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Anvisa



QUESTIONS & ANSWERS

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Subject:

Main questions
about RDC 09/2015
(Clinical Trials
Conduction)

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1. INTRODUCTION

With no harm to the existing determinations in the legal provisions, this document is intended to present the questions received until now about the RDC 09/2015 through all customer service channels.

The document was divided into sections that group the doubts around a theme. Anyway, some of the questions could fit in multiple sections; in order to avoid repetition and easier access, no question was repeated in different sections.

We suggest the use of the "Find" tool for a faster research.

The questions received will be assessed to subsidize the document review and the resulting publication of a new version, at every update.

The abbreviations used in this document have the same meaning of those described in the RDC 09/2015 and the manuals associated with the standard.

A history of changes was added to the document for a better control of the changes performed since the last version.

2. SCOPE

This document covers doubts received by COPEC about RDC 09/2015 and applies to all parties interested in obtaining information about clinical trials conduction in Brazil.

3. QUESTIONS AND ANSWERS

3.1. SUBMISSION

3.1.1. **Can the documents to be filed at Anvisa be submitted foreign language (e.g.: English, Spanish, German, French...)?**

According to the guidance of the Manual for Submission of Medicine Clinical Development Dossier (DDCM) and Specific Dossier of Clinical Trials, we recommend that all documentation be submitted in Portuguese, especially the clinical protocol and the investigator's brochure, because the technical area evaluator may issue a requirement asking for the free translation of the submitted documentation.

3.1.2. As soon as a DDCM is filed, is there any deadline to file a clinical trial specific dossier?

There is no deadline; however, the absence of a specific dossier is reason for rejection. According with the RDC 09/2015:

Art. 34. The sponsor must submit a DDCM to Anvisa only in those cases in which they plan to perform clinical trials with medicines on national territory.

Sole paragraph. For analysis purposes of the DDCM, at least one specific dossier must be filed for a clinical trial to be conducted in Brazil.

3.1.3. Upon the submission of a DDCM by a CRO representing a sponsor with no affiliate in Brazil, is it necessary to present a letter delegating responsibility from the sponsor to the CRO along with the dossier?

According to Art. 20, §2 of RDC 09/2015, any functions associated with a clinical trial that are transferred to a CRO and taken on by it must be specified in writing in a document signed by the sponsor and the CRO. However, this document does not need to be filed along with the DDCM because this type of documentation will be checked during the GCP inspections.

3.1.4. Art. 38, item VII, subparagraph i, of RDC 09/2015 informs that in case the investigational drug already holds a registration in Brazil, only data about proposed post-registration changes should be sent. If the investigational drug has already been submitted to Anvisa for a registration request, but is still awaiting analysis, does all data on the investigational drug need to be sent in the DDCM?

Yes. Because the medicine has not yet received its registration approval, all the data must be sent. However, we kindly ask that the dossier bears the information that the medicine is awaiting for its registration approval along with the respective registration process number at Anvisa.

3.1.5. What needs to be requested or filed manually?

All the requests need to be made electronically. Regarding the filings, only the DDCM will be made manually. All the remaining documents (specific clinical trials dossiers and secondary filings) must be filed electronically. So, for the DDCM the request is electronic, and the filing is manual. For the remaining documents, both the request and the filing are electronic.

3.1.6. In case the sponsor decides to study new indications, doses, pharmaceutical forms, different from those foreseen in the plan, does a new DDCM need to be sent to Anvisa?

No. Any change associated with the same API/active substance continues to be part of the same DDCM.

3.1.7. How should the submission be made in the case of an association of two medicines?

If it is a fixed dose combination (FDC), the sponsor needs to send a single DDCM.

If they are distinct medicines, but of combined/joint use in all indications, a single DDCM must be sent.

If they are distinct medicines, but used independently, two DDCMs must be sent, with one

DDCM (e.g., DDCM “A”) being linked with the specific clinical trial dossier, and the other DDCM (e.g., DDCM “B”), send a note in both DDCMs (A and B) informing that that specific dossier has been filed in the previous DDCM (DDCM “A”). We highlight that in this exceptional situation the evaluation of DDCMs will only occur when both are requested and the respective CEs (Special Communication) will only be cleared after the evaluation of both, due to the need to evaluate the quality of both investigational drugs. In addition, the company responsible for the specific dossier in the DDCM A will be the one that must submit adverse events, reports and other obligations as described in RDC 09/2015. It is worth highlighting that in these cases, it is important to indicate in the DDCM Request Form and at the moment of requesting the DDCM, if there are clinical trials approved at the time of RDC 39/2008 validity, assessing the investigational drug, for inclusion in the Special Communication.

Always follow the same rationale as if submitting a registration request.

3.1.8. Do Phase IV/Observational studies that involve importation or exportation procedures need to be linked to a DDCM?

For those cases in which a medicine already has a filed DDCM, the study shall to be sent as a Clinical Research Notification – Phase IV/Observational connected to the DDCM (subject code 550).

In case the medicine at issue has no DDCM, the study shall to be sent as a Clinical Research Notification – Phase IV/Observational non-connected to the DDCM (subject code 10040).

3.1.9. When a study that has been approved per RDC 39/2008 is linked to a DDCM, will Anvisa inform the company that had filed this clinical trial about the link?

No. It is the sponsor's responsibility to inform the delegated companies about this link.

3.1.10. Is it possible to register a study in a data base other than the bases mentioned in Art. 3 and Art. 38 of RDC 09/2015? In case the proof of registration in the international database is not yet available, is it acceptable to send a letter along with the dossier explaining such a situation and, in the future, amend the process with the proof of registration in the international database?

We cannot accept exceptions to what is established in the standard. According to Art. 3 and Art. 38, VII, d, proof of registration of the clinical trial in the registration database of the International Clinical Trials Registration Platform / World Health Organization (ICTRP/WHO) or others recognized by the International Committee of Medical Journals Editors (ICMJE) must be presented.

3.1.11. How do centers have to proceed when they do not have their own CNES (National Register of Health Establishments), but are linked to an institution that has one? In this case, it is acceptable to send the CNES of the institution to which the site is linked.

3.1.12. In those approvals by lapse of time (according to Art. 36) will a CE be issued after the clearance of Document for Importation of Products under Investigation of the DDCM?

In the approvals by lapse of time the Document for Importation of Product(s) under investigation of the Medicine Clinical Development Dossier (DDCM) will be issued. In this case there is no

issuance of a CE. The CE is only issued if, for any reason, this trial is reassessed by Anvisa at any time in the future.

3.1.13. Will the CE be updated at every clinical protocol that is filed? Will the company filing the clinical trial receive the updated CE?

The CE or the Document for Importation of Products under Investigation of the DDCM will be updated at every protocol that is filed.

For any update of the CE or Document for Importation, only the company that has filed the DDCM will receive this documentation. It is this company's responsibility to forward the updated document to the companies that have filed the specific clinical trials dossiers.

3.1.14. Item "d" of Art. 38, subsection VII (*description of the comparator medicine when it is modified for the clinical trial, including information that ensure the maintenance of the medicine's original characteristics*) is not listed in the checklist of the subject code 10755 – CLINICAL TRIALS – Approval in a process of Medicine Clinical Development Dossier (DDCM) of CROs – Biological Products. The checklist was corrected mentioning the documentation according to the RDC.

3.1.15. In case there is the desire to conduct a clinical trial with an already registered investigational drug, how to proceed to check whether the medicine already has a DDCM filed or approved by ANVISA?

If the intended clinical trial fits the standard scope, i.e., the clinical trial with a medicine intended for registration (in this case, post-registration), the trial must be presented via DDCM following the instructions established in the RDC 09/15 (according to Art. 2). In case it is a trial intended exclusively for academic purposes (the data obtained by

the trial will not be able to support any registration intention), then the RDC 09/2015 is not applicable, yet the trial must hold the necessary ethical approvals.

In order to check if the product already has a DDCM filed or approved by Anvisa, it is necessary to check this information with the medicine registration holder and check whether they authorize the applicant to use the information previously submitted by them. If the registration holder does not authorize the use of their information, then the sponsor-investigator must submit literature information to Anvisa to support the rationale of the proposed development, as explained in Art. 38, item VII subparagraph “j” of the resolution.

3.1.16. In field 8 of the Request Form for DDCM Approval (name of the investigational medicine manufacturer) do all companies involved in all manufacturing phases need be listed or only the primary manufacturer?

As the information of all manufacturers will be described in the investigational medicine dossier (according to the Manual of submission of Quality Requirements relative to Products under Investigation Used in Clinical Trials, section 3.2 – “Overall Description of the manufacturing and packaging process), in the field 8 only the primary manufacturer needs to be listed.

3.1.17. In those cases, in which the comparator medicine of a clinical trial belongs to another company, can the field 23 be filed in the Clinical Trial Submission Form (countries where the comparator medicine is approved) as “Not Applicable”? Yes.

3.1.18. Is the information regarding CROs asked in item 48 of the Clinical Trial Submission Form relative to the CROs hired in Brazil or all the participating countries?

Only for Brazil.

3.1.19. Do fields 36 to 50 of version 3 of the Clinical Trial Submission Form (FAEC) need to be filed only for modified comparator or placebo?

No. These fields must be filed for any kind of active comparator to be used in the clinical trial (modified or not) and placebo.

3.1.20. How to fill field 64 of the Clinical Trial Submission Form (FAEC) version 3 when the study is phase II/III?

In this case, the company must select options "II" and "III" concomitantly.

3.1.21. How does the Clinical Trial Submission Form (FAEC) need to be filed when there is more than one concentration of the investigational medicine?

