



**ANVISA PUBLIC CONSULTATION No. 65 of 1 AUGUST 2014  
PROPOSED REGULATION FOR THE CONDUCT OF CLINICAL TRIALS INVOLVING  
DRUGS**

**Introduction:**

The Biotechnology Industry Organization (BIO) welcomes the opportunity to provide comments to Public Consultation #65 published by the Board of Directors of the National Health Surveillance Agency on August 4, 2014 which proposes a new regulation defining the procedures and requirements for conducting clinical trials involving drugs in Brazil and which also includes rules for the production of a drug clinical development dossier (DCDD) that is to be closely monitored by ANVISA through the entire clinical development of a drug and which ultimately will serve as the basis of a drug market approval application.

At the outset BIO commends ANVISA for its efforts to revisit its policies and establish clear and workable rules for conducting clinical trials involving drugs in Brazil. BIO recognizes that the goal of the Public Consultation is to establish rules that encourage clinical trial development in Brazil and sees this as a favorable development given that clinical trials are a source of highly skilled jobs and contribute to the transfer of biopharmaceutical know how, issues that are central to the Brazilian government's desire to become an important player in the global biopharmaceutical arena. The development of clearer regulations for conducting clinical trials may also help to attract, train and retain qualified technicians, improve clinical standards and promote academic inquiry and, consequently, attract additional research funding and research infrastructure investment. We believe that these aspirations to improve clinical trial regulations in Brazil should therefore be lauded and generally supported.

Brazil has taken several initiatives to participate actively and contribute to the global biotechnology industry. Major investments from the government, as well as local and foreign companies that are members of BIO have also helped to grow the local biotechnology industry. For these reasons, among many others, BIO is very attentive to legal and regulatory developments in Brazil that affect the biotechnology industry, such as potential changes to the rules for conducting clinical trials in the country. BIO therefore appreciates the opportunity to engage with ANVISA to share the concerns of its members in order to ensure that decisions are made that continue to strengthen the biotechnology sector, particularly in the health area, in Brazil for years to come.

BIO is a global not-for-profit industry association representing more than 1,100 companies, universities, research institutions, investors and other entities in the field of biotechnology in more than 32 countries throughout the world, including Brazil. The members of BIO, which range from entrepreneurial companies developing a first product to Fortune 500 multinationals, are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. As the world's largest biotechnology organization, BIO has been involved with governments



around the globe in helping to determine global best practices for implementation of biotechnology development policies. It is with this broad experience and large global membership pool that BIO hopes to share with ANVISA its concerns regarding the newly proposed regulations regarding the conduct of clinical trials in Brazil.

In this light BIO hopes that its contributions below to the Public Consultation represent just the first of several opportunities to engage with ANVISA on developing positive and clear regulations on clinical trials that help to create a regulatory environment that places patient safety at the forefront while also driving technological advances and spurring innovation in the biopharmaceutical field.

### **General Considerations:**

- **Unclear relationship and coordination between ANVISA Proposed Regulation and CEP/CONEP Ethical Regulations:**

One of the major challenges in Brazil for creating a clear and workable clinical trial regulatory system is that ANVISA is responsible for the patient health and safety regulations affecting clinical trials and the CEP/CONEP system of the Ministry of Health is responsible for the ethical evaluation of clinical trials. It is understood that improving the regulatory system within ANVISA addresses only half of the clinical trial regulatory environment in Brazil and BIO encourages greater collaboration and coordination with the Ministry of Health to establish an overarching clinical trial regulatory framework that encompasses the health and safety as well as ethical concerns involving clinical trials.

- **Drug clinical development dossier (DCDD):**

The current regulation also introduces a new concept in Brazil associated with clinical trials – the creation of a drug clinical development dossier. BIO encourages ANVISA to discuss more clearly the benefits of the drug clinical development dossier and if ANVISA can address more directly the impacts this may have on the review of new drug applications including biosimilar applications that are based or will be based on clinical trials conducted in Brazil.

- **Scope of Regulation**

It must be clarified if clinical trials conducted in Brazil that will not have their data used for registration in the country fall under the scope of this regulation.

