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

RE: Draft Guidance for Industry: Pharmacogenomic Data Submission
(Docket 2003D-0497, 68 Federal Register, 62461-62463, November 4, 2003)

Dear Sir or Madam,

Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ about 78,200 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets leading innovative prescription drugs used to treat a number of diseases and conditions including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

Novartis Pharmaceuticals Corporation is a company that is devoted to discovering, developing and successfully marketing innovative products to cure diseases, to ease suffering and to enhance quality of life. In our desire to enhance a patient's quality of life, there is a continuous need to create therapy that is more specific and targeted. In addition, it is important to focus our attention towards variability in absorption, metabolism and excretion pathways amongst patients that could potentially alter efficacy and the side effect profile of the drug. As part of our goal to create optimally efficacious therapy that will enhance a patient's quality of life, we recognize the value of the Draft Guidance for Industry regarding Pharmacogenomic Data Submission.

The Draft Guidance for Industry regarding Pharmacogenomic Data Submission is valuable because it cultivates scientific advancement and encourages the development of

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innovative products. Additionally, it is a valuable tool that ensures alignment between the Agency and Sponsor towards the common goal of providing and developing therapy that will enhance patient response and optimize therapy while taking inter-patient variability into account. In recognizing the importance of scientific progress, Novartis Pharmaceuticals Corporation commends the Agency in its efforts to create a Guidance of this nature. Furthermore, we are appreciative of the opportunity to review the Draft Guidance and provide appropriate comments.

Novartis recognizes the Draft Guidance for Industry regarding Pharmacogenomic Data Submission as an important initiative from the Agency that will aid in the advancement and utility of pharmacogenomics. However, there are some key concerns that need to be addressed in order for Sponsors to gain understanding and clarity. The major areas within the guidance that we had focused our attention include:

- **Formatting**
 - Lack of clarity amongst non-clinical data, clinical pharmacology, and clinical data
- **Decision-making**
 - Vague nature of the phrase “use in decision-making”
 - It is not clear if genomic data used for business decisions is to be submitted to the Agency
- **Biomarker**
 - Clarity about the process to attain known valid and probable valid biomarker status
 - Communication between the Agency and community regarding the most current information on biomarker status
 - Extrapolation of biomarkers from animals to humans and vice versa
 - Changes in biomarker status post-approval, and the consequences for biomarker analysis and data submission
- **GLP Toxicology Studies**
 - Impact of pharmacogenomics sampling from GLP toxicology studies
- **VGDS**
 - Lack of clarity about whether raw data should be submitted through VGDS

- Data submissions for which Sponsors may use their discretion
- Electronic submissions
- **IPRG**
 - Mechanism of IPRG communication with the Sponsor and scientific community
 - Process for the Sponsor to arrange meetings with the IPRG (or the Review Division) to seek guidance on issues with pharmacogenomics data
- **Clinical Efficacy, Safety and Epidemiology**
 - Relationship between Pharmacogenomics Guidance and pending Risk Management Guidance
- **Global Implications**
 - Impact of ICH efforts on the Agency's efforts towards the Pharmacogenomics Guidance

After reviewing the draft guidance, Novartis Pharmaceuticals Corporation has compiled these specific comments regarding the draft with the hopes of assisting the Agency in developing a more clear and concise guidance. These points are pertinent in the development of a finalized guidance.

Format

The guidance is complex since there is no separation of non-clinical and clinical issues within the guidance. The objectives for performing studies, process of collecting information and interpretation of data for each of these disciplines is distinctive and unique. Addressing non-clinical, clinical pharmacology, and clinical studies within the same sections of the guidance document results in a lack of clarity about the individual disciplines. The DIA public workshop was designed to focus on the three different areas: non-clinical, clinical pharmacology, and clinical studies separately. This approach facilitated discussions regarding the individual disciplines allowing the attendees to focus on specific types of data and issues most relevant to each.

In recognition of the divergent nature of these three disciplines, **we strongly advocate that the guidance be written as three separate sections, with the appropriate concerns included under the major subheadings. The Agency should incorporate information about data collection and other pertinent issues relevant to each of these disciplines under the appropriate headings.** This will result in improved utility and less confusion when referencing the guidance for direction.