In fields 29 to 35 of FAEC's version 3 the information of each formula must be added, according to the following example:

29	Form. No.	30	Pharmaceutical Form	31	Components of the formula	32	DCB/DCL/CAS RN Code	33	Type	34	concentration Quantity/ Volume	35	Formula Demonstration Unit
1		XXX		API Name	XXX	XXX	XXX	100 mg	XXX				
				Excipient A	XXX	XXX	XXX	XXX					
				Excipient B	XXX	XXX	XXX	XXX					
2		XXX		API Name	XXX	XXX	XXX	200 mg	XXX				
				Excipient A	XXX	XXX	XXX	XXX					
				Excipient B	XXX	XXX	XXX	XXX					

3.1.22. What is the difference in filling the FAEC submitted for the first time to Anvisa and the subsequent submissions?

When there is change of any information in the form, item 18 has to be answered as YES, then selecting which is the change performed.

3.1.23. How to fill field 10 of the Request Form for approval in DDCM process when the medicine is already registered, but by different manufacturers?

In this case, make a comment in field 10 that the registered medicine belongs to another manufacturer and inform the registration number of this other manufacturer.

3.1.24. In the request form of the DDCM (field 15) and in the FAEC (field 54) the list of participating countries is requested. Would it be possible to put only the participating regions in the DDCM form and the full list in the FAEC?

Yes.

3.1.25. If some of the information requested by RDC 09/2015 is not yet available due to the development stage of the investigational medicine, is it acceptable to justify the absence of such information and send them to Anvisa when they become available?

Anvisa understands that the amount and detailing of the documentation is directly related to the development phase. Thus, its absence must be justified. However, if this information is essential for the DDCM approval, a requirement will be issued, and the analysis will only be finished after this information is submitted.

3.1.26. In the development plan, not always all information about each clinical trial will be available (e.g.: endpoints, hypotheses, comparator, statistical planning). It is acceptable to place a comment that the information is not yet available?

Yes. We know that not always all information requested will be available at the moment of the DDCM submission. However, we highlight that at the moment of submitting a specific dossier for the clinical trials that contained missing information in the development plan, Anvisa will consider that this is a clinical trial

not foreseen in the Development Plan, once it was not possible to carry out a prior evaluation of the information described in subparagraph h, item III, Article 38 of RDC 09/2015. Thus, in this case, the company must consider this request as "10818 - CLINICAL TRIALS - DDCM Change - Inclusion of clinical trial protocol not foreseen in the initial development plan".

3.1.27. Is it possible to submit along with requirements fulfillment, information that has been updated or changed in the period between receiving the requirement notification and its fulfillment? (Example: Expiry date change)

No. Changes must be submitted according to specific subject.

3.1.28. How to proceed in cases in which a Phase II study is submitted and there is still an ongoing Phase I study?

If the Phase II study depends on the results of the Phase I study to be started, it is necessary to await its completion to submit the Phase II one. Otherwise, the Phase II trial submission can be done concomitantly.

3.1.29. In the checklist of all electronic requests, the CD-ROM and the proof of Inspection Fee payment (or exemption) are listed as documents to be sent. Considering it is an electronic request, do they need to be sent?

No. System's error has already been corrected.

3.1.30. Regarding subparagraph "j", item VII of Art 38, how must the indexed literature be sent? Is it necessary to print or just list the articles?

It is recommended that the indexed literature is mentioned in the physical document and sent electronically in the same CD-ROM in which the DDCM documentation is sent.

3.1.31. Does the DDCM need to strictly follow all subitems listed in the quality requirements submission manual regarding all products under investigation?

We recommend that the manual items are followed, for the analysis to be carried out faster. If it is not followed, technical rationale must be sent justifying the absence of documentation.

3.1.32. What kind of documentation must be sent when using an active comparator not registered in Brazil, but registered in other countries?

The company must inform in which countries the medicine is registered and the reason for not using as comparator a medicine already registered in Brazil.

3.1.33. In case of two fixed dose combinations, registered separately, containing the same APIs, but in different concentrations, do two DDCMs or a single DDCM need to be filed?

If they are the same APIs, and the medicine in different concentration belongs to a same manufacturer, a single DDCM must be filed.

3.1.34. Once Anvisa requests a CD-ROM containing separate DDCM files with the copy/paste function active, is it still necessary to number and initialize the CD files pages?

Regarding CD-ROM files, which in some cases may contain documentation greater than the physical one (such as articles backgrounding some understanding regarding the process) it is not necessary to number and

initialize, but regarding the physical documentation, this requirement is still necessary.

3.1.35. Article 38, subparagraph VII, item i of RDC 09/2015 informs that if the investigational medicine already holds registration in Brazil, only data supporting proposed post-registration changes must be sent. If the investigational medicine already holds registration in Brazil, and it is being studied for a new indication, does all data of the investigational medicine need to be sent in the DDCM?

Data supporting the study of this new indication (such as clinical and non-clinical safety and efficacy data) must be submitted. If the dose, dosage, route of administration and pharmaceutical form is different from the registered one(s), product quality data must also be submitted in the DDCM.

3.1.36. For the conduction of a clinical trial for registration renewal, does the company need to file all the registration documentation in the DDCM?

The company must follow the same rationale as for post-registration change. According to item "i" do subparagraph VII of Art. 38 of RDC 09/2015, if the investigational medicine is already registered in Brazil, only the information supporting the proposed post-registration changes must be submitted in the DDCM. Thus, only the information necessary to support the clinical trial conduction for registration renewal must be submitted along with the DDCM.

3.1.37. How does the DDCM or DICD submission need to be in the case of a product that is an investigational medicine and an investigational medical device? And if the medical device is already registered? The DDCM/DICD submission must follow the same rationale that would be done in case of submission for registration, i.e., if the registration will be together (investigational medicine + investigational

device), the company should file a dossier (DDCM or DICD) based on where the product will be registered (in the General Management of Health Products/GGTPS or in the General Management of Medicines and Biological Products/GGMED). If the medicine and the investigational device registration is performed separately, the company should file a DDCM with quality information of the investigational medicine and a DICD with quality information of the medical device. In this case, it is important to mention in the DDCM that a DICD has been submitted in parallel for the medical device and even, if possible, inform the corresponding process number.

If the medicine is investigational, but the medical device is registered, the company should only submit the DDCM.

3.1.38. For the DDCM, the sponsor's local affiliate must be responsible for the initial submission and for the updates. However, can the safety notifications (for example, investigational medicine development safety update reports – DSUR) be transferred to a CRO?

Due to the system's conditions, only the applicant that filed the primary request at Anvisa is able to make subsequent submissions, including safety notifications, such as the DSUR. According to paragraph 1 of Article 37 of RDC 09/2015, "the party responsible for DDCM before Anvisa must be the same for all subsequent submissions related to it", and paragraph 2 "submissions by CRO may only be made when the sponsor does not have a headquarter or subsidiary in Brazil".

Therefore, it is not possible that activities of documentation submission to Anvisa, related to the DDCM, are delegated to a CRO when the initial submission of the dossier was carried out by the sponsor.

3.1.39. If a CRO is the holder of a molecule DDCM, do all notifications of serious adverse events, annual reports, etc., regarding the studies with that molecule need to be performed by this CRO?

Every update related to the DDCM (for example, update of an Investigator's brochure) must be performed by the company that filed the DDCM, in this case, the CRO.

Updates related to a specific clinical trial (for example, notification of serious adverse event) must be sent by the company that filed the referred clinical trial.

3.1.40. After finishing the participation in a certain phase 3 study, participants will be recruited to participate in another protocol (also phase 3), in which they will only be followed up. In this second protocol, there will be no administration of investigational medicine. Because this is a phase 3 study, does the long-term follow-up protocol need to be submitted as "specific dossier for each clinical trial" (Approval on Clinical Research Process) or do we have to follow another procedure for submission, once there will be no investigational medicine administration?

As the follow-up protocol will not have investigational medicine administration, the study must be submitted to Anvisa as an observational study, with the subject code 550 - CLINICAL TRIALS - Notification in Clinical Research - Phase IV/Observational linkable to the DDCM.

3.1.41. Can a DDCM containing only one clinical study already approved during RDC 39/2008 validity be submitted?

No. In compliance with the Sole Paragraph of Article 34 of RDC 09/2015, "for the purpose of DDCM analysis, at least one specific dossier of clinical trial to be performed in Brazil must be filed." Therefore,

if there are only clinical trials approved by RDC 39/2008 that would be linked to the DDCM, the company must wait for the preparation of a new clinical trial to be performed in Brazil to file the DDCM. Meanwhile, each clinical trial approved by RDC 39/2008 must keep following the wording of the standard in force at the time of its approval.

3.1.42. Regarding safety and efficacy, what kind of information is expected in the investigator's brochure (subparagraph IV of Article 38), in the summary of safety aspects (subparagraph V of Article 38) and in the critical analysis of the non-clinical and clinical trials (items "g" and "h" of subparagraph VII of Article 38)?

Regarding safety and efficacy, the investigator's brochure is expected to have a summary of the results obtained so far with the investigational medicine, including results from non-clinical and clinical trials, assistance programs (expanded access, compassionate use, post-study supply) and, if applicable, post-marketing information. In the summary of safety aspects, a summary of all medicine safety data is expected, with a focus on the safety alerts and risks associated to the investigational medicine. Finally, for a critical analysis of non-clinical and clinical trials, a discussion of the results obtained so far and how these results support the next stages of clinical development is expected. For the latter document, the company must not send a summary of the clinical and non-clinical data, as this information is already available in the Investigator's Brochure.