- **General Recommendation to follow ICH Definitions**

To the degree to which it may be possible, BIO encourages that ANVISA throughout this regulation follow ICH definitions in an effort to ease the uniform application and interpretation of the proposed regulation. Furthermore, this would facilitate performing global clinical trials and help to make Brazil a more attractive market for hosting clinical trials.



## **Specific Concerns by Chapter:**

### **CHAPTER I – INITIAL PROVISIONS**

#### **Section II - Scope**

##### *Article 2*

There is uncertainty in this article as to the full scope of the proposed regulation. For example, there remains a question as to whether this Resolution is to apply retroactively to pending applications or applications currently being reviewed. It is recommended that this Resolution only be applicable to those applications that are first submitted after the date of publication of this Resolution.

#### **Section III - Definitions**

##### *Article 6*

BIO encourages that ANVISA provide a definition of CONEP – the National Commission of Ethics in Research. Considering that CEP/CONEP ethical evaluation of clinical trials is a complementary and necessary step in obtaining approval to conduct clinical trials in Brazil, BIO understands that the ANVISA regulation should more clearly address the relationship between the ANVISA clinical trial regulation and the ethical regulations. This alignment and coordination would be helpful in creating a clearer regulatory environment that would benefit patients and the local biopharmaceutical research and development community.

### **CHAPTER II – OF THE RESPONSIBILITIES**

#### **Section I – Responsibilities of the Sponsor**

##### *Article 10*

A focus should be made in this article on ensuring quality rather than on providing a guarantee of implementation of quality control of a clinical trial. Furthermore, the language of this article could be altered to specifically address ensuring quality control in all sites involved in the clinical trial.

BIO suggests the following language: The Sponsor shall ensure quality assurance and quality control in all sites involved in the clinical trial.

This is based on ICH Guidelines for Good Clinical Practice E6 (R1), Guidelines # 5.1.1 [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf). According to this rule, the sponsor is responsible for implementing



and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

#### *Article 11*

BIO also kindly asks for ANVISA to consider altering language in this article such that the constitution of an independent data safety monitoring committee to assess the progress of a clinical trial is not necessarily required. In accordance with Guidelines 5.5.2 of the aforementioned ICH Guidelines for Good Clinical Practice E6 (R1), it is encouraged that a sponsor may decide whether to establish an independent data-monitoring committee.

Accordingly, BIO suggests that the text be altered: The Sponsor may constitute a safety monitoring committee to assess the progress of a clinical trial, including safety and efficacy data, and to recommend the Sponsor whether a study should be continued, modified or discontinued.

#### *Article 13*

In order to provide greater clarity of a Sponsor's responsibilities and to also be in accordance with National Health Council Resolution # 466/2013, BIO recommends that language be altered accordingly: The Sponsor is responsible for all expenses related to procedures and tests, especially those for diagnosis, treatment and hospitalization of study participants and other actions required for resolution of adverse events while they are related to participation in the study.

#### *Article 14*

The language in this Article should be aligned with the Declaration of Helsinki so that "compensation" shall read "treatment and/or compensation". It is also the opinion of BIO to not include "foreseen" in the language of the Article due to the potential for the undue inducement of subjects to participate in a given trial. For example, the provision of monetary compensation – i.e. beyond treatment – for foreseen risks may induce subjects to enroll in trials.

### **Section II – Responsibilities of the Investigators**

#### *Article 24*

It is encouraged in this Article to consider revising the current phrasing from any adverse event unrelated to trial participation as this may potentially induce patients to participate in clinical trials. Although this Article is applicable to investigators and, hence, does not directly present an obligation to the sponsor, there is a potential that this would create a situation in which investigators seek reimbursements from sponsors.



### **Section III – Responsibilities of the Investigator-Sponsor**

#### *Article 26*

The roles of primary and secondary sponsor in this Article seem unclear and it would be helpful if ANVISA would consider providing some clarification on the roles and responsibilities of the primary and secondary sponsors.

Along similar lines, for sponsor-investigator studies, the sponsor-investigator can delegate the responsibility for conducting the study but it may not be appropriate to delegate sponsor responsibilities. Greater clarification on these points is encouraged.

Also, safety reporting should be listed as a specific unit in a primary sponsor's structure as listed in Section 4.

