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

Re: Docket No. 2000N-1484 RIN 0910 AA97; Safety Reporting Requirements for Human Drug and Biological Products; Proposed Rule

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic and infectious diseases, neurological disorders, and oncology. In 2002 alone, Bristol-Myers Squibb dedicated $2.2 billion for pharmaceutical research and development activities. The company has more than 5,000 scientists and doctors committed to discover and develop best in class therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises approximately 50 compounds under active development. For these reasons, we are very interested and well qualified to review and comment on the FDA's Proposed Rule for Safety Reporting Requirements for Human Drug and Biological Products.

SUMMARY OF BMS COMMENTS ON PROPOSED RULE

BMS supports the FDA's objective of simplifying, clarifying and harmonizing safety reporting requirements. BMS commends the FDA on the development of the Proposed Rule as it endorses the ICH guidelines on the preparation and submission of PSURs, the use of MedDRA, the elimination of duplicative reporting of safety information in the NDA Annual Reports, the appropriate handling of cases from class action law suits and the establishment of "full" and "minimum" data sets and use of such datasets in collecting and reporting safety information.

There are, however, elements of this Proposed Rule that BMS believes introduce certain inconsistencies with already established and accepted global practices in collecting, managing and reporting drug safety related information. Further, BMS believes the implementation of the Proposed Rule may result in lack of global harmonization in international Pharmacovigilance

00N-1484 C 51

initiatives such as CIOMS and ICH and may detract from timely identification of safety signals.

As a general suggestion, BMS proposes that the FDA extend the effective date of the Final Rule to 12 months after publication in the Federal Register. The additional time will allow Industry, Health Care Professionals, and IRBs to make the necessary and appropriate modifications to processes and systems to fully comply with the new FDA regulations.

DETAILED BMS COMMENTS

In order to facilitate review of BMS comments, the discussions herein are arranged according to each issue addressed by the Proposed Rule rather than according to the numbering schema of the Federal Register publication.

Definition of an SADR

BMS agrees with the FDA goal of international consistency in identifying adverse drug reactions. One way to promote such consistency is to apply standard terminology worldwide for adverse drug reactions and to identify adverse drug reactions using standard definitions. BMS is concerned that introducing new terminology ("SADR") and a broader definition are not consistent with these goals.

Current adverse drug reaction terminology is well established by worldwide Health Authorities and provides consistency and harmonization in identification of adverse drug events. Thus, a new term and definition for adverse drug events is not needed, especially when that term applies only to US cases. Further, the particular acronym chosen ("SADR") is confusing for two reasons: First, the term "SADR" itself is redundant: according to the ICH E2A, a reaction (the "R" in the SADR) implies a possible causal association (as does the "S" in the SADR); Second, the "S" is commonly understood to mean "Serious", therefore the new acronym may be misunderstood to refer to a "serious" adverse event ("SAE") rather than a "suspected" adverse drug reaction.

In addition to the confusion created by introducing the specific acronym "SADR", the proposed definition for SADR is too broad to identify primarily those events that are potential safety issues. It is anticipated that the SADR definition of "*reasonable possibility*" where *"the relationship can not be ruled out"* will result in significantly larger numbers of Serious and Unexpected expedited reports being submitted to Health Authorities, Investigators and IRBs. This significant increase of information flow may impede the identification of safety signals by Health Authorities ("needle in the haystack" concept). The increase in unnecessary expedited reports may actually slow the transmission to IRBs, investigators and patients of important safety issues. Finally, unblinding of the majority of Serious and Unexpected SADRs during the conduct of clinical trials can clearly jeopardize the integrity and statistical power of blinded trials.

In summary, BMS recommends that the FDA apply the standard adverse drug reaction terminology and definitions already in place in the E2A document. Use of such terminology promotes global harmonization of regulations as implemented by ICH, and optimizes timely and appropriate identification of safety issues.

Active Query

BMS agrees with the FDA goal of improving the accuracy and completeness of postmarketing reports. BMS encourages the FDA to evaluate the benefits of a variety measures in improving the accuracy and completeness of reports rather than mandating specific channels of communication by specific personnel.