The ICH E2F guide Development Safety Updated Report (DSUR) covers the summary of safety aspects and the critical analysis of clinical trials, and therefore, can be submitted replacing these items. However, we highlight that for the item of critical analysis of the non-clinical and clinical trials, there are other information besides those of safety and efficacy and these must be submitted, as described in the DDCM Submission Manual and Clinical Trial Specific Dossier.

3.1.43. How to proceed in the cases where two products have the same molecule, but with different registration numbers, process and trade name due to the distinct dose and/or indications? Does the registration holder need to submit one DDCM per product or a single DDCM for the molecule or combination?

If the medicine belongs to the same manufacturer, the company must submit a single DDCM. In case of different manufacturers, the DDCMs will be separated.

3.1.44. Do Phase IV clinical trials that do not have importation and exportation process also need to be notified at ANVISA?

Yes, provided that they have information to support the registration (such as clinical trials assessing the medicine safety after its registration). According to Article 3, the post-marketing clinical trials (phase IV) are not primary object of this standard and are only subjected to Clinical Trial Notification.

3.1.45. In addition to the treatment with the study medication, the protocol indicates the use of adjuvant therapy. Is it necessary to provide information about the medicine used as adjuvant therapy or just list it in the clinical trial presentation form (item of the products to be imported) is enough? Considering that this adjuvant therapy is not the study comparator, but only the background therapy, the medication must only be informed in the clinical trial presentation form, if it is intended to be imported. However, it is expected that further details about this therapy are described in the referred protocol (such as the rationale for choosing this therapy and the rationale for choosing the doses).

3.1.46. In which situations does the clinical trial protocol need to be sent to CETER?

There is no need to send a clinical trial protocol to Ceter, but rather the results of pharmacokinetic studies or literature, depending on the case, as defined in two specific Technical Notes.

Technical Note 09/2015: Related to the Relative Bioavailability studies for demonstration of pharmacokinetic interaction in the ADF cases through subject 10839 - Pharmacokinetic Interaction Studies for Clinical Trials Approval. In this case, it is a primary request from which Copec needs to have data of this study in order to start the evaluation of the ADF clinical trials, since the evaluation of the relative bioavailability will drive the development plan regarding the conduction of Phase 2 or 3 clinical trials.

Technical Note 118/2016: Comparative pharmacokinetic studies for biosimilar DDCMs. In this case, the evaluation between Copec/Ceter occurs jointly. Copec evaluates the pharmacodynamic data Ceter the pharmacokinetics, as explained in the technical note. Thus, the document to be sent to Ceter is a request secondary to the DDCM (10900 - Comparative Pharmacokinetic studies for investigational medicines – Biosimilar Products - submitted as DDCM).

Further information can be obtained through the Technical Notes available on Anvisa's website (<http://portal.anvisa.gov.br/informes-medicamentos>).

3.1.47. How to know if a PK/bioequivalence study has to be a primary request sent for Therapeutic Equivalence Coordination (CETER) analysis? How to know at which moment

does this request need to be submitted (before DDCM's submission or concomitantly)?

Submission of requests to Ceter must be according to Technical Notes 09/2015 and 118/2016, available at Anvisa's website (<http://portal.anvisa.gov.br/informes-medicamentos>).

3.1.48. Regarding the pharmacokinetics interaction studies, what is the deadline for CETER's analysis? Will CETER issue a CE? Can't the analysis exceed the deadline foreseen in RDC 09/2015?

There is no legal deadline for CETER's manifestation, however, in these cases, CETER analysis will be prioritized. CETER will not issue a CE. In the cases of primary requests (ADF assessment), the deadline established by the DDCM does not apply, once it is a CETER specific request. In the case of secondary requests, related to biosimilar products comparative pharmacokinetics studies, the deadline for the first DDCM manifestation regarding Copec's assessment will be the deadline established by the standard.

3.1.49. When should I use the subject code 10821 – Investigator's Brochure Update?

As soon as there is a new available version of the brochure, the company must file it in the DDCM process. If this update also leads to a substantial change or amendment, the company must file it concomitantly to the substantial change or amendment requests.

3.1.50. How does the link of a study approved by RDC 39/2008 to the DDCM have to be done in the system?

As described in the "MANUAL FOR SUBMISSION OF MEDICINE CLINICAL DEVELOPMENT DOSSIER (DDCM) AND SPECIFIC DOSSIER OF CLINICAL TRIALS" available on the Anvisa's website, "At the time of the electronic filing of one of the DDCM subjects, the applicant must answer the following

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question: "Are there approval processes filed at Anvisa to be linked to DDCM? ". If yes, the responsible for the filing must inform the process numbers of the approval subjects related to the DDCM investigational medicine, already filed at Anvisa (which may have already been analyzed, approved, rejected, canceled, be under requirement or awaiting technical analysis), which are part of the product's clinical Development Plan. Therefore, the approval processes already submitted to Anvisa must be linked to a single DDCM per investigational medicine."

It should be noted that the link must be made at the moment of the DDCM submission. After the DDCM submission, the company will no longer be able to link a previously approved clinical trial. In this case, the company must contact COPEC through the Call Center for the Agency to make this link, which may jeopardize the speed the Special Communication issuance. It should be noted that completing field no. 16 of the Request form for DDCM process approval is not enough for linking the clinical trial process approval to the DDCM process. Following is the template of the process linking screen:

Transaction Number ██████████	
Processes Linking	
01	Are there approval processes filed at ANVISA to be linked to the DDCM? <input type="radio"/> Yes <input type="radio"/> No
<input data-bbox="692 1458 788 1480" type="button" value=" << Anterior "/> <input data-bbox="815 1458 911 1480" type="button" value=" Próximo >> "/> <input data-bbox="943 1458 1023 1480" type="button" value=" Cancelar "/>	

3.1.51. When should I use the subject code “10917- COPEC – Withdrawal of request/process upon request” and subjects “10826 – CLINICAL TRIALS – DDCM cancellation upon request, “10767 - CLINICAL TRIALS - Clinical Trial Protocol cancellation upon request”?

The subject withdrawal upon request (10917) must be used when there is no conclusion about the request (approval/rejection) yet. The cancelling (10826 or 10767) must be used in the cases in which the decision has already been expressed by Anvisa.

3.1.52. In case of a previously approved DDCM, when should I include a new protocol with the subject of the specific dossier and when does it have to be submitted through the subject code “10818 – CLINICAL TRIALS – DDCM Change – Inclusion of Clinical Trial protocol not foreseen in the initial development plan”?

The specific dossier subject should be used when a previously approved DDCM Development Plan containing all items in item h, subparagraph III, Article 38 of RDC 09/2015 was submitted for that protocol to be filed. If there has been any change to the data previously informed in the Development Plan, these have been provided incompletely or the study was not previously comprised in the submitted plan, the company should make the filing using the subject code 10818 - CLINICAL TRIALS - DDCM Change - Inclusion of clinical trial protocol not foreseen in the initial development plan.

3.2. AMENDMENTS, CHANGES, SUSPENSIONS AND CANCELLATIONS

3.2.1. What is the difference of subject code for the amendments related to RDC 39/2008 and RDC 09/2015?

In the case of **RDC 39/2008**, all the amendments must be sent as notification, with the subject code 1395 CLINICAL TRIALS – Notification of amendment to the Clinical Research Protocol. As it is a notification, there will be no payment of fee.

While for **RDC 09/2015**, only the substantial amendments must be sent with the specific subject code. The subject code to be used is 10824 CLINICAL TRIALS – Substantial Amendment to a Clinical Protocol. In this case, as the amendment is subjected to Anvisa's approval, there will be payment of fee. The non-substantial amendments must be sent along with the annual clinical trial follow-up report. It should be noted that the definition of Substantial Amendment and Non-Substantial Amendment is available on the Manual for Submission of Changes, Amendments, Suspensions and Cancellations", available at Anvisa's website. It is important to not confuse the subject codes, once it may generate a new submission of the document and a delay on its analysis and approval.

3.2.2. What is the subject code for notification of principal investigator change and inclusion or exclusion of sites by RDC 09/2015?

This kind of change must be notified using the subject code 10823 – Change in the Clinical Trial Submission Form.

This type of change does not generate the issuance of a new CE. However, the immediate update is important for the clinical trial information to be always correct at Anvisa's website. In addition, this updated information is necessary for assessment in GCP inspections.

3.2.3. How to submit an extension study? And the extension of an ongoing study?

The extension of an ongoing study is done through non-substantial amendment, provided the same enrolled participants, same design, methods and objectives of the original project are maintained. If there is any of these changes, or there is a new protocol as extension study in advance, a clinical trial specific dossier linked to a DDCM must be filed. Therefore, a study extension is a non-substantial amendment and an extension study is a new clinical trial specific dossier.

3.2.4. Should substantial amendments continue to be sent even after the study is finished in Brazil?

In this case, it is not necessary to send them. However, if there is a new protocol to be linked to the DDCM, these amendments must be sent.

3.2.5. How to proceed in the cases in which a substantial amendment to be filed does not have an approval unified opinion from the IRB yet?

According to Article 22 and Article 23 of RDC 205/2017 (establishing special procedure for approval of clinical trials, certification of good manufacturing practices and registration of new medicines for treatment, diagnosis or prevention of rare diseases), as of 27/Feb/2018, IRB opinion letter no longer needs to be submitted to Anvisa for approval in clinical protocols and subsequent amendments.

3.2.6. In case there is a substantial change to the DDCM that may also fit as a substantial amendment to the clinical

trial, will there be fee payment for both requests? Is it possible to reduce one of the fees?

Yes, there will be payment for both requests. Fee-related issues must be discussed directly with Fee Collection Management (GEGAR) of Anvisa.