#### *Article 27*

BIO understands that according to this language a company providing a study drug for an investigator-initiated study would become sponsors and subject, therefore, to the responsibilities of sponsors established in the preceding articles of this Chapter. Accordingly, it is encouraged to consider rephrasing this Article.

### **Section IV – Structure of the Clinical Trial Site**

#### *Article 29*

BIO kindly requests that ANVISA consider clarifying whether this Article requires written documentation and, if required, whether ANVISA would clarify what is the minimum information to be contained in this documentation.

## **CHAPTER III - REQUIREMENTS FOR SUBMISSION OF THE DRUG CLINICAL DEVELOPMENT DOSSIER (DCDD):**

### **Section I – General Requirements for Request**

#### *Article 33, § 1 and 2*

BIO believes that clinical trials for biologics should be reviewed within a reasonable time and recommends that ANVISA introduce timelines for review. Establishing a reasonable timeframe is in accordance with the desire for Brazil to attract clinical trial research and develop the country as a global reference in this space.



Also, it is encouraged that different formats be proposed for Phase I and Phase II clinical trials given the different objectives and scope of the studies in comparison with Phase III clinical trials.

Furthermore, as aforementioned, and as provided in a separate section below, it is important to coordinate with CEP/CONEP in an effort to establish how to more efficiently analyze the proposals within reasonable timeframes.

For example, is ANVISA approval required before Ethics Committee submission or can Ethics Committee approval be submitted prior to ANVISA approval?

#### *Article 33*

During this period of 90 days for ANVISA to review a DDCD, BIO encourages ANVISA to provide additional language that will halt this 90 day period if an ANVISA request for more information is issued and the 90 day period will only be counted again at the moment of filing response to the request for information.

#### *Article 35 § 1*

It is recommended that language be included to provide for situations in which transfer of sponsorship may occur in order to clearly establish the obligations of the involved parties in subsequent communications with ANVISA.

### **Section II - Content and Format of the Request**

#### *Article 36, VII, a)*

With respect to the dossier of the product being studied and the request for a description of the active ingredient, it may not be possible to ensure stability of the active ingredient for the entire duration of a clinical trial. Therefore, BIO kindly requests that ANVISA reconsider the phrasing of this section of the Article so that results from stability studies are included that are sufficient to provide assurance that the drug product will be stable during its intended storage period.

#### *Article 36, VII, e)*

A request for a medicinal product's label or model thereof that is being studied does not seem appropriate for early development drugs. Accordingly, BIO requests that ANVISA consider altering this language or provide clarification on this specific section.

#### *Article 36, VIII, d)*

BIO is concerned with the timing of the request in section d) to provide a receipt of submitting for registration to the Brazilian clinical trial database. It would be unusual to



register a non-approved trial and it is BIO's understanding that this is not the intention of the article and, therefore, greater clarification on this specific point is requested.

*Article 36, VIII, e)*

Further clarification is also requested on whether this specific section is requesting a report from the local ethics committee, CEP, or a report from the national committee, CONEP.

It is also encouraged that ANVISA throughout this regulation provide clarification as to the interactions with the ethical committees CEP/CONEP, as aforementioned and as discussed in a separate section below.

*Article 37*

BIO would like ANVISA to clarify whether the Council for International Organization of Medical Sciences CIOMS Form I will be accepted in English and whether the translations are only applicable for the DDCD.

*Article 38*

BIO partially agrees with the terms of article 38 because BIO understands that it is very important to allow ANVISA to request further information it deems necessary for its assessment and monitoring of clinical development to ensure the safety of ongoing and proposed clinical trials.

However, BIO understands that this request for further information must be well grounded by ANVISA in order to not create significant obstacles preventing the development of the clinical trial.

In this sense, BIO kindly recommends the alteration of article 38 to allow ANVISA the possibility at any time request further information it deems necessary for its assessment and monitoring of clinical development so long as ANVISA provides adequate justification.

In addition, it is requested that a timeline be proposed for potential follow-up questions and dialogue between ANVISA and the parties involved in the clinical trial.