There is no single route of communication with Health Care Providers that is most likely to predictably result in complete and accurate reports. There are several factors that contribute to improving the quality of reports, including ensuring adequate training of company Health Professionals who collect follow-up information, using targeted questionnaires, and ensuring active follow-up for serious, unexpected adverse events or those of special interest to Health Authorities. In many clinical settings, qualified non-physician Health Care Providers routinely furnish written information on patients for a variety of reasons, such as for insurance claims, and thus have direct access to the most accurate set of patient information. Thus, both written and oral communication may yield optimal results depending upon the particular hospital, clinic, physician, ancillary staff or local medical records policies. In addition, some EU countries (e.g., Italy) do not permit company representatives to actively obtain follow-up information; such follow-up is relegated to specific personnel of the respective local Health Unit or Ministry of Health. Further, if active query is overly used it may discourage future voluntary reporting. Thus, in some cases it is neither possible or advisable to obtain safety information via direct verbal contact.

BMS believes that active query should be confined to cases when medically significant information can lead to prescribing information changes, i.e., high risk cases. In cases other than these high risk cases, the preferred method of communicating with the Health Care Provider should be up to the discretion of a qualified company Health Professional. Such methods may include active query or exchange of letters, emails and/or focused questionnaires which allow the Health Care Providers to respond to company personnel in more detail in a setting that is most appropriate to obtain accurate and complete responses. BMS also proposes that a sponsor should also be allowed to obtain a waiver on a specific product for specific events generating expedited cases.

In summary, BMS believes there is no single communication method that is superior for obtaining accurate and complete reports on marketed products. BMS maintains that qualified company Health Care Professionals should employ a combination of methods (e.g., oral, written, targeted questionnaire) to ensure the quality of reports. The qualified Health Care Professional should target active queries primarily to high risk cases. Limiting communications to only active queries may limit the ability to obtain accurate and complete information due to Health Care Provider logistical or other constraints and may not meet Health Authority regulations in certain countries.

Management of Follow-up Information

BMS agrees with the FDA in striving for timely and complete follow-up of expedited reports. The current policy mandates that the sponsor submit new information on expedited cases when such information is available. BMS scrupulously adheres to this principle as a major tenant of due diligence training for our Health Professionals.

Policies are in place within BMS to ensure timely and complete follow-up of expedited reports. Thus, mandating additional specific intervals for sending in follow-up information on expedited cases does not increase the flow or timeliness of information from BMS to Health

Authorities. Further, the proposed additional timeframe does not promote a globally harmonized approach to safety reporting according to ICH-defined standards and instead introduces additional regulatory clocks that unnecessarily complicate regulatory compliance.

For BMS, and for a number of other sponsors, the proposed mandate to submit 30-day follow-up for expedited reports (even if no new information is available), does not achieve the stated goal of obtaining additional safety information, but does give the Health Authorities large numbers of follow-up narratives to review that do not contain additional useful safety data. Conversely, if a sponsor does not routinely forward follow-up information on expedited reports to Health Authorities, ensuring such reports are forwarded may yield useful additional information for Health Authority safety evaluations. Given the close scrutiny of the FDA towards company follow-up of expedited cases, the FDA should be able to identify which companies to target in order to make this additional follow-up step most beneficial for FDA safety evaluations. Further, the proposed process to mandate addition of information in the follow-up narrative regarding attempts to collect follow-up information introduces extraneous verbiage that does not aid Health Authorities in learning more about patient follow-up. Rather, individual company compliance with existing guidance results in timely and accurate follow-up.

In summary, BMS believes that for BMS and many other companies, the proposed requirement of an additional, mandatory, 30-day follow-up for expedited reports (regardless of whether new follow-up information has actually been received), yields relatively little new safety information for Health Authorities to review. Such policies should be reserved for specific situations where lack of compliance with existing regulations is apparent. BMS proposes that the requirement for an additional 30-day follow-up is removed and replaced by FDA routine inspection of individual company compliance with follow-up requirements.

Minimum Data Set and Full Data Set

BMS commends the FDA on its clearly stated requirement to require a Full Data Set exclusively for expedited reports. This policy will allow Industry to better focus its resources in collecting and analyzing quality information on cases of utmost medical importance to the FDA.