Decision Making

There is use of language within the guidance that is not clear, particularly important is the term “use in decision making” when determining whether data must be submitted to the Agency. There are different degrees of consequence in the use of such information. We believe this phrase is meant to refer to decision making that has significant regulatory consequence rather than business consequence. It would appear clear as to the regulatory relevance of such a data submission when the conduct of the trial has been significantly influenced by the use of pharmacogenomic data (i.e. use in exclusion or inclusion criteria or stratification within a clinical trial). However, it is less clear as to the necessity to submit genomic data when it has been used by a Sponsor to change the timing of conduct of an otherwise routinely necessary study within accepted regulatory limits. An example of the later case would be to advance the conduct of a carcinogenicity study based on an observation involving a non-validated signal of a proto-oncogene expression change. We do not believe that it is the intent of the Agency that the submission of pharmacogenomic data be required in the later case. In general, there are numerous points in a drug’s development where genomics data may influence corporate management decisions and be influenced by non-validated pharmacogenomics data. Many of these decisions do not impact the safety of a testing program nor study design. We would like the Agency to explicitly indicate in the guidance that genomics data contributing to these types of decisions need not be submitted except as required under the regulations governing submission of information to an NDA. We urge the Agency to elaborate on the phrase “the test results will be used in decision-making in any clinical trial or in an animal trial used to support safety” to differentiate this application from the use of such information in business decisions.

We recommend that the Agency be more specific and clear within the guidance in defining information they feel is valuable enough in decision making to require a full submission to the IND or NDA. We recommend that the Agency clarify their intent by the phrase “use in decision making”. We suggest that it be elaborated by more specific language, such as “use in decision making of significant regulatory impact.” Using specific language will differentiate the application from use of such information in business decisions. Specificity within the guidance will provide clarity for the Sponsor regarding the type of data that is useful to the Agency for “decision making.” We further recommend that exploratory pharmacogenomics data of unknown validity be specifically excluded from required submission under the “use in decision making” criteria.

Biomarkers

Pharmacogenomic data submission evolves around the status and utility of a biomarker. It is clear that a known valid biomarker is defined as an entity that is not only validated

through analytical test systems, but is also widely recognized by the scientific community. It is also clear that a probable valid biomarker is one that is similar to a valid biomarker with the exception that it may not have been multiply replicated or it may not be as widely accepted by the scientific community. However, there is no clarity about how a probable valid biomarker would attain the status of a known valid biomarker. Furthermore, there is not enough clarity regarding how an exploratory biomarker would attain the status of a probable biomarker. Therefore, similar to the algorithms provided describing data submission to an IND, NDA, and BLA, there may be some value in providing an additional algorithm addressing this issue.

We strongly urge the Agency to provide some structure relating to how a biomarker can attain the status of a probable valid biomarker from the status of an exploratory biomarker, and how to attain known valid biomarker status from probable valid biomarker status. Considering the fact that the science around biomarkers is emerging, it is obvious that the Agency will not provide exact ways in which a biomarker would attain an alternative status. However, it would be valuable to provide the Sponsor with current processes and methodology for accepting a biomarker to known or probable biomarker status. Also, there is no process of development of known valid or known probable biomarkers with regards to non-clinical data, and it is not clear, in the non-clinical context, what would constitute the various levels of such biomarkers. There would be some value in providing minimal fulfillment criteria to attain a given biomarker status. Moreover, providing current examples of biomarkers that have exploratory, known valid, and probable valid biomarker status in the non-clinical and clinical domains would be useful. Despite the fact that the CYP2D6 is a valuable example, it would be more valuable if the Agency focused on biomarkers that have recently gained more attention and possibly undergone changing status. Examples of these may include the BCR-ABL translocation, mutations in BRCA1, EGFR and RET, polymorphisms in CYP2C9, TPMT and UGT1A1 and amplification of HER2/neu. It would be valuable to know how these biomarkers are currently classified by the Agency and the basis upon which the Agency has classified them.

It would be valuable for the Sponsor and the scientific community to be aware of the Agency's thought process concerning biomarkers, their changing status, and it would be helpful for Sponsors who intend to conduct future studies involving pharmacogenomic biomarkers. The most valuable way to communicate this information would be through a list that specifies what the Agency considers is a known valid, probable valid and exploratory biomarker at a given time. Furthermore, if there are some inconsistencies amongst the Agency, Sponsor and scientific community, this would be a valuable tool to gain some degree of alignment through open scientific discussion between the Agency and the community.