**CHAPTER IV - MODIFICATIONS:**

*Article 39*

With respect to submitting modifications to the DDCD, it is unclear to BIO whether a new 90-day period is triggered for ANVISA to provide a response or whether there is a shorter timeline for ANVISA's review of relevant modifications to the DDCD. It is further



encouraged that timelines are established for responding to submissions for modifications to clinical trials.

#### **CHAPTER V - AMENDMENTS:**

##### *Article 43*

Similar to the comment above concerning Article 39, there is some uncertainty as to whether the presentation of an amendment will trigger an additional 90-day period for a response from ANVISA or whether there are shorter timelines for review. Again, it is encouraged that ANVISA propose timeframes for providing responses to these important submissions.

#### **CHAPTER VI - SUSPENSIONS AND CANCELLATIONS:**

##### *Article 46, § 1*

Greater clarification is requested with respect to what ANVISA may refer to when stating that upon the cancellation of a DCDD, that no clinical trial related to the DCDD may continue. There is uncertainty as to whether this applies to trials involving just the same compound, class of compounds, indication or patient population. BIO encourages that ANVISA provide guidance on this question.

##### *Articles 47 and 48*

Article 46 of the Public Consultation provides that the sponsor may cancel or suspend a DCDD at any time provided that the cancellation or suspension is adequately justified and provided that a plan for monitoring the participants of clinical trials in place that have already begun has been established.

BIO agrees and supports this language. However, BIO is concerned with the short timeframes of 15 and 7 days respectively in articles 47 and 48 to provide ANVISA the necessary technical-scientific justifications for any decision to cancel or suspend a clinical trial. Accordingly, BIO requests ANVISA to review the terms provided by articles 47 and 48 to allow flexibility in preparing this report and specifically allowing for the opportunity to submit a report late so long as adequately justified within the proposed timeframe of 15 or 7 days.

##### *Article 49*

It is kindly requested that ANVISA propose timelines for reviewing requests to reinstate clinical trials that have been suspended.

##### *Article 50*





BIO partially agrees with the terms of article 50 because BIO understands that it is very important to allow ANVISA, at any time, to terminate or suspend the DCDD or any linked clinical trial, if it deems that the conditions for approval were not met or there are safety/efficacy reports that significantly affect the clinical trial participants or the scientific validity of the data obtained.

However, BIO understands that this allowance must be well grounded and justified by ANVISA. Also, BIO understands that it is necessary to allow the entities sponsoring the clinical trial the possibility of presenting an administrative appeal against any decision by ANVISA to cancel a clinical trial or DCDD.

In this sense, BIO kindly recommends and requests ANVISA the alteration of article 50 to allow ANVISA the possibility at any time to terminate or suspend the DCDD or any linked clinical trial so long as it is justified by ANVISA's technical committee and so long as the entities sponsoring and/or conducting the clinical trial have the right to file an administrative appeal against such decision.

## **CHAPTER VII - MONITORING OF SAFETY AND ALERTS:**

### **Section I – Monitoring Adverse Events**

#### *Article 52*

The data to be collected and ultimately submitted to ANVISA according to this Article appear to present some potential issues to the design and structure of certain clinical studies. For example, in order to determine whether an event occurs more frequently in the experimental group compared to the control the study needs to be unblinded. It follows that such an assessment would not be performed by the sponsor until the end of the study. Would ANVISA please therefore clarify whether the expectation according to this Article is that sponsors should perform unblinded analyses prior to database lock?

It is further noted that comparisons may be performed by a data and safety monitoring committee but this information should not be included in the annual report in the opinion of BIO as this may compromise the integrity of studies.

Accordingly, BIO greatly appreciates clarification on these specific issues.

#### *Article 53, sole paragraph*

Further clarification is requested concerning the obligations of the investigator and the sponsor accompanying the pregnant trial participant. There may be privacy issues, for example, that may need to be considered that may affect Sponsors.

### **Section I - Subsection I - Immediate Measures:**

#### *Article 54, § 1*



It is encouraged that this language be altered to make it clear that these measures may include the temporary suspension of a clinical trial. Otherwise, there is the potential that a severe adverse event may result in the suspension of the trial. BIO kindly requests clarification on these points.

#### *Article 55*

This Article refers to the notification of, among others, "definite adverse events". It is requested that ANVISA consider defining more clearly the term "definite adverse event".