3.2.7. In case there is change of the information related to products under investigation (for example, change of the storage conditions) and there are several trials being conducted, does the change need to be filed for each clinical trial, in addition to the DDCM?

Yes, this type of change must be filed for each clinical trial that was affected by the change. The subject code to be used is 10823 CLINICAL TRIALS – Change of Clinical Trial Submission Form.

For the DDCM, in case the change is a substantial change, it must also be filed as such.

3.2.8. On page 4 of the Manual for submission of changes, amendments, suspensions and cancellations, the update of the comparator medicine package insert is mentioned as an example of a non-substantial change, but it is not an item required in RDC 09/2015.

In some situations, the comparator medicine package insert is also sent. However, for a better understanding, this example will be removed from the next version of the manual.

3.2.9. Which changes in the form can be submitted in the annual report and in the safety report as mentioned on page 5 of the Manual for submission of changes, amendments, suspensions and cancellations?

None of the form changes must be sent in the annual report or the safety report. They must be

sent as soon as there is data change. The subject code to be used is 10823 CLINICAL TRIALS – Change of the Clinical Trial Submission Form (for a specific change of a clinical trial) or 10822 CLINICAL TRIALS – Change of the DDCM Request Form (for changes of the DDCM data).

3.2.10. On page 8 of the Manual for submission of changes, amendments, suspensions and cancellations “Change in the product under investigation, change in the dosage of the product under investigation, and change of the form of administration of the product under investigation” are mentioned as examples of substantial amendments. Aren’t those examples of changes to the DDCM?

Yes, those are substantial changes to the DDCM, but that can also fit as substantial amendments.

3.2.11. On page 9 of the Manual for submission of changes, amendments, suspensions and cancellations, the “Change in the clinical protocol design” is mentioned as an example of a substantial amendment. Could this change also be a substantial change?

No, once there is no inclusion of a non-foreseen or different protocol from the established or any other situation defined as a substantial change.

3.2.12. On page 9 of the Manual for submission of changes, amendments, suspensions and cancellations, the “Change in the documentation used by the study team to obtain and record data” is mentioned as an example of non-substantial amendment. However, this kind of information is not in the protocol.

This change in the documentation would be, for example, change the Case Report Form in paper for an electronic version. However,

for better understanding, this example will be removed from the next version of the manual.

3.2.13. Will the approval of substantial amendments, that do not result in a CE change, be informed by Anvisa through an official letter to the sponsor?

An updated CE will be sent informing the new version of the protocol regarding the amendment assessed.

3.2.14. For a substantial change due to the inclusion of a clinical protocol not foreseen in the development plan, how should the Clinical Trial Specific Dossier be filed?

In this case, the subject code is "10818 – CLINICAL TRIALS – DDCM change – Inclusion of clinical trial protocol not foreseen in the initial development plan" is a primary request and will be the Clinical Trial Specific Dossier itself. Therefore, only for this case, there is no need to file a clinical trial specific dossier, because the substantial amendment subject itself includes the specific dossier. It was necessary to do it this way for the company not to pay the fee twice (one for substantial change and another for specific dossier).

This information will be included in the next version of the Manual for submission of changes, amendments, cancellations and suspensions.

3.2.15. Considering that the inclusion of a clinical protocol not foreseen in the development plan is the clinical trial specific dossier itself, it is possible that the request is made through a company different from the one that filed the DDCM (for example, a CRO). In this case, how should the development plan update be submitted?

Considering that the sponsor filed the DDCM and the CRO filed the inclusion of a clinical protocol not foreseen in the development plan, there are two options to submit the plan update:

A) The sponsor sends the updated development plan to the CRO, and the latter submits the plan along with the other required documents.

B) The sponsor submits the updated development plan directly in the DDCM and the CRO makes a note that the updated plan will be submitted by the sponsor. In this case, the request analysis will only be completed when all the documents are available.

3.2.16. How to proceed in the cases in which the DDCM was approved by Anvisa, but for some reason, the linked clinical trial will no longer be conducted in Brazil?

The company must cancel the clinical trial through the subject code 10767 - CLINICAL TRIALS - Clinical Trial Protocol Cancellation upon request."

3.2.17. How to proceed in the cases in which the DDCM was submitted, but was not yet approved by Anvisa, and for some reason, the linked clinical trial will no longer be conducted in Brazil?

The company must cancel the DDCM through the subject code 10826 - CLINICAL TRIALS - DDCM cancellation upon request."

3.2.18. Considering a medicine whose DDCM is under analysis process at the Agency and during this period, the medicine registration is granted, does the company need to cancel the DDCM and submit clinical trial specific dossier as phase IV notification?

If the clinical trial may fit as a phase IV study, i.e., the medicine will be studied for the same indication and conditions claimed in the registration, the company will have the following options:

- 1) If the DDCM is already under analysis, the company must wait for Anvisa's manifestation;

2) If the DDCM still waits for analysis, the company may cancel the DDCM and file a Phase IV Clinical Trial Notification or wait for technical analysis.

3.2.19. Considering the parallel assessment of a DDCM and registration request of a medicine, how to proceed in the situations below?

- A) The registration is granted and the DDCM is still under analysis
- B) The registration is rejected and the DDCM is approved
- C) The DDCM is rejected and the registration is approved

Situation A: check the answer to question 3.2.18.

Situation B: It is necessary to understand the reason for the rejection to assess if the DDCM must be interrupted or not. If the rejection is, for example, due to lack of clinical data that will be studied in the approved DDCM, the DDCM will not be interrupted.

Situation C: Like in Situation B, it is necessary to understand the reason for the DDCM rejection to take any action regarding the registration.

3.2.20. Chapter V of RDC addresses the protocol changes. Can the same rationale be used for clinical trial changes, but that do not necessarily change the protocol? (e.g.: exclusion of sites)

Yes. In the specific case of site inclusion, for example, the company must perform the FAEC change request.

3.2.21. The exclusion of a clinical trial foreseen in the development plan fits as substantial change. However, does this protocol exclusion refer to a protocol whose specific dossier has already been filed at Anvisa or does it refer to a protocol mentioned in the development plan? Does this clinical trial refer to a protocol to be conducted in Brazil or another country?

The protocol exclusion refers to any protocol that was foreseen in the development plan, regardless if it was filed as clinical trial specific dossier and regardless if this study would be conducted in Brazil or only in other countries.

3.2.22. The "Manual for Submission of Changes, Amendments, Suspensions and Cancelations" published as a complement to RDC 09/15 contains an Attachment II (REQUEST FORM FOR SUBSTANTIAL AMENDMENT TO CLINICAL TRIAL PROTOCOL). Is it possible that this form be made available in the Word format, allowing the electronic filling? Yes. The forms in Word format are available at Anvisa's website (Medicines > Clinical Research > Guides and Manuals for Anvisa's new resolution providing for the Regulation for the Conduction of Clinical Trials with Medicines in Brazil > Attachments I and II Modifications and Amendments Manual).

3.2.23. In fields 1 and 2 of the Request Form for Substantial Amendment to Clinical Trial Protocol, should the DDCM process number or the clinical trial specific dossier be informed? It must be filed with the clinical trial specific dossier process number. In the 3rd edition of the Manual for Submission of Changes, Amendments, Suspensions and Cancelations, the form (Attachment II) was updated with this information.

3.2.24. The "Manual for Submission of Changes, Amendments, Suspensions and Cancelations v1" mentions that non-substantial amendments of clinical protocols must be filed under subject 1391 – Annual Report. However, there is another subject available, 1395 – Notification of Protocol Amendment. In this case, which subject must be used?

Subject code 1395 must be used for processes approved at the time of RDC 39/2008 validity. For processes approved according to RDC 09/2015, non-substantial amendments will be submitted as part of the annual report (subject code 1391).

3.2.25. For subject code "10820 - CLINICAL TRIALS - DDCM Change - Change that potentially impacts the quality or safety of the product under Investigation", which form must be submitted? The request form for approval of the DDCM process previously submitted in the initial dossier or request form for DDCM substantial change described in the Manual for submission of Changes, Amendments, Suspensions and Cancellations?

The mandatory document is the form initially submitted with the DDCM. "REQUEST FORM FOR MEDICINE CLINICAL DEVELOPMENT DOSSIER (DDCM) SUBSTANTIAL CHANGE", according to text of the manual itself, it is of optional submission and aims only at further clarifications regarding the changes that are being submitted.

3.2.26. At which moment an update of the development plan must be filed?

The development plan update must be sent only when there is a petitioning for a substantial change for inclusion of clinical trial not initially foreseen in the plan.

Only in cases where the plan update does not impact the clinical trials to be conducted in Brazil this update can be considered as a non-substantial change, being sent

along with the annual investigational medicine development safety update report.

The manual for submission of changes, amendments, suspensions and cancellations will be changed to include this clarification.

3.2.27. Is it possible to reduce the fees for amendments and substantial changes, following the same rationale of registration and post-registration fees?

Fee-related issues must be discussed directly with Anvisa's Fee Collection Management (GEGAR).

3.2.28. When a clinical trial is early cancelled, should an End of Clinical Trial Notification be sent or is the Study Cancellation upon request enough?

In this case, the study cancellation upon request is enough.

3.3. QUALITY ASPECTS

3.3.1. Which information will be necessary in the label templates? Is there any legislation about this?

There is no legislation about this for clinical trials. RDC 09/2015 requires only that the labeling template is sent. However, the Quality Requirements Submission Manuals regarding the Products under Investigation Used in Clinical Trials have some labeling recommendations (item 9 of the manual for synthetic and semi-synthetic medicines, 2nd edition and item 8 of the manual for biological products, 2nd edition).

3.3.2. Regarding the label template, does it need to be filed in the specific dossiers of each clinical trial or in the DDCM?