In recognizing the importance of communication amongst the Agency, Sponsor and scientific community, we recommend that the Agency periodically provide a current list of known and probable biomarkers. We recommend the Agency post the most current information regarding biomarker status on their website. This would be valuable because it can be viewed by Sponsors and the scientific community. Also, the Agency should provide a mechanism through which Sponsors and scientists may have face to face meetings to address concerns and contradicting information about the status of a biomarker. We urge the Agency to do this in the form of a scientific forum. Aside from this, there should also be a tool that allows Sponsors and scientists to provide feedback and comments regarding the information posted on the website. There are instances when such discussions and communication is valuable in order for the Sponsors to provide the Agency with adequate and appropriate information that would be used for regulatory decision making versus business decisions. Such communication is critical especially in the scope of metabolizing enzymes and transporters where novel data may not support previously held assumptions regarding metabolizing status. The glucuronidating enzyme UGT1A1 is a good example to demonstrate this point. UGT1A1 is a member of a large superfamily of independently regulated metabolic enzymes, and is responsible for glucuronidating bilirubin *in vivo*. Individuals with Gilbert's syndrome have reduced UGT1A1 activity, resulting in an impaired ability to break down bilirubin. This condition typically manifests as mild jaundice, particularly after fasting. UGT1A1 also acts as a metabolizing enzyme by glucuronidating xenobiotics, thus making them more soluble for excretion. There is a substantial literary support demonstrating that genetic variation in UGT1A1 is linked to Gilbert's syndrome. However, the correlation is not exact, and the relationship between genetic variation and metabolic activity and safety is less well explored. Therefore, in this example it is not clear if the development of a compound which is metabolized by UGT1A1 is a candidate for further regulatory evaluation from a biomarker perspective. Further clarification is needed from the agency. At what stage would the data on UGT1A1 status be required to be provided to the Agency and what effect would the data have on an NDA evaluation or the status of this biomarker if no clear correlation was established.

Considering the current emergence of biomarkers there are additional concerns that have not been addressed by the Agency. An important overlooked area is the lack of information regarding biomarker extrapolation from humans to animals and vice versa. Furthermore, it is not clear if the definition of a biomarker is all inclusive of animals or limited to humans. **We urge the Agency to provide some current information and clarity around whether the biomarker definition is or is not limited to humans. Furthermore, there is a need for increasing clarity about whether or not information attained from animal data can be extrapolated to humans.**

The algorithms within the guidance address, to some degree, when information has to be submitted to an IND and NDA. However, these algorithms do not address concerns around changes that may occur in the status of a biomarker. Specifically, after submission

has been made, a biomarker may undergo a change in status. For example, a biomarker may be considered exploratory at the time of submission of a study but could be elevated to valid biomarker status later during the IND stage or after approval of the NDA. In this case there is no clarity as to the responsibilities from the Sponsor. It is not clear if a Sponsor would be responsible for analysis and submission of their previously collected pharmacogenomics data to the IND or NDA. **We urge the Agency to provide specific information regarding the expectations from the Sponsor when the status of a biomarker has changed post-submission. We recommend the Agency not obligate the Sponsor to submit this additional information provided safety and efficacy have been satisfactorily addressed through traditional drug development approaches.**

GLP Toxicology Studies

The necessity for and the timing of submission of non-clinical pharmacogenomics data is an extremely important consideration in relation to overall drug development. Availability of such data to the Review Division, although not considered valid, could weigh heavily in regulatory considerations, particularly in the early stages of development where long term clinical and non-clinical experience with the investigational drug is absent. It is important that this issue be dealt with comprehensively by the Agency in order to achieve the stated objective of fostering the development of pharmacogenomics.

The guidance clearly states that non-clinical laboratory studies must comply to 21 CFR part 58, and it also states that this does not include exploratory pharmacogenomics studies. However, it is not clear under what conditions sampling in GLP toxicology studies can be considered exploratory and under what conditions and in what format submission of analyses is required. It is also unclear as to how pharmacogenomics information obtained through GLP toxicology study sampling that is exploratory is to be submitted to the NDA, nor in what format this information is to be submitted, and if necessary if it is to be submitted to annual IND reports. The format of data submission needs to be clarified. It is not clear if the study protocol needs to include specific declarations about pharmacogenomic sample collection and sample analysis from the GLP toxicology study. Also, it is not clear whether the information, if submitted, can be a separate report or would necessitate an amendment of the toxicology report, if the latter had been previously submitted. We note that in many circumstances the findings from existing or even later conducted toxicology or clinical studies may result in exploratory pharmacogenomics sample analysis long after the study from which the samples were collected will have been reported to the Agency.