Information available on medically significant cases is often variable due to the nature and source of reports and the need to provide important safety information on expedited cases in the shortest time period feasible. BMS is concerned that the proposed definition of a Full Data Set applies to paper submissions (3500A and CIOMS I) only, leading to inconsistent interpretations by Industry and FDA, delay in transmission of important safety information, and delays evolution towards electronic reporting as is currently supported by both ICH and the FDA. BMS proposes that the definition of a Full Data Set requires the company to be responsible for following-up with the reporter to collect all relevant available information. Such a statement would recognize the limitations that may exist in collecting very detailed information due to the nature or source of those reports.

In summary, BMS recommends the FDA restate the requirement for a Full Data Set to allow for transmission in a timely fashion of important safety information, even if complete information is not obtainable. Given electronic means for updating, further transmission of information can facilitate initial and subsequent transfer of important medical information to Health Authorities.

Supporting Documentation

BMS agrees with the FDA as to the importance of obtaining source documentation, especially when evaluating medically important signals. Every attempt should be made to obtain, where possible, autopsy report/death certificate/discharge summaries for all deaths and all hospitalizations.

There are multiple challenges in obtaining source documentation. In the US, such regulations may conflict with the HIPAA regulations. Outside the US, such a mandate may conflict with current local regulations preventing transmitting patient information to companies outside of country borders. Further, in some countries, death certificates cannot be obtained. In some instances, although there is no specific prohibition, reporters may avoid voluntary reporting due to reluctance in sharing such private information with company personnel. Source documentation that is obtainable should be available and on file within the company should the FDA wish to examine specific documents. Important safety information obtained from patient documents should be summarized and included on FDA form 3500A. Complete transmission to the FDA of supporting documentation on a routine basis is not recommended. However, for evaluation of important safety signals, detailed documentation (translated into English) should be forwarded to relevant Health Authorities on an expedited basis.

In summary, BMS proposes that companies obtain, where possible, autopsy report/death certificate/discharge summaries for medically important signals. However, mandating the collection of such source data for every case may be in conflict with local and country regulations. Source documents should be kept on file within the company, and medically important information should be summarized and included on FDA form 3500A.

Always Expedited Reports

BMS agrees with the FDA that for a given product there may be medically significant reports that should be "always expedited". However, automatically classifying some events as "always expedited" does not take into consideration the important role of the Investigator's Brochure, product labeling and ongoing company Health Professional medical interpretation of events. Further, expediting reports of events that are known and well described in the IB or product labeling will not significantly contribute to a better understanding of the safety profile of that product.

BMS recommends the FDA reconsider requiring expedited reporting of a predetermined list of events. Rather, BMS proposes such event are upgraded to serious rather than transmitted in an expedited manner.

Solicited reports

BMS commends the FDA on its clarification of differences between solicited and spontaneous reports. This clarification recognizes the expansion of contacts between Industry, consumers and Health Care Professionals.

The proposed text for solicited reports does not differentiate between solicited reports confirmed by a Health Care Professional and direct reports initiated by consumers. This lack of specificity would result in a significantly increased volume of both expedited reports and reports within PSURs. Such over-reporting would make safety signal detection more difficult.

BMS proposes that solicited reports are identified as study reports with the added

clarification that the primary reporter is a Health Care Professional.

Class Action Lawsuits

BMS commends the FDA for eliminating the requirement to submit cases from class action lawsuits in an expedited manner. BMS proposes that the FDA broaden the exclusion to include individual lawsuits. The reasoning that supports eliminating the requirement for class action lawsuits applies equally to individual lawsuits.

Medication Errors

BMS recognizes that medication errors represent an important Public Health issue that needs to be addressed by a broad healthcare sector initiative rather than solely by Industry. Most medication errors are the result of prescriber or pharmacy errors not related to Industry practices. The proposed mandate to require expedited reporting of such errors is unwarranted as most medication errors either result in no adverse event(s) or event(s) that are non-serious and self-limiting. Enforcement of expedited reporting of medication errors may not be appropriate outside the US and may discourage voluntary reporting within the US. Over-reporting of medication errors may divert Health Authority attention from true medical safety issues.