The rule is that the label template is filed in the DDCM. However, if the template differs from a study to the other, the label template can be filed if the specific dossier of each clinical trial and a clarification note must be attached to the DDCM to inform that the label templates are in the specific dossiers.

3.3.3. In the case of a comparator medicine to be used in a clinical trial, if the medicine is purchased in Brazil, can its original labelling be maintained or is it necessary to include a label with labelling wording according to the Manual of quality requirements provided at ANVISA's website?

If it is an open-label study, there is no need for new labelling of the comparator medicine already registered.

3.3.4. It is necessary that the production line to be certified for GMP in case of investigational medicine production?

No. RDC 09/2015 requires that the production occurs under GMP conditions, but no certification is required for such.

3.3.5. For validation and stability data, at this moment of the clinical research, the sponsor has not yet adapted to the Brazilian standards. Would ANVISA accept international data, considering the controlled clinical research environment? The negative could make clinical trials in Brazil unfeasible.

International data can be accepted and when not performed according to the stability studies described in RE 1/2005, the sponsor must justify its respective peculiarities.

In addition, for the Phase III clinical trials where there is medicine dispensation to the research participant for home use, in addition to the already available stability data, the following must be presented: 1) Result of long term stability study

in zone IVb or 2) Results of accelerated stability study 3) Instruction for the clinical trial participants reinforcing the storage conditions of the investigational medicine. The template attached to the 2nd edition of the manual for quality data submission regarding products under investigation can be followed.

Regarding the analytical methods validation, international data will be accepted for all phases of the clinical trial. For phase I studies, the suitability of the analytical methods used must be confirmed.

For Phase II and III studies, the analytical methods applied to the products under investigation must have their suitably demonstrated according to the current legislation, as applicable for each clinical development phase, or technical justification must be presented for the use of an alternative approach, based on scientifically acknowledged references.

The manual for quality data submission regarding products under investigation used in clinical trials was updated with this information (2nd edition).

3.3.6. In the Manual for Quality Requirements Submission regarding Products under Investigation used in Clinical Trials – Biological Products, it is defined that the comparator biological product is the biological product already registered at Anvisa based on the submission of a complete dossier, and that has already been marketed in the country. In international studies, it is common to use biological comparators registered in other countries, but not yet registered in Brazil. Could this biological product be used as comparator?

For studies investigating new biological products, in the case an active comparator is used, a comparator registered in other countries can be used, with the appropriate justification for the choice of this comparator. In case of trials investigating biological products that are not

new, the comparator must be registered in Brazil through an individual development way, in which a complete dossier was submitted, and that has already been marketed in the country.

3.3.7. According to GGMed/ANVISA's Service Guidance 02/2013, for medicines which Active Pharmaceutical Ingredient (API) is manufactured outside Brazil and internalized for the medicine production, the company must present documentation regarding the API stability studies according to RDC no. 45/2012, i.e., at minimum the accelerated stability study and the ongoing long-term study, according to the CLIMATIC ZONE IVb. For the cases in which the company does not yet have the ongoing long-term stability study, the protocol can be presented. The "Manual for Quality Requirements Submission regarding the Products under Investigation used in Clinical Trials – Synthetic and Semi-Synthetic medicines" requests presentation of data ensuring that the product remains stable for enough time for the conduction of the Phase I and II clinical trial and complete API's data for accelerated and long-term stability data for Phase III. At the moment of filing the DDCM with Phase 3 clinical trials of a synthetic product from imported API, is it possible to send complete API's Long-Term stability studies, in the climatic zone of the country of origin and then, at the moment of the product registration filing, to complement it with ongoing API's Long-Term stabilities or study protocol in zone IVb, according to SG no. 02/2013?

Yes. The company may send the complete report of the API's long-term stability study conducted on the climatic zone of the country of origin and then, at the moment of the product registration filing, complement it with the information contained in the

API's ongoing long-term stability study report or study protocol conducted in climatic zone IVb.

Service Guidance no. 02/2013 continues effective and, in general terms, it is understood that, for API manufactured in Brazil or imported for the medicine production in the national territory, long-term stability study in zone IVb is required. Additionally, for API present in the imported medicine composition, it is not mandatory to present these studies in the mentioned zone, and long-term stability study in climatic zone of the ingredient production or medicine production has to be presented, whichever is the worst case between these two options.

3.3.8. The "Manual for Quality Requirements Submission regarding the Products under Investigation used in Clinical Trials – Synthetic and Semi-Synthetic medicines" informs that in the case of APIs already registered in Brazil, only the documentation regarding the "Physicochemical and organoleptic characteristics" and "General Information" of the General Obtention Method can be presented. Does Anvisa refer only to the API that is registered in Brazil, regardless of the company that has performed it or is it only possible to fit in the case above-mentioned if the company responsible for the DDCM is the same one that holds the API registration at Anvisa?

It is not necessary that the API registration belongs to the DDCM applicant. The API registration can be in the name of another company.

3.3.9. In case a synthetic medicine that is already registered and marketed in Brazil is used and a new indication is intended to be studied, in this case, is it necessary to send the documentation regarding the TSE transmissibility control, once the same medicine that is already marketed will be used in the study?

If the medicine is purchased in Brazil, there is no need to send the documentation regarding TSE. If the product is imported, the purchase invoices must be sent at the moment of the importation.

In the DDCM process, for clarification purposes, present justification for the absence of this document (item "e" of subparagraph VII of Article 38 of RDC 09/2015).

3.3.10. Is it necessary to include in the label: "FOR EXCLUSIVE USE IN CLINICAL TRIALS", "EVERY MEDICINE MUST BE KEPT OUT OF REACH OF CHILDREN" for medicines of hospital use?

We clarify that the manuals provided by the area are a non-binding regulatory measure, adopted as a complement to health legislation, with the educational purpose of guidance regarding routines and procedures for compliance with the legislation, not intended for the expansion or restriction of established technical or administrative requirements. However, we recommend that the sentence "EXCLUSIVE FOR USE IN CLINICAL TRIALS" is placed on the labels of any medicine, regardless if it is for hospital use or not. This sentence is important so that if someone outside the clinical trial team accidentally has access to the medicine, he/she will be able to identify that the product is an investigational medicine.

The sentence "EVERY MEDICINE MUST BE KEPT OUT OF REACH OF CHILDREN" can be adopted for medicines that are dispensed to patients for home use.

3.3.11. If there is a reduction in the shelf life with the maintenance of the storage conditions, it is possible to notify only Anvisa, for safety reasons to the research participants?

Yes. In this case, the company must submit a FAEC update.

3.3.12. Is the notification of pilot batches still necessary by RDC 09/2015?

No.

3.3.13. According to RDC 09/15, data regarding the investigational medicine batch used in the clinical study will be sent through the DDCM. But if the company needs to produce a new batch for the clinical study, will it be necessary to inform the production of this new batch?

It is not necessary to inform about the production of a new batch, provided there is no change in scale or in any process that impacts the quality or safety of the investigational product.

If there are changes, the company must submit a Substantial Change request (10820 - CLINICAL TRIALS - DDCM Change - Change that potentially impacts the quality or safety of the product under investigation) in the case of processes evaluated according to RDC 09/2015 or a Batch Notification request (10056 - CLINICAL TRIALS - Notification of special batches manufacturing exclusively aimed for clinical research) in the case of processes evaluated according to RDC 39/2008.

3.3.14. Do the Good Manufacturing Practices (GMP) mentioned in the answer to Question 4 of Item 1 (v.1) refer to the internationally accepted GMP conditions or do they refer to the RDC 17/2010 ones?

The GMP conditions refer to the internationally accepted good practices, such as for example, what is preconized by ICH Q7 Guide.

3.5. IMPORTATION

3.5.1. For a study approved by RDC 39/2008 to become valid by RDC 09/2015, it must be listed in the DDCM's CE. The products to be imported will be listed in this CE and this information can be obtained in the Importation Quantitative Estimate Form of RDC 39/2008. However, for most of the products to be imported, there is no information about the storage conditions and shelf life, which are also described on the CE of RDC 09/2015. In this case, how will this information be described?

For the trials approved by RDC 39/2008 that will be part of a DDCM and that will need importation of products under investigation, we request that a Study Submission Form (FAEC) is sent with the subject code 10823 CLINICAL TRIALS – Change of a Clinical Trial Submission Form in the clinical trial approval process. This form must be amended to the clinical trial request approved by RDC 39/2008 and not to the DDCM request.

3.5.2. According to RDC 09/2015, will there no longer be pre-shipment authorization? Are the PAFs prepared for the new importation model?

In the context of the old RDC 39/2008, the CE was issued without the description of the products to be imported, because it was listed in the Importation Licensing requests, evaluated separately and individually. In the case of RDC 09/2015, the pre-shipment authorization is no longer applicable. Now, all products to be imported for all clinical trials will be described in the CE, CEE or Importation Document. Thus, each Clinical Trial Submission Form (FAEC) submitted along with the specific dossiers must contain all the products to be imported for that trial. The CE, CEE or Importation Document issued for the DDCM, will contain

the list of all products. The importation will be mediated only by the health authority on the clearance site.

The writing of the RDC 09/2015, mainly regarding importation, was made along with the Ports, Airports and Customs Borders General Management (GGPAF). In addition, COPEC performed training sessions at the PAFs of major impact in order to ensure that the procedures are harmonized and conducted with no problems.

3.5.3. Do observational studies with no medicines, but involving importation and exportation procedures, have to be submitted to ANVISA anyway?

Observational studies with no medicines, but involving importation/exportation procedures, must be notified as a Clinical Research Notification – Phase IV/Observational not linkable to the DDCM.