We would recommend that the guidance clearly stipulate that sampling from GLP toxicology studies that is indicated in the protocol as “for exploratory purposes” need not be submitted to the IND. Furthermore, if the exploratory samples are analyzed, they should only be reported to the NDA by study title as a separate

report. All pharmacogenomic data that involves GLP study sampling should be considered exploratory and should not be required to be submitted to the IND unless it is a “known” valid biomarker. The option to make a VGDS submission would still be available under such conditions. We believe such a stipulation is consistent with both the exploratory nature of the data likely to be collected in most circumstances and that such a proposal provides the Agency with appropriate information about the studies conducted in an NDA. This further ensures the separation of exploratory pharmacogenomics information from regulatory decision making without the context of more traditional clinical and non-clinical data available over the course of routine development.

VGDS Submissions

It is unclear how the FDA will view and interpret data submissions to VGDS from a company perspective and whether this data will impact the outcome of another sponsor's submission. In the past there was discussion of a “safe harbor” which was, in concept, an agreement that the data would not be used for regulatory decision making if submitted voluntarily. In a large part, this appeared to be assured by submission to a review group that did not include the IND review Division staff.

There is also lack of clarity around how data is to be submitted, the kind of data meant to be submitted, and whether or not there are electronic submission requirements. For example, there are some types of data that may not be of value to the Agency. An example of this may be a multitude of data sets without any actual interpretation.

We recommend that the Agency allow the Sponsor to determine which data is relevant to be submitted if the biomarker is not a “known” valid biomarker. We recommend that the Agency provide clarity on how the data submitted to VGDS will be used and who would review such information. Lastly, it would be helpful if there was information regarding how this data would impact the Agency's decision making. We would recommend that to assure that data that is not deemed a probable validated when submitted under VGDS need not be submitted to the IND, and that it is sent only to the independent pharmacogenomics review group. This data, if deemed relevant for regulatory action by that body, could be forwarded to the review division by a request from the Agency to the sponsor to submit the data to the IND. We also suggest that the sponsor have the opportunity, at their discretion, to submit any VGDS data to the IND Review Division or the IPRG in conjunction with a meeting to discuss any issues deemed relevant as a type C meeting.

We recommend that the Agency provide specific information about the type of data they would like to receive as VGDS. Specifically, if they would want a Sponsor to send raw

data sets or data that has been interpreted and summarized by the Sponsor. Furthermore, specific recommendation around electronic submissions would be valuable to the Sponsor. For example, if an IND or NDA is submitted as an electronic submission it is unclear if the Agency will require the VGDS to also be submitted electronically.

Again, the Sponsor should be permitted to use their discretion as to which data sets (summary, raw data limited to specific markers, or complete raw data sets) will be submitted and how it will be submitted for VGDS. We recommend that a Sponsor not be required to submit data electronically. However, to the extent that the Agency is moving towards electronic submissions for pharmacogenomics data we recommend that this interest be communicated to the Sponsor to facilitate compliance from the Sponsor. This would be helpful because the Sponsor would need to begin allocating resources addressing these additional submissions.

IPRG

It has been made clear that the IPRG is a group of experts that will review the data that is submitted by the Sponsor. Moreover, it is clear that this group will review the data submitted to VGDS, as well as create policies and provide recommendations about acquired data. However, there is not enough clarity and specificity around the degree of involvement that this group will have on regulatory decision-making around a particular submission made to the Agency. Furthermore, there is not information about how, when, and if the Sponsor can interact with this group regarding submissions through VGDS or to an IND. Specifically, a Sponsor may want to consult this group about interpretation of data submissions or policy. It is not clear if there are specific timeframes in which the Agency would respond or arrange for the Sponsor to meet with this group (i.e. PDUFA III). Additionally, there is lack of clarity as to how or when this group will communicate to the Sponsors about any major findings or policy changes.

