigilance guidance document, Volume 9. Volume 9 requires companies who engage in license arrangement to have in place detailed safety agreements setting forth each company's responsibility for collecting, exchanging and reporting safety data. Volume 9 reads as follows: "When marketing authorizations holders are involved in relationships including those that are contractual, arrangements for meeting pharmacovigilance obligations should be clearly specified in writing to the competent authority at the time the authorization is granted, and subsequently when any changes to the arrangement are made. ...Where co-marketing arrangements exist, the marketing authorization holders may enter into practical arrangements, in order to meet their obligations. Such arrangements must be notified in writing to the competent authorities when the authorization is granted and subsequently when any changes to the arrangement are proposed. Such arrangements for joint pharmacovigilance data collection and analysis are acceptable to the competent authorities, provided the market authorization holder confirms in writing to the competent authority that it understands that legal responsibility in respect of pharmacovigilance rests with it.

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	...where the marketing authorization holder has entered into relationships with a second company for the marketing of, or research on, the suspected product, the clock starts as soon as any personnel of the marketing authorization holder receives the minimum information; however, whenever possible, the time frame for regulatory submission should be no longer than 15 calendar days from first receipt by the second company and explicit procedures and detailed agreements should exist between the marketing authorization holder and the second company to facilitate achievement of this objective." Wyeth encourages FDA to take a similar approach. FDA should not regulate the exchange times between companies, but rather should only define the final outcome of submission to FDA. Rather than adopting the "5 day rule," Wyeth recommends that FDA require companies who engage in licensing arrangement to develop specific safety reporting agreements that detail each party's obligations and responsibilities to ensure that FDA requirements are met. Wyeth proposes that the reporting time frame between the two companies (collectively) to FDA be 20 calendar days (since FDA currently allows for 5 days from company 1 to company 2 and 15 days from company 2 to FDA, FDA is already receiving these reports in 20 days) or "whenever possible" no longer than 15 calendar days from first receipt by the company 1. The details of which company actually reports to FDA should be left to negotiations between the license partners. This proposal would meet FDA's stated goal of harmonization and high quality reporting while permitting companies the flexibility to enter into arrangements that meet their business needs. Finally, Wyeth suggests that any requirement FDA imposes on contracting parties in the final rule should apply *prospectively only* – that is, companies should *not* be required to re-negotiate past license arrangements. Re-negotiating existing agreements would impose a substantial burden on industry.

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Semiannual Submission of ICSRs FR 12442-43, "Semiannual submission of individual case safety reports." 314.80(c)(3)(v) and 600.80(c)(3)(v). Semiannual submission of ICSR.	FDA specifically sought comments on semiannual submission of ICSRs. Wyeth has several comments on FDA's proposal. First, any additional, batched submission of ICSRs should await implementation of E2B. Submission of paper copies of ICSRs will be a burden for companies without providing FDA any usable data to analyze. That is, the volume of ICSRs received from all companies will be so great that it is unlikely that FDA will have the resources to load the information into their database. Until FDA can database these reports, it is unlikely that FDA will be able to use these reports to perform pharmacovigilance. Second, Wyeth recommends a time limit to submitting ICSRs of five years from the date of approval. From a pharmacovigilance perspective, the usefulness of submitting all ICSRs every six months is reduced the more experience gained about a drug after commercial marketing. This is particularly true as information on ICSRs is already being analyzed and submitted as part of the PSUR. Third, Wyeth suggests that any submission of ICSRs be incorporated as part of the PSUR schedule finally adopted by FDA. Finally, Wyeth questions why FDA is proposing to require submission of serious, expected ex-US ICSRs when that requirement was removed from the regulations in 1985. These ICSRs will be summarized as part of the analysis in the PSUR. In the absence of a signal, Wyeth questions the public health monitoring value of submitting any expected ICSRs. Rather, Wyeth encourages FDA to harmonize requirements by adopting ICH E2C recommendations of submitting line-listings and tabulations for non-expedited reports as part of the PSUR rather than submitting ICSRs.