Medication errors due to packaging or dosing information confusion represent a relatively small proportion of prescribing errors. Medication errors due to poor handwriting, oral communication, careless writing or transcription errors, use of non-standard abbreviations, language barriers, complex or poorly designed technology, or access to drugs by non-pharmacy personnel are issues far beyond the purview of Industry. Further, since only a small fraction of the 44,000 – 98,000 deaths due to medical mistakes are actually attributed to medication errors, as described in the IOM Report of 1999, the proposed rule for expedited reporting of all medication errors appears to be an extreme measure to address a potential public health issue of uncertain magnitude.

Enforcement of expedited reporting of medication errors may not be appropriate for cases outside the US. Within the US, such expedited reporting may discourage voluntary reporting.

The overwhelming number of separate, expedited reports of medication errors is projected to yield relatively minimal numbers of true reports of medical significance. However, such over-reporting will delay and interfere with the ability of Health Authorities to identify significant safety issues. When such expedited reporting is compounded by applying the active query and 30-day follow-up rules, the net effect is to further divert Health Authority efforts away from addressing the healthcare sector issues that drive medication errors.

BMS proposes classifying medication errors as follows:

(1) "Potential" medication error. "Potential" medication errors are identifiable medication errors without an adverse event. Such "potential" medication errors should not be reported expeditiously, but should be accumulated and reported at the time of a PSUR.

(2) Actual medication errors:
   (a) Serious and unlabeled events: Serious and unlabeled "actual" medication errors should continue to be reported in an expedited manner if they are serious and unlabeled and therefore may trigger a change in the prescribing information package.
   (b) All other actual medication errors: "Actual" medication errors that resulted in an adverse event that is already described in the current package insert should be

reported as part of the next PSUR.

In summary, BMS believes that expedited reporting of all medication errors may be counter-productive to Health Authority goals of addressing and improving the situations where medication errors occur. BMS recommends categorizing medication errors and applying appropriate reporting rules to promote evaluation of medication errors.

Contractor Definition

BMS agrees with the need for prompt safety data exchanges in licensing or other contractual agreements. However, BMS believes that the proposed definition of a contractor that includes co-marketers whose name appears on the label, co-licensing partners, etc, is too broad. Given the variety of types of alliances at international and local levels involving multiple partners, the issue of safety data exchanges needs to be carefully applied.

Co-licensing, co-marketing, co-development, co-packaging, co-promotional and other similar agreements may cover many (in certain cases the majority) of a sponsor's products. There are no "standard" licensing agreements, each is unique. Licensing partners may hold independent marketing authorizations in different countries which may include local divestment arrangements for "legacy" products.

The new rule as stated would require that all (serious and non-serious) reports for these products must be exchanged between the two parties within the 5-day timeframe. While BMS agrees with the requirement for prompt exchange of safety data among relevant parties, a 5-day exchange cycle conflicts with the 15-day expedited reporting time frame. Further, a 5-day calendar may result in repeat iterations of cases that do not meet the minimum required Data Set. Such repeated reporting may lead to increased confusion and differing interpretation of the same case by two parties rather than clarity in transmitting reports between parties and to other Health Authorities. The potential exists for duplicate reports when FDA exchanges data with other Health Authorities for signal detection purposes. Finally, the stated goal of the FDA towards active query and translation of reports would not be feasible using a 5-day timeframe.

BMS proposes that the notification requirement remain similar to the present regulation: that it is the responsibility of the NDA holder or its agent to submit expedited cases to FDA within 15 calendar days. As part of the PSUR, the FDA will also be aware of any of these types of agreements for a specific product. BMS proposes that the FDA compliance team handles incidents of late reporting with relevant companies rather than mandate a system that may divert Health Authority attention towards confusion created by duplicative raw reports.

In summary, BMS believes the current 15-day FDA notification requirement for expedited cases is reasonable given the multitude of contractors located in diverse regions, the need for prompt reporting of accurate and non-conflicting safety reports, and the FDA emphasis on obtaining translated information and results of active query for medically significant events.

Licensed Physicians

BMS agrees with the FDA that physicians need to be responsible for the medical content of safety reports and that is it inappropriate for clerical staff to submit safety reports without proper medical review and evaluation. Accordingly, as a global pharmaceutical company engaged in worldwide Pharmacovigilance, the Pharmacovigilance group within BMS is specifically staffed with

personnel having health care professional credentials (biomedical, scientific, etc.) both in the U.S. and overseas. Such personnel are specifically trained, highly qualified, experienced in Pharmacovigilance, and meet the needs of the FDA for appropriate medical/safety decision making regardless of the state or country of origin of their medical license.