3.5.4. Article 73, sole paragraph, addresses the special control products. Do these products refer to Ordinance 344/98 items? In those cases, would they have a previous authorization from Anvisa?

The products mentioned on the sole paragraph of Article 73 are those under special control foreseen by Ordinance SVS/MS 344/98. For these products, in addition to the inspection by the health authority at the customs clearance site, a prior authorization for shipment abroad is necessary by the Agency headquarters (Controlled Products Coordination – CPCON), given the special control they are subject to.

It is noteworthy that according to RDC 11/2013, Article 1, §2, the substances included in list C4 of ATTACHMENT I of Ordinance SVS/MS 344/98 and its updates, as well as the medicines that contain them, are **free** from prior authorization for shipment abroad.

3.5.5. How to import an investigational medicine, whose clinical trial is not for health registration purposes?

If the intended study is Phase IV or observational, then it may fit under Article 3 of RDC 09/2015. If it is not applicable, we ask that the importation issues be checked with Anvisa's responsible area, in this case, Ports, Airports and Borders General Management (GGPAF).

3.5.6. What is the best moment to change the CLINICAL TRIAL PRESENTATION FORM (FAEC) in the case of a change in the materials to be imported for a clinical trial that still awaits analysis by Anvisa? Do we already have to send this update at this moment, or do we have to wait for this process' initial opinion?

The changes of the materials to be imported can already be informed to Anvisa through subject code 10823 - CLINICAL TRIALS – Change in the Clinical Trial Submission Form, so that at the moment the CE or the DDCM Document for Importation of Products under Investigation is issued, the document already includes the correct list of materials.

3.5.7. If there is no importation of material, does field 66 (Medicines and Products to be imported for the clinical trial conduction) of the Clinical Trial Presentation form (version 3) remains blank?

Yes. The company may fill this field as "not applicable".

3.5.8. Which qualitative information and which specifications of the products under investigation will be informed in the Special Communication, as described in Article 76?

These are the information described in item 66 of the Clinical Trial Submission Form (FAEC), version 3.

3.6. DEADLINES

3.6.1. In the DDCM analysis process, will all the amendments submitted before the CE issuance, whether substantial or not, be considered in the initial analysis?

This depends on the moment these requests take place. If it is possible to consider them before the initial manifestation, they will already be assessed before the CE issuance. Otherwise, they will be analyzed according to the deadlines of Article 36.

3.6.2. What is the deadline for analysis of a clinical trial specific dossier?

If the dossier filing takes place before the beginning of a DDCM analysis, the deadline is the same as the DDCM's (i.e., complies with Article 36 of the RDC). If a specific dossier has been filed during the DDCM analysis, the evaluation of this dossier will depend if the DDCM analysis is already almost completed or if it is still in the beginning. In case the DDCM analysis is close to completion, the specific dossier will follow the same rationale as described in the paragraph below.

If the filing takes place after the DDCM approval, the deadline will depend on the following situation:

- If it is a protocol already foreseen in the plan, there is no legal deadline for the analysis. However, this protocol will be evaluated within a shorter period than the DDCM analysis deadline;
- If it is a protocol not foreseen in the plan, this is characterized as a substantial change. In this case, the deadline follows that of Article 42 of the RDC.

3.6.3. What will be the estimated time for the approval of a request to change the shelf life?

Subject code 10849 – CLINICAL TRIALS – DDCM change – Shelf life change was created for this specific request to be analyzed faster.

3.6.4. How will the deadline be for cases of analysis prioritization that also fit the 90-day analysis (Article 36)?

The deadline that expires first will be the one to be respected. That is, if the analysis prioritization is approved before 90 days elapse, Anvisa will do its first manifestation within 45 days from the approval publication date of the analysis prioritization request. In case the prioritization is approved after 90 days, the DDCM can be started by lapse of time, on the 91st day after filing.

3.6.5. According to Article 53 of RDC 09/2015, when there is a request to reactivate clinical trial protocols or suspended DDCMs, they can only be restarted after Anvisa's approval. What is the forecast for this approval?

There is no legal forecast. The analysis period will be on a case by case basis. However, if in the future it is possible to identify an average analysis period, we can inform this type of forecast.

3.6.6. According to the presentations of the Clinical Research Workshop held in November/2015, it could be notice that the DDCMs of products already approved are with the same analysis period as the non-registered ones. Would it not be expected that there was more agility in the analysis of these DDCMs?

Yes, the evaluation usually occurs faster in these cases. However, there may be other requirements that do not depend on the product being already registered or not, such as statistical analysis of the clinical designs, new indication, new formulation, etc.

3.6.7. Is there an internal deadline for evaluating the fulfillment of requirements by the Agency?

There is no legal deadline. However, the requirement fulfillment request is always considered a priority by the area.

In the case of process with approved prioritization request, the legal deadline is 45 days.

3.6.8. At what moment does the DDCM come out of the analysis line?

The DDCM comes out of the line when the specialist starts the analysis.

At this moment the status changes to "under analysis" and the process comes out of the line. The ones in line are those that still await analysis.

3.6.9. What is the reference date used to count the deadline described in Article 36?

The reference date for counting the deadline is the document entry date at Anvisa (GEDOC) and not at the technical area (COPEC).

3.7. REPORTS

3.7.1. What is the difference between the annual and final follow-up reports of the clinical trial protocol and the safety update report of the investigational medicine development?

The annual report refers to the national sites data and the final report refers to all participating sites data. These reports are related to a clinical trial.

The safety update report of the investigational medicine development is the same report as the DSUR (Development Safety Update Report) format of the ICH E2F guide. Because it refers to a report related to the medicine development, this report refers to the DDCM.

3.7.2. In the case of a safety update report of the investigational medicine development that is in the DSUR template, is it acceptable to submit only the report summary?

A DSUR summary can be submitted, but Anvisa may request the complete report at any time.

3.7.3. Until when must the safety update report of the investigational medicine development be sent? Does the PSUR (Periodic Safety Update Report) also need to be sent?

The safety update report of the investigational medicine development must be submitted by the time the Medicine Development Plan is completed. After the plan is completed, in case the sponsor decides to conduct new studies (due, for instance, to the research of new indications, new doses, new pharmaceutical forms), the safety update report is sent again.

The PSUR report must not be sent to COPEC at any time.

3.7.4. What happens to the DDCM after the medicine development plan and registration are completed?

The DDCM remains as it is until new protocols are linked, a substantial change is filed, or it is suspended or cancelled.

3.7.5. Article 56 of RDC 09/2015 mentions that “the sponsor or Independent Safety Monitoring Committee must systematically collect and assess aggregate data of adverse events occurred in the clinical trial, submitting the results of this assessment to Anvisa at the safety update report

of the investigational medicine development". The Independent Safety Monitoring Committee issues one letter per clinical trial. Does this letter need to be submitted along with the DSUR for all the clinical trials approved in the DDCM or does it need to be submitted in the clinical trial annual report?

It is expected in the safety update report of the investigational medicine development (DSUR) the result of the data collected and assessed by the sponsor or Independent Safety Monitoring Committee in that period (according to item 3.3 of the ICH E2F guide, that requests the description of the actions taken for safety reasons).

Regarding the recommendation letters issued by the Independent Safety Monitoring Committee for the clinical trials, these will be sent with the annual follow-up report of each clinical trial.

3.7.6. When a study approved at the time and validity of the RDC 39/2008 comes into force under RDC 09/2015, which annual reference date must be considered to submit the clinical trial annual follow-up reports? The RDC 39/2008 or the RDC 09/2015 date?

The same date used in RDC 39/08 must be considered, i.e., the approval date of the CE issued according to RDC 39/08.

3.7.7. Is there any template of clinical trial annual report according to RDC 09/2015? Can the report template available at Anvisa's website be used?

COPEC does not yet consider that an annual report template is necessary, once the information must be based on a worldwide standardized report (ICH H3) or minimally contain what is requested in the standard. As time goes by, if necessary, we may disclose a template. The report template available at Anvisa's website refers to RDC 39/2008.

3.7.8. Article 68 of RDC 09/15 informs that the annual report must have:

"VI- description of all adverse events occurred by site in the assessed period, identifying the clinical trial participants with the codes used in the Case Report Form adopted in the clinical trial protocol." What kind of adverse event must be submitted in the annual report?

Any adverse event, including the non-serious ones, occurred in Brazilian sites.

3.7.9. What must be submitted for description of the deviations and violations in the clinical trial follow up annual report?

The company must minimally submit the number and description of the non-compliances, classifying them as deviation or violation and separating them by site. As a suggestion, the company may follow the table template provided in the Annual Reports Template of RDC 39/2008 available at Anvisa's website (Medicines > Clinical Research > Forms).

3.8. ADVERSE EVENTS

3.8.1. How does the causal relation of the adverse event (AE) to the investigational products have to be established, according to Article 61?

The causal relation for the investigational medicine, comparator or placebo must be described in the form used for AE. For other investigational products, the causal relation, if applicable, must be described in the case narrative.

3.8.2. Will Notivisa be changed to comply with the requirement of Article 58? When will the adverse events submission manual be published?

The adverse event notification remains through the clinical research electronic system on Anvisa's website, as currently occurs (Notivisa-

EC). The current form did not need to be changed, and any action taken that is not available in the system options must be described in the report narrative. The 1st edition of the manual for adverse events notification and safety monitoring in clinical trials is available at Anvisa's website.