Furthermore, BIO requests clarification on which standard is to be used for the notification described in this Article. Would the standard to be used be CIOMS?

#### *Article 56*

BIO supports and agrees with the terms of article 56. However, it is not very clear to BIO who will comprise this clinical trial safety monitoring committee.

In this sense, BIO kindly requests ANVISA to clarify this point and provide suggestions as to how this independent committee will be formed.

Furthermore, Article 11 states that an independent data monitoring committee is said to be mandatory and not an independent safety monitoring committee. In addition, relating back to Article 52, any reports would be closed to protect the integrity of the study.

In general, greater clarification on this Article is requested in order to address the mandatory elements being requested by ANVISA and to determine how to properly address severe adverse events.

### **Section I - Subsection II – Notification of Adverse Events by the Investigator**

#### *Article 57*

With respect to the potential death of a study participant in Section 1, it is suggested that language be provided requiring the investigator to provide a report to the sponsor which includes an opinion on causality.

With respect to Section 3, BIO would like to request ANVISA to please also consider adding the protocol to the document pre-specifying the adverse events that are not immediately reportable by the investigator.

#### *Article 58*

Again, it is encouraged in this Article to consider revising the current phrasing from any adverse event unrelated to trial participation as this may potentially induce patients to participate in clinical trials. Although this Article is applicable to investigators and, hence,



does not directly present an obligation to the sponsor, there is a potential to create situations in which investigators seek reimbursements from sponsors. Furthermore, it is also noted that some adverse events may not be applicable and there may be no treatment for them. Accordingly, further guidance is kindly requested on these specific points.

## **Section I - Subsection III e IV – Notification of Adverse Events and Deadlines**

### *Articles 59 and 62*

In general throughout the regulation ANVISA requests that it be notified of information and particularly in these two articles of significant adverse events. However, the regulation is unclear as to which technical department of ANVISA should be promptly notified. Considering the tight deadlines to present information and the importance of the information to be shared, greater clarity on who and which department specifically should be contacted is critical to ensure that the information is properly processed by the responsible ANVISA coordinating team. BIO encourages greater clarity therefore on these points throughout the proposed regulation.

In addition, there are no clear criteria on what sort of standard is to be used in these reports. For example, is the sponsor to follow CIOMS protocol in drafting reports or does it refer to another form of report with consolidated data?

Furthermore, the 7 day timeframe is different from the EU 15 day timeframe. Would ANVISA be willing to allow for a slightly extended timeframe, particularly in view of the provision provided for in Article 82 stating that international guidelines may be used in order to resolve certain unforeseen cases?

### *Article 60*

With respect to Article 60, there is a question as to how investigators are to be notified. For example, are expedited (CIOMS) or periodic reports (PSLL) to be provided? Are the reports to include global events or only those reported to ANVISA and are events to be reported only from this study or from all ongoing studied on the same substance?

Given these questions, BIO encourages ANVISA to provide additional guidance on the application of this specific article.

## **Section II - Subsection I – Monitoring Reports of Clinical Trials**

### *Article 66*

In an effort to provide optimum reports with detailed analysis of clinical trials, it is important that the 90 day timeframe for submitting a final report is struck from Section 2 of this Article. A 90-day window to submit a final report is not sufficient, particularly



for results of primary efficacy, and BIO suggests that the final report be submitted within the deadline informed by the Sponsor in the study's termination form.

It is encouraged that a 12-month period after completing the last visit is considered as a reasonable timeframe for submitting a final report.

## **CHAPTER IX - Importing**

### *Article 73 § 1a) and b)*

There may potentially be situations where a Certificate of analysis is not available, and therefore it is suggested that the language of a) and b) be replaced with the following: "release certificate of the imported drug product under investigation, certificate of origin or similar document signed by responsible technical representative."

### *Article 75*

There may potentially be situations where a Certificate of analysis is not available, and therefore it is suggested that a) and b) be replaced with "release certificate of the imported drug product under investigation, certificate of origin or similar document signed by responsible technical representative."