BMS proposes replacing the word "licensed" in the Proposed Rule with the term "Medically Qualified". The word "licensed" is unique to the U.S. and may restrict Industry from utilizing fully (Medically Qualified) physicians to perform Pharmacovigilance activities if the origin of their "licensure" is outside a given state or country. Use of a standard term (Medically Qualified) promotes the FDA goal of global harmonization of safety reporting, rather than use of a term unique to a particular country.

BMS proposes that while Medically Qualified individuals are responsible for the content of the safety reports, these Pharmacovigilance experts should not be the ones identified with each ICSR and periodic report. Instead a company contact person should be identified to facilitate direct FDA communications with company Medically Qualified personnel. This ensures that the FDA would have immediate access to company expert Pharmacovigilance personnel in the event of change of responsibilities of staff members, staff attrition and rotation, which are inevitable in large corporations.

In summary, BMS recommends that Medically Qualified Pharmacovigilance experts within companies are responsible for the content of safety reports and that a specific contact person within the company be designated to ensure direct access of the FDA to such Pharmacovigilance experts.

Periodic Reporting

BMS commends the FDA on its direction to adapt the ICH E2C guideline on the preparation and submission of PSURs following the International Birth Date. The approach however of implementing PSURs in the U.S., as stated in the proposed rule, has several differences as compared to the ICH E2C process currently implemented by many Health Authorities and therefore may not serve FDA's and ICH's goals of a single harmonized document for worldwide distribution.

The proposed Rule introduces additional points in the PSUR schedule for the submission of IPSRs at 7.5 and 12.5 years and ICSRs on a perpetual semiannual basis. These two additional requirements are not consistent with the ICH E2C and CIOMS V recommendations stating that 5-year reports after the first 5 years post approval should be sufficient for the monitoring of the safety profile of the product. BMS appreciates the FDA's attempt to lessen the burden on Industry by eliminating the requirement of submitting ICSRs at the time of PSURs, TPSRs and IPSRs and by keeping the FDA database current with the requirement on Industry to submit ICSRs semiannually. However, this change creates a significant increase in separate reports to Health Authorities that may result in confusion rather than clarification of PSUR information.

Consistent with the ICH guidances, BMS proposes that Industry submits a single PSUR with the descriptive document as well as the supporting ICSRs in the timeframe described in the ICH E2C document and the requirements for IPSRs and semiannual ICSR submissions are removed.

Additional BMS comments

BMS appreciates the FDA offer to provide comments on three additional issues related to this Proposed Rule and reporting of safety information:

Use of MedDRA vs. SNOMED

BMS is pleased by FDA's clarification of the MedDRA terminology to be used by Industry for regulatory reporting. Both FDA and Industry, as partners in the ICH process, have made significant investments in implementing MedDRA and integrating MedDRA in the drug development process. This decision was made by all interested parties for several reasons; among them accepting the scientific validity of the terminology and selecting a common global vocabulary to be used in the communications across companies and Health Authorities of Pharmacovigilance related information. Additionally, the size of the MedDRA terminology lends itself for data mining and trend analysis as currently investigated by both FDA and Industry using various methodologies, where the significantly larger SNOMED terminology has not yet been adequately tested in this area.

Coding of Incidental events vs. Index events

BMS strongly believes that it is not appropriate to code incidental findings, i.e. events that were not the ones intended by the reporter to drive the particular case. This view is discussed at length in the CIOMS V document. Rather than further elaborate on the rationale, the CIOMS V document clearly articulates that capturing these findings introduces "noise" in both Industry and Health Authority databases, inhibiting signal detection and in turn Risk Management.

Impact of the Proposed Rule on electronic submissions using the ICH E2B(M)/M2 standards

BMS has worked very closely with the FDA and other Health Authorities to implement the ICH E2B(M) and M2 standards over the past several years. BMS agrees with the FDA on the benefits of these standards to both Industry and Health Authorities, i.e. eliminating the burden of data entry on FDA's behalf, ensuring the same safety messages are transmitted globally, facilitating exchange of ICSRs between Industry partners, etc.