3.8.3. Article 66 says that “the sponsor must ensure that all relevant information about adverse events mentioned in Article 63 that are fatal or life-threatening are documented and notified to Anvisa, through an electronic form, within a maximum of 7 (seven) calendar days from the date of the sponsor awareness on the case. Sole paragraph. Complementary information about the follow-up of the adverse events mentioned in the caput must be included in the form within 8 (eight) calendar days from the notification date”. After the first follow-up report (Follow-up 1) is informed at NOTIVISA within 8 calendar days from the notification of the initial case, what is the deadline to notify the remaining follow-up reports (Follow-up 2, 3, 4 and so forth)?

The notification of serious adverse events is made through the clinical research electronic system on Anvisa's website (Notivisa-EC) and not on NOTIVISA. For the following notification updates, there is not an established deadline, but the follow-up must be made (and updated on the system) until the resolution or stabilization of the adverse event, according to Article 62 of RDC 09/2015.

3.8.4. Article 63 mentions that "the sponsor must notify Anvisa, through specific electronic form, the unexpected serious adverse events occurred in the national territory, whose causality is possible, probable or defined regarding the investigational product". Does the provided information have already to contain the unblinding?

No. The unblinding must be defined by the sponsor itself in the clinical trial protocol.

3.8.5. Regarding Article 57 da RDC, how long does Anvisa recommend that mother and child are followed up after the delivery? Is there a minimum and a maximum period?

There is no pre-established follow up period, as it will depend on the kind of medicine and its characteristics, such as the plasma half-life time. The company must establish this deadline and submit a rationale that justifies the chosen period.

3.8.6. To which adverse events does Article 59 refer?

Article 39 of RDC 09/2015 informs that even if unexpected serious adverse events have been notified to Anvisa, the sponsor must submit the Investigator's Brochure, amendments, reports or clinical trial early termination. That is, the fact of having notified the serious adverse event does not exempt the responsibility of submitting the documents mentioned above.

The kind of unexpected serious adverse event that must be notified to Anvisa is that described in Article 63 (The sponsor must notify Anvisa, through specific electronic form, the unexpected serious adverse events occurred in the national territory, whose causality is possible, probable or defined regarding the investigational product), i.e., only the adverse events occurred in Brazil.

3.8.7. Regarding Article 66 Sole Paragraph, "*The complementary information about follow-up of the adverse events mentioned in the caput must be included in the form within 8 (eight) calendar days from the notification date*". Does this notification refer to the initial notification of the case by the sponsor to Anvisa or to the notification of the information by the investigator to the sponsor?

The notification refers to the initial notification by the sponsor to Anvisa.

3.9. INVESTIGATOR-SPONSOR

3.9.1. Who is responsible for the DDCM submission, the primary sponsor of the secondary sponsor?

Considering that Anvisa's system only accepts submission by legal entity, the primary sponsor is the responsible for this submission.

3.9.2. If the clinical trials to be filed are an initiative of an investigator-sponsor and the company that will donate the medicine will not be considered as the sponsor, could the company submit this DDCM to the investigator-sponsor?

The company must submit the DDCM only for the case described in Article 28 of RDC 09/2015:

Article 28. In the case of donation of medicines already registered in Brazil for conduction of a clinical trial, the donor will be the sponsor if there is agreement of transfer or property of the data obtained in the research to the donor.

In the case of investigator-sponsor interest research, with no interest of the company, but with donation of non-registered medicines, the primary sponsor (institution) is the responsible for the DDCM submission. However, we emphasize that, according to Article 29 of RDC 09/2015, the donor shares the sponsor responsibility.

3.9.3. Is it possible for a sponsor to submit a DDCM whose clinical trial to be presented belongs to an investigator-sponsor, which will be responsible for the study conduction in Brazil?

The sponsor can submit the DDCM of an investigational medicine. However, if the clinical trial will be investigator-sponsor, it is the primary sponsor that must file this

specific protocol. In the case of investigator-sponsor, the primary sponsor is the institution.

3.9.4. Considering that an investigator-sponsor wants to study a new indication of an already registered medicine, does the registration holder company that donates the medicine for this new study, but has no interest in registering this new indication, have any responsibility regarding the DDCM submission?

If the clinical trial is not for registration purposes, it is not in the scope of RDC 09/2015. According to Article 2, this Resolution is applicable to all clinical trials with medicines that will have all or part of its clinical development in Brazil for registration purposes.

3.9.5. Is it possible to pay the fee as an individual entity (responsible researcher)?

No. The investigator-sponsor must always be represented at Anvisa by the Institution to which he/she is linked, according to Section III, Chapter II of RDC 09/2015.

3.10. TRANSFER OF RESPONSIBILITY

3.10.1. When there is an importation on behalf of a CRO in the CE, CEE Document for Importation of the successor company, how will the new document be issued?

If the contract between the successor company and the CRO for importation purposes is sent in the transfer request, this information will be corrected in the CE, Document for Importation, CEE to be issued on behalf of the successor. The new document will contain information that the successor company delegates importation activities to the CRO. If this delegation agreement is not sent together with the request for transfer of responsibility, the information on the delegation of importation to the CRO will be removed from the CE, CEE or

Document for Importation, and the importation will only compete to the successor company.

3.11. MISCELLANEOUS

3.11.1. Due to the increasing number of requirements associated with the clinical trial statistics, what are the minimum requirements necessary for the statistical analysis?

The protocol must follow item 8.8 of the Document of the Americas. The background for choosing the main aspects of the study must be informed, such as the sample size calculation (including the formula used, parameters, parameter references and margins), study endpoints, margins (clarification about the margin definition including references from previous studies and clinical relevance), and the definition of the statistical hypotheses in the data analysis.

3.11.2. Some protocols have their own definitions or different definitions for protocol deviation. In this case, can we follow the protocol definition?

Yes. The deviation definition can be the one specified in the protocol.
However, Anvisa may evaluate this definition.

3.11.3. From what time is a clinical trial approved by RDC 39/2008 considered as inserted in the DDCM and starts to comply with RDC 09/2015 (according to Article 80)? What is the impact of the clinical trial if it is not inserted in a DDCM?

The clinical trial approved by RDC 39/2008 must start complying with RDC 09/2015 when the DDCM CE is issued or the DDCM Document for Importation of Investigational Product is issued.

The studies approved by RDC 39/2008 follow all the writings of this resolution until they are inserted in a DDCM. In case the study is not inserted in a DDCM until it is completed, there is no impact to it, because it will continue complying with RDC 39/2008

until completion. The secondary request subject codes specific for RDC 39/2008 remain valid for these cases.

3.11.4. How do I inform Anvisa about the presence of a co-participating site?

The co-participating sites must be informed in the list of sites of each FAEC, considering "zero" participants and providing a brief description of the activities to be developed in these sites in the table footer. We emphasize that even having more than one site, the principal investigator remains responsible for all the activities performed, regardless if they occur in the main site or in a co-participating site.

3.11.5. Will there be a joint review between the regulated sector and Anvisa of the manuals released by COPEC regarding RDC 09/2015?

The manuals are constantly being reviewed by Anvisa. We ask that any contribution to the manuals is made through the call center, meetings and specific appointments.

3.11.6. How is the initial screening of the DDCMs made by Anvisa?

COPEC's experts conduct a document review of the DDCM and a risk-benefit assessment based on criteria such as medicine status (registered or not), development plan evaluated by other agencies, presence of medicine safety alerts, specific status in other agencies (fast-track, breakthrough therapy, etc.), type of comparator used, innovative nature of the medicine (either by the pharmaceutical form, or by the mechanism of action or other characteristics). After this initial evaluation, the specialist may release the dossier by lapse of time, request a meeting or carry out a more detailed/complete evaluation of the dossier.

3.11.7. Do open-label, Phase 3 studies need to have an Independent Safety Monitoring Committee?

According to Article 60, the rule is that a phase III clinical trial is monitored by Independent Safety Monitoring Committees. However, if there are no committees, its absence must be justified.

3.11.8. Is there a limit by Anvisa for reiterations of requirements?

No.

3.11.9. Does Anvisa consider to ever make the regulatory analysis completely independent from the ethical review?

According to Article 22 and Article 23 of RDC 205/2017 (that establishes special procedure for approval of clinical trials, good manufacturing practices certification and registration of new medicines for treatment, diagnosis or prevention of rare diseases), as of 27/Feb/2018, IRB's opinion no longer needs to be presented to Anvisa for approval of clinical protocols and subsequent amendments.

3.11.10. What is the concept of investigational product, once the definition contained in RDC 09/2015 differs in some points from that contained in the Document of the Americas/Good Clinical Practices?

The definition adopted by RDC 09/2015 was thought mainly regarding the importations necessary for conducting each clinical trial and due to this fact, the definition of "investigational product" includes all the products to be used in a clinical trial, including comparator medicines, equipment and lab kits. To comply with the requirements of RDC 09/2015, the concept of "investigational product" described above must be used.

3.11.11. Regarding the Special Communication (CE), Specific Special Communication (CEE) or Document for Importation of Investigational Product(s) of the Medicine Clinical Development Dossier (DDCM) issued for clinical trials that comply with RDC no. 9/2015, will the list of Investigators and Institutions participants of the study no longer be part of the CE/CEE/Document for Importation issued by ANVISA?

The investigators and institutions are no longer listed in the DDCM CE, CEE, Document for Importation of Investigational Products. However, whenever an investigator or institution is changed, this information must be notified to Anvisa under subject code 10823 - CLINICAL TRIALS – Change of the Clinical Trial Submission Form, because this data reflect the publicity of the clinical trials at Anvisa's website and will be used to guide Good Clinical Practices inspections.

3.11.12. Is the Technical Note about Amendment available at Anvisa's website still applicable? ("Amendments to Clinical Research Approval Processes that do not demand issuance or correction of Special Communication or Importation Licensing must only be filed along with the annual or final reports.").