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Identifiable Patient FR 12445, "Single form for each identifiable patient."	FDA's preamble states that a separate form is required for each identifiable patient in a scientific article (that is, six FDA Form 3500As should be completed for an article describing six patients). Wyeth questions the value of creating six reports if only the minimal criteria for an AE is available and no information is available to differentiate the six patients from each other. That is, a literature article may reference six patients who experience myocardial infarction with drug x. No further information (age, sex, demographics) is provided for any of the patients. Wyeth requests FDA clarify whether they believe that in this example the minimum criteria for an AE report are met. In the example, there is no additional information to distinguish one patient from the next. The report of the CIOMS V Working Group suggested that one case be created to capture this information and that the number of patients potentially involved be noted in the narrative. If additional information is obtained, additional cases may be created when there are details regarding each of the patients. Wyeth recommends that FDA adopt this approach. There is no added safety surveillance benefit to creating multiple cases when only minimal information is available for a group of reports mentioned in a literature article particularly since the literature article is being submitted with the report. Wyeth also requests that FDA provide additional clarification on what constitutes an identifiable patient in the context of published literature. As in the case of information reported via the internet, the information available on individual patients in literature articles is often very limited. Wyeth suggests FDA adopt a definition of identifiable patient that incorporates the concept of a unique individual on which the company can perform follow-up.
NDA/BLA Annual Report FR 12447, "Current 314.81(b)(2) requires applicants of marketed products..."	Wyeth supports the proposal to delete the requirement of requiring safety information in the NDA and BLA annual reports. Wyeth agrees with the Agency that this information is duplicative of the information provided in periodic safety reports.

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Implementation FR 12449, "Proposed Implementation Scheme."	FDA is proposing that any requirement to require coding using MedDRA become effective one year after publication in the federal register and that all other proposals become effective 180 days after the publication date. Wyeth requests that FDA provide a longer implementation period for the "other" requirements of the proposed rule. The implementation period should be at least a year for all requirements of the final rule. FDA's proposal has suggested a number of significant systems changes that will require significant re-programming of companies' drug safety computer systems. This reprogramming will take time, as will the validation of any changes made. The proposed rule will also require significant procedural changes requiring additional training. Since the proposed rule imposes a significant burden on industry, companies may also need to hire and train additional staff. These changes will also take a significant amount of time to accomplish. Wyeth suggests that FDA acknowledge the burden imposed on the industry by the proposed requirements by allowing sufficient implementation time in the final rule.
Analysis of Impacts FR 12449-12450, "Analysis of Impacts."	FDA postulates that if the proposed rule reduced the incidence of hospitalizations due to SADRs by only two percent, $252.2 million would be saved. 68 Fed.Reg. 12454. It is not clear, however, how FDA reaches its estimate of either a reduction of hospitalizations or the costs savings. Wyeth requests that FDA make available for public review the actual numerical analysis of how this figure was reached. FDA appears to be postulating that hospitalizations would be reduced because "improved timeliness and analysis of SADR data would lead to a better understanding and more rapid communication of the risks of SADRs." However, as discussed above, by increasing the compliance burden on industry without improving safety surveillance, the requirements of the proposed rule are more likely to detract industry resources away from early detection of SADRs and hence the proposed rule is unlikely to decrease hospitalizations. FDA also postulates that the proposed rule would result in a more efficient allocation of resources due to the "international harmonization of the safety reporting requirements." As discussed throughout these comments, FDA's proposed rule fails to harmonize global reporting

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	requirements in several key respects. For example, FDA's 30 and 45-day reports are new reports not required by any other worldwide reporting agency that increase the compliance burden without providing any additional safety information. As another example, FDA's PSUR proposal – which the Agency believes harmonizes worldwide periodic reporting requirements – actually creates a significant additional work load for companies because FDA is proposing significant US only appendices. As a result, the cost of implementing the proposed rule is much greater than that estimated by FDA as there are few, if any, cost savings to industry from harmonization.
Estimate of Time Burdens FR 12455, "New time burden."	FDA has specifically requested comment on its estimates of time burdens. Wyeth believes that FDA has significantly underestimated the time burden to industry of the proposed rule. Perhaps even more importantly, FDA has completely neglected to consider the time burden of the proposed rule on the health care system as a whole. Wyeth requests that FDA provide industry the data used to support their estimates of time burdens. For example, FDA estimated that the active query requirement would cost companies one hour each for a health care professional and regulatory affairs professional to determine/obtain a minimum data set, SADR outcome (if unknown), obtain a full data set, and supporting documentation (hospital discharge summary, death certificate, autopsy report). Even if we accept FDA's one hour estimate, citing a burden of one hour is potentially misleading as it is one hour per case per company. Wyeth receives tens of thousands of serious reports per year. That means active query will require tens of thousands of hours per company, which is an enormous time burden particularly when multiplied across the industry. Moreover, the one hour does not account for the time spent by the reporter answering the questions and hence the burden on the health care system. As discussed above, imposing a broad requirement for active query will expend HCP time and may discourage future reporting. The same can be said for all of FDA's time burden estimates. Even if we assume that the time