BMS has identified four areas in the Proposed Rule that currently would conflict with ICH standards currently implemented by both FDA and Industry:

(1) The current SGML parsers and import tools of safety systems such as AERS require a Minimum Dataset, i.e. identifiable patient, reporter, suspect drug, adverse event. The current definition of a potential medication error lacks an identifiable patient and an identifiable adverse event.

(2) The various Gateways that are compliant with the ICH M2 document and are currently in place both in Industry and FDA do not support the transmission of attachments in a binary format, i.e. PDF files. Such formats would be required under the Proposed Rule in order to transmit supporting documentation, i.e. death certificates, autopsy reports, hospital discharge summaries, for reports involving death and hospitalizations. The alternative of transmitting all such reports, as well as literature cases, on physical media rather than via the Gateway, would create a dual reporting schema based on the type of reports being submitted that would be inconsistent and error-prone.

(3) The current length (20,000 characters) of the case narrative (E2BM field B.5.1) will no

longer be sufficient to accommodate the additional text required to document all follow-up attempts as part of the Proposed Rule requirement of a mandatory 30-day follow-up. Consequently, follow-up reports with a narrative exceeding 20,000 characters will need to be submitted on paper, thus defeating the advantages gained by having initial reports electronically submitted.

(4) The Proposed Rule requires six-month datasets (using E2B(M) for manufacturers submitting electronically) vs. PSURs and IPSRs, thereby creating a discrepancy between the two sets of data that complicates the tracking of cases that are part of those submissions. Any given 5-year PSUR will include and discuss all U.S. cases, all serious non-U.S. cases and all non-serious and unlisted non-U.S. cases. However, the PSUR may discuss cases that the FDA may not receive as part of the six-month datasets: the 10 six-month datasets that are intended to communicate to FDA either via MedWatch 3500A forms or electronically in the E2B(M)/M2 format will only contain all U.S. cases and all serious non-U.S. cases. In addition, the possibility exists that a non-U.S. non-serious case that was part of one PSUR is upgraded to a serious case. In this example, the next PSUR will list this case as a follow-up report and the next six-month dataset will include this case as an initial report. Additional guidance is required on whether Industry should track these cases as initial or follow-up submissions to FDA.

CONCLUSIONS

BMS appreciates the FDA's interest in Industry comment on the Proposed Rule prior to issuing the Final Rule. BMS shares with FDA the vision of global Pharmacovigilance policies that protect the safety of patients and ensure Health Authorities are fully informed of medically important safety reports. BMS is committed to working with the FDA and other Health Authorities to update the current policies consistent with these goals.

In particular, BMS commends the FDA on many aspects of the Proposed Rule including the endorsement of ICH guidelines on the preparation and submission of PSURs, the use of MedDRA, the elimination of duplicative reporting of safety information in the NDA Annual Reports, the appropriate handling of cases from class action lawsuits and the establishment of "full" and "minimum" data sets and use of such datasets in collecting and reporting safety information.

However, BMS believes that premature implementation of the Proposed Rule in its current form may result in lack of global harmonization in international Pharmacovigilance initiatives such as CIOMS and ICH and may detract from timely identification of safety signals. For example, BMS believes that premature reporting of incomplete data sets, expediting of a wider category of safety reports and mandating direct contact with healthcare personnel will be counter-productive to the stated goals of the Proposed Rule.

BMS appreciates the FDA's interest in enforcing compliance of safety reporting. Thus, the Pharmacovigilance group within BMS is specifically staffed with highly trained Medically Qualified personnel who are familiar with the existing guidances and who maintain or exceed the standards set by Health Authorities. BMS shares FDA's concern that such compliance with reporting should be maintained by all Industry sponsors. Given the close scrutiny of the FDA towards safety reporting

of medically important cases, the FDA should be able to identify which companies to target in order to make additional follow-up compliance steps most beneficial for FDA safety evaluations.

BMS is pleased to provide additional pertinent information as may be requested. Thank you again for the opportunity to review and comment on the Proposed Rule.

Sincerely,

Laurie Smaldone

Laurie Smaldone
Senior Vice President
Global Regulatory Sciences