The Technical Note continues valid for the clinical trials approved when RDC 39/2008 was in force. For those approved or that started complying with RDC 09/2015, this note is not applicable.

4. RECOMMENDATIONS

This section indicates some recommendations regarding the documents submitted in the DDCM. The recommendations do not necessarily need to be followed, however, they are suggestions that the technical area proposes for more celerity in completing the process analysis, based on the analysis performed since the standard was implemented.

4.1. Organization of the dossier

- ✓ Include a general index to facilitate the search for document
- ✓ Include clarification notes, if applicable, to justify the absence of a document in the corresponding section or to inform that a certain document or certain information is in another section.
- ✓ Send in the CD-ROM the electronic documentation divided into folders, containing editable Word or PDF documents with the "copy and paste" functions activated. See in Attachment 1 an example of how to save the documents in the CD.

4.2. Investigational Medicine Dossier

- ✓ Send a summary/comment of the RDC items and manuals. We have noticed that the dossiers that contained file presenting the full description of the items requested by RDC 9/2015 and following the guidance of the "Manual of Quality Requirements Submission relative to Products under Investigation Used in Clinical Trials" (or referring to some other section of the dossier that contained the most complete information) were the ones we analyzed faster in relation to other dossiers that only referred the documentation.

- ✓ Follow the order described in the RDC and in Anvisa's specific manuals. If any item is not applicable, we recommend mentioning it as "not applicable" instead of not describing the item.

4.3. Fulfillment of Requirements

- ✓ Submit the responses in Portuguese
- ✓ Submit the documentation regarding the fulfillment of requirements also in electronic format, containing the editable Word or PDF documents with the "copy and paste" functions activated.

5. RELATED STANDARDS AND REFERENCES

[Resolução da Diretoria Colegiada - RDC nº 9, de 20 de fevereiro de 2015](#). Provides for the regulation for conduction of clinical trials with medicines in Brazil. Diário Oficial da União, 01 de março de 2015.

[Resolução da Diretoria Colegiada - RDC 39, de 05 de junho de 2008](#). Approves the REGULATION FOR CONDUCTING CLINICAL RESEARCH and other provisions. Diário Oficial da União, 06 de junho de 2008.

[Resolução da Diretoria Colegiada - RDC 205, de 28 de dezembro de 2017](#). Establishes special procedure for approval of clinical trials, good manufacturing practices certification and registration of new medicines for treatment, diagnosis or prevention of rare diseases. Diário Oficial da União, 29 de dezembro de 2017.

[Resolução da Diretoria Colegiada - RDC 11 de 06 de março de 2013](#). Provides for the importation of substances subject to special control and the medicines containing them. Diário Oficial da União, 08 de março de 2013.

[Resolução - RE nº 1, de 29 de julho de 2005](#). Authorizes ad referendum, the publication of the Guide for Conducting Stability Studies, Diário Oficial da União, 01 agosto de 2005.

[Manual para submissão de dossiê de desenvolvimento clínico de medicamento \(DDCM\) e dossiê específico de ensaio clínico](#). 3ª Edição, 2017. COPEC/GGMED

[Manual para submissão de modificações, emendas, suspensões e cancelamentos](#). 2ª Edição, 2017. COPEC/GGMED

[Manual de submissão dos Requisitos de Qualidade referente aos Produtos Sob Investigação utilizados em Ensaio Clínicos - Produtos Biológicos](#). 2ª Edição, 2017. COPEC/GGMED

[Manual de submissão dos Requisitos de Qualidade referente aos Produtos Sob Investigação utilizados em Ensaio Clínicos – Medicamentos Sintéticos e Semissintéticos](#). 2ª Edição, 2017. COPEC/GGMED

[Manual para submissão de relatórios de acompanhamento e formulários de início e término de ensaio clínico](#). 1ª Edição, 2016. COPEC/GGMED

[Manual para notificação de eventos adversos e monitoramento de segurança em ensaios clínicos](#). 1ª Edição, 2016. COPEC/GGMED

[Nota técnica 09/2015, de 03 de setembro de 2015](#). Clarifications on relative bioavailability studies to demonstrate pharmacokinetic interaction for purposes of Fixed Dose Combinations registration or Medicine Clinical Development Dossier – DDCM approval. CETER/COPEC/GGMED/SUMED/ANVISA. Available on Anvisa's website:
<http://portal.anvisa.gov.br/documents/506392/0/NOTA+009+2015.pdf/7ef000d6-a39a-4b06-bbab-4c5ed21f4db4>

[Nota técnica 118/2016, de 15 de abril de 2016](#). Clarifications about Biological Products comparative pharmacokinetic studies. CETER/COPEC/GGMED/ANVISA. Available on Anvisa's website:

<http://portal.anvisa.gov.br/documents/506392/0/Nota%2BT%C3%A9cnica%2B118.2016.pdf/47fda684-fc28-45eb-b872-a2f18d40c8cb>

[Orientação de Serviço nº 02/2013, de 01 de fevereiro de 2013](#). API stability studies – Climatic conditions of the stability studies of the API to be presented for registration, post-registration and medicine renewal purposes and for the API registration. GGMed/ANVISA. Available on Anvisa's website:

<http://portal.anvisa.gov.br/documents/33836/352852/Orienta%C3%A7%C3%A3o+de+Servi%C3%A7o+n%C2%BA+02+de+2013+-+GGMED%2C+de+01+de+fevereiro+de+2013/92b4e625-d090-400e-bbc2-f90ec3a93b57>

[Boas Práticas Clínicas: Documento das Américas](#). IV Conferência PanAmericana para Harmonização da Regulamentação Farmacêutica [on line]. República Dominicana, 2005. OPAS. Available at:

http://www.anvisa.gov.br/medicamentos/pesquisa/boaspraticas_americas.pdf

[ICH E2F: Development Safety Update Report](#). 17 de Agosto de 2010, ICH (International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

[ICH E3: Clinical Study Reports](#). 30 de novembro de 1995, ICH (International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

[ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients](#). 10 de Novembro de 2000, ICH (International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

6. HISTORY OF EDITIONS

Edition	Date	Change	Justification
1 st	2015	Initial issue	Not applicable
2 nd	31/Jan/2018	New layout, with changes of the sections number: Submission (2 to 3.1), Amendments, Changes, Suspensions and Cancellation (3 to 3.2), Quality Aspects (4 to 3.3), Importation (5 to 3.4), Deadlines (6 to 3.5), Reports (7 to 3.6), Adverse Events (8 to 3.7), and Miscellaneous (9 to 3.10)	Change to reflect the new GG MED's Questions and Answers layout.
2 nd	31/Jan/2018	Inclusion of sections: Scope (2), Investigator-Sponsor (3.8), Transfer of Responsibility (3.9), Recommendations (4), Related Standards and References (5), History of Editions (6) and Attachments (7).	Sections 2, 5 and 6 were included to comply with the new layout. The other sections were included to facilitate the search by specific subject.
2 nd	31/Jan/2018	1. Introduction: Addition of the last paragraph "A history of changes was added to the document for a better control of the changes performed since the last version."	Inclusion to explain the reason for having a history of changes.
2 nd	31/Jan/2018	3.1. Submission: Questions 1 to 14 of version 1 were renumbered to 3.1.1 to 3.1.14. Questions 16 to 19 were renumbered 3.1.15 to 3.1.18.	Renumbering was done due to the document layout change.
2 nd	31/Jan/2018	3.1. Submission Question 3.1.1: bolded items were included: "Can the documents to be filed at Anvisa be submitted in foreign language (e.g.: English, Spanish, German, French...)? "	Question update due to questionings made regarding several foreign languages and not only to English.
2 nd	31/Jan/2018	3.1. Submission Question 3.1.2: the answer was updated.	As the RDC was published in 2015, there was no due time to adapt the standard.
2 nd	31/Jan/2018	3.1. Submission Question 3.1.14: the answer was updated.	The error was corrected.
2 nd	31/Jan/2018	3.1. Submission Question 15 of v1: "Is it possible to pay the fee as an individual entity (responsible researcher)?" was transferred as Question 3.8.5 of Section 3.8 of edition 2.	Transference of the question to a more specific section, created in Edition 2.
2 nd	31/Jan/2018	3.1. Submission Addition of questions 3.1.19 to	Inclusion of the questions made after v1 publication.

QUESTIONS & ANSWERS

Edition	Date	Change	Justification
		3.1.52.	
2 nd	31/Jan/2018	3.1. Submission Item "RECOMMENDATIONS" was removed to section 4 of edition 2.	Transference of the item to a more specific section, created in Edition 2.
2 nd	31/Jan/2018	3.2 Amendments, Changes, Suspensions and Cancellations: Renumbering of questions 20 to 32 of v1 to 3.2.1 to 3.2.13 of edition 2.	Renumbering was made due to document layout change.
2 nd	31/Jan/2018	3.2 Amendments, Changes, Suspensions and Cancellations: Question 3.2.5: the answer was updated.	Due to the publication of RDC 205/2017, the answer was updated.
2 nd	31/Jan/2018	3.2 Amendments, Changes, Suspensions and Cancellations: Question 3.2.11: the following excerpt was removed from the answer: <i>We emphasize that if the development plan is updated, this would be considered as a non-substantial change and, therefore, must be sent at the moment of submission of the Safety Update Report of the investigational medicine development.</i>	This excerpt caused several questionings and for this reason, a new question was created to clarify when a clinical development plan update must be filed at Anvisa (Question 3.2.26)
2 nd	31/Jan/2018	3.2 Amendments, Changes, Suspensions and Cancellations: addition of Questions 3.2.14 to 3.2.28.	Inclusion of the Questions made after v