We recommend that the Agency clearly provide some information about how they envision the interaction of the Sponsor to interact and the IPRG. Furthermore, there should be clear timelines about when and how the Sponsor can expect to meet with the IPRG when seeking clarity and direction. Since the IPRG will have access to a wide range of data they may be in a unique position with regard to the importance and interpretation of this information. It may be useful for the IPRG to hold regular (annual) public advisory meetings as a forum to interact with the scientific community. In these forums, the Agency would not discuss product specific data unless agreed upon with a Sponsor but they could discuss data interpretation and policy topics. A specific example would be that the Agency aim to have a meeting within 30 or 90 days upon then request of the Sponsor. We recommend that IPRG clearly state the mode in which they attempt to communicate to all Sponsors. It would also be valuable to understand how this group will interact and communicate with the internal divisions of the Agency. We recommend that the

guidance clearly explain of how the Agency envisions this group to interact with Sponsors, and how they will be involved in regulatory submissions by Sponsors to the Agency.

Clinical Efficacy, Safety and Epidemiology

There has been no reference made to further validation of biomarkers in clinical designs especially biomarkers that are exploratory or probable. In addition, it is unclear how one is to incorporate validation of a biomarker into a clinical design. **It is understandable that this is beyond the scope of this guidance but we recommend that the Agency determine how to incorporate validation of biomarkers into a clinical design in future scientific and regulatory forums. Further, given the non-validated, questionable status of most pharmacogenomic biomarkers, information collected in clinical trials related to pharmacogenomic parameters, even when described in the clinical protocol, should not be required to be submitted if they are not for "known valid biomarkers" or have not otherwise influenced the study design. This should apply equally for safety and efficacy pharmacogenomic parameters.**

There is no mention of the relationship between this guidance and the pending FDA guidance on Risk Management, particularly as it relates to pre-marketing risk assessment and the development of risk management plans. This is relevant to the interpretation of use of decision making of significant regulatory impact.

We recommend that the Agency provide information on how they envision the relationship between this guidance and the pending Risk Management guidance. Furthermore, we recommend that a risk management plan not be required to utilize biomarkers which have not been established as known valid.

Global Impact

The necessity for a global policy on the regulatory application of pharmacogenomics data is clear. We are aware that there are current meetings involving the issue of pharmacogenomics within the ICH. However, **we would encourage the Agency to fully develop their pharmacogenomics guidance prior to entering any formal ICH discussions of such guidance, so as not to delay the availability of some regulatory guidance in this important area. This is very important because engaging in discussions with the ICH could possibly delay the implementation of this guidance by the Agency. We do encourage the Agency to engage in informal discussions with the all of its ICH partners.**

In summary there are some major points that have been addressed in this letter. Our major recommendations include changes in the structure of the guidance. It would be valuable if three distinct sections were created in the guidance addressing non-clinical, clinical pharmacology, and clinical data requirements. The term "decision-making" is very vague and could be interpreted to imply that essentially all data must be submitted to the Agency. This would include data used for business decision making as well as regulatory decision making. This does not seem to be the intent of the Agency and it should be clearly stated in the guidance. There are issues around biomarkers that involve the changing status of the biomarker. The Agency should provide structure as to how a biomarker will transition from exploratory to know or probable biomarker status. There is also a need for a clear channel of communication amongst the Agency, Sponsors and scientific community about their views about biomarkers. This should be done through a website which lists what the Agency considers are "probable" and "known" biomarkers. Also there should be a proposed structure as to how face to face meetings can be arranged to address the information reported in this website. We recommend that reporting clinical data and GLP toxicology data not be mandatory for submission to the IND, and in the NDA such studies need only be referenced by title unless it pertains to a "known" valid biomarker. There is lack of clarity as to how data submitted to VGDS will be interpreted and used, and we recommend the Agency to clearly state that the Sponsors use their discretion as to the format in which they submit this data under voluntary circumstances. We recommend that the Sponsor not be obliged to submit data in electronic submission format. We recommend that the Agency clearly outline the process in which they envision Sponsors to interact with the IPRG. Also, we recommend that exploratory biomarkers and those of questionable status ("probable") not be required to be incorporated in risk management plans. Lastly, we encourage the Agency to hold discussions with their ICH partners in such a way as to not delay the development and implementation of this guidance.

In closing, Novartis Pharmaceuticals is thankful for the opportunity to provide our insight and hope this response will assist in the development of the guidance.

Sincerely,

Nainandu Shilow signed for John Cutt

John R. Cutt, Ph.D.
Executive Director, DRA