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	burdens are accurate, the estimate needs to account for the number of cases received and processed. Moreover, FDA's estimates of 8 hours of health care professional, regulatory affairs professional and clerical person time to prepare a report of information sufficient to consider a product administration change, 40 hours to prepare a PSUR, and 1 hour for a contractor to submit SADRs to applicants in five business days is unrealistically low. For example, the current average time to prepare a PSUR ranges from two to four times FDA's estimate per PSUR even without accounting for the additional time it would take to prepare the FDA only appendices. This includes time to gather and analyze the information, write the report, assemble all the supporting materials and have the report approved internally. Similarly, it is unlikely that a thorough and high quality report discussing a product administration change could be prepared and submitted in one day. And finally, FDA's one hour estimate for exchange of information between license partners is based on FDA's misunderstanding of information exchange between license partners. Under most license arrangements, parties do not merely fax source documents from one company to another, rather, companies exchange reports once they are processed and exchange information regarding the safety of the products under the agreement to ensure proper safety surveillance and consistency in reporting. These exchanges require more than one hour of time. Wyeth requests that FDA further review its estimates for the time burdens cited in the proposed rule. As discussed above, Wyeth believes that FDA's estimates grossly under estimate the cost of the proposed rule to both industry and the health care system.
Submission of "Similar" IND SADR Reports 312.32(c)(1)(i). Serious and	FDA is proposing to maintain the requirement that sponsors be required to identify "all safety reports previously filed with the IND concerning a similar SADR, and must analyze the significance of the SADR in light of previous, similar reports." Wyeth requests clarification of FDA's expectation of what constitutes a "similar" SADR and "analyze the significance." These

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Unexpected SADR	terms are very subjective and are open to interpretation. Companies should already have processes and procedures in place to periodically review and analyze safety data to detect "signals." In addition, for post marketing study reports under an IND, does FDA expect an "analysis" of reports filed to the IND (the literal language of the rule), or all reports for the product including postmarketing, spontaneous reports? Wyeth suggests that FDA remove this requirement for postmarketing studies as analysis of all AEs are already being performed in the PSUR. Wyeth also suggests that FDA remove this requirement for IND studies because, as stated above, companies should already be performing these analyses and updating their investigator brochures with significant new safety information.
Information Sufficient to Consider Product Administration Changes 312.32(c)(1)(ii). Information sufficient to consider product administration changes. 314.80(c)(2)(ii) and 600.80(c)(2)(ii). Information sufficient to consider product administration changes	FDA is proposing that companies submit written narrative reports to FDA and, for investigational products, to investigators of information that "based on appropriate medical judgment" might "materially influence" the benefit-risk assessment of an investigational drug or would be "sufficient" to consider changes in either the product administration or in the overall conduct of the clinical investigation. Wyeth requests that FDA provide additional guidance and clarification on what information it believes is "sufficient to consider product administration changes," specifically, FDA's expectation of the phrases "based on appropriate medical judgment," "materially influence," and "sufficient." None of these terms are sufficiently clear to guide companies in the preparation and submission of these proposed reports. Currently, Wyeth has processes in place to detect safety signals involving their products and to take action based on those signals including, if warranted, implementing labeling changes. If by a "product administration change" FDA means a labeling change, Wyeth questions the value of preparing in fifteen calendar days, a separate report to FDA when companies are already submitting/discussing this information with FDA as part of regulations surrounding labeling changes.

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Use of MedWatch Form 312.32(c)(1)(iii). Submission of written reports. 314.80(c)(4) and 600.80(c)(4). Reporting Format.	FDA would continue to require that domestic reports be submitted using a MedWatch Form 3500A. Wyeth suggests that sponsors be allowed to use MedWatch or CIOMS form for all reports as this would meet FDA's stated goal of harmonization.
Full Data Set Definition 314.80(a) and 600.80(a). Definitions. Full Data Set.	FDA proposes to define a full data set as completing all applicable elements on the MedWatch or CIOMS forms, including a concise medical narrative of the case. Completing all MedWatch fields may not be appropriate for every case. Rather, Wyeth suggests that FDA adopt the CIOMS V Working Group "List of Data Elements that Determine Whether Follow-up Information is Needed for Particular Types of Adverse Event Reports" (available at Appendix 7 of the CIOMS V Working Group report) to define a full data set depending on the type of SADR at issue.
MedDRA 314.80(c)(4)(ii) and 600.80(c)(4)(ii). Reporting Format.	Wyeth supports FDA's proposal to require MedDRA for ICSR coding. This proposal not only meets FDA's stated goal of harmonizing worldwide reporting practices but also recognizes that MedDRA was developed with this goal in mind with significant investment by both industry and worldwide regulatory authorities. It also provides reassurance that FDA does not intend to use an alternate terminology for coding purposes, something that would entail a significant waste of resources and effort by both industry and FDA to convert to yet another terminology. Wyeth also suggests that FDA make clear that incidental events not identified by the reporter as SADRs should not be coded. The proposed rule would require each SADR to be coded using the "preferred term" from MedDRA in use at the time the applicant becomes aware of the report. Wyeth requests clarification on how to handle follow-up information received after a MedDRA upgrade, which

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	might result in a different code from the MedDRA version in place at the time of initial receipt.