## **Appeal for Greater Collaboration between CEP/CONEP and ANVISA Clinical Trial Regulations within the National Council of Health:**

In Article 33 of the proposed regulation, ANVISA clearly demonstrates its interest in providing timely responses to proposals to initiate clinical trials in Brazil. However, as aforementioned, in order to realize clinical trials in Brazil a sponsor must obtain approval by a clinical trial site's ethics committee (CEP). It is well known that one of the major obstacles in realizing clinical trials in Brazil is the significant delay of obtaining approval from the ethics committees and the need to present proposals to two different government entities – ANVISA and CEP/CONEP – prior to initiating any clinical tests.

Given that the ethical questions with respect to clinical trials fall outside the scope of ANVISA's regulatory authority, BIO recognizes how ANVISA is unable to remedy delays experienced by sponsors before the CEP/CONEP ethical committees.

Nonetheless, aware of the importance of establishing realistic timelines that are competitive globally, BIO understands that ANVISA may be an important ally in presenting before the National Council of Health arguments to improve clinical trial regulations as a whole that address the patient safety issues that fall under the scope of ANVISA's regulatory obligations while also addressing the ethical considerations that are the responsibility of CEP/CONEP.

Therefore, in order to truly improve the clinical trial regulatory environment in Brazil, BIO encourages ANVISA to coordinate with the National Health Council in an effort to



improve regulations with respect to ethical approval of clinical trials so that the efforts and compromises of ANVISA to review in a timely manner applications are not done in vain while sponsors continue to experience unreasonable delays from the ethical review boards.

BIO believes that only through this coordinated effort across government institutions will Brazil be able to make the jump to becoming a true global and regional force in attracting impactful clinical trials that will improve patient access and positively influence the local environment for innovation and biopharmaceutical expertise.

### **Compassionate Use Program**

This is not the main theme and is not mentioned directly by the Public Consultation #65, but it is a topic intrinsically related to clinical trial regulations and a topic which BIO would like to take the opportunity to address. The compassionate use program guarantees free orphan drug supply to those who have participated in a phase III clinical trial in Brazil and that benefitted from the drug. However, because the patient population for a rare disease is limited by nature, the sponsor's Brazilian market for the respective orphan drug may be entirely or significantly comprised of its successful phase III trial patients, creating difficult challenges for producers of an effective drug to effectively commercialize their product in Brazil. BIO kindly requires ANVISA to revisit this policy, bearing in mind that an alteration to this compassionate use program regulation may, particularly in addition to the strong proposed regulations contained in the Public Consultation no. 65, result in a noticeable increase of clinical trials in the country.

### **Conclusion**

BIO views the proposed regulations as a positive development in Brazil that demonstrates the desire of ANVISA to establish clearer rules for clinical trial regulation and that seeks, secondarily, to address backlogs in reviewing drug market approval applications through the close coordination of the review of a dossier with the monitoring of clinical trial studies.

The rules offer clear guidance as to how ANVISA will review clinical trial proposals. The rules also demonstrate ANVISA preoccupation and desire to be more efficient in reviewing proposals and demonstrate ANVISA's wish to closely monitor the realization of clinical trials in Brazil in an effort to create a safe environment for Brazilian patients.

BIO encourages ANVISA to coordinate with CEP/CONEP and the National Council of Health in order to create overarching norms that will, in addition to the proposed ANVISA regulations, help make Brazil a competitive country for conducting clinical trials. This coordination is particularly important to address the concerns regarding the ethical approval of clinical trials which are not addressed by this Public Consultation considering that this regulatory authority falls outside the scope of ANVISA.



In addition to the close coordination with the Federal Government on these questions, BIO believes that through the continued close collaboration with the global biopharmaceutical industry ANVISA and the Brazilian government will be able to continue to develop rules for establishing a clinical trials framework that will strengthen the biopharmaceutical sector in Brazil for years to come.

BIO again applauds your efforts to re-evaluate your existing policies and appreciates the opportunity to work with ANVISA to achieve a positive, innovation and patient-safety focused regulatory framework that addresses the short-, medium- and long-term concerns of ANVISA and the Brazilian population.

Respectfully submitted,

A handwritten signature in black ink that reads "Joseph M. Damond". The signature is written in a cursive style with a large, stylized initial "J".

Joseph Damond  
Senior Vice President, International Affairs  
Biotechnology Industry Organization (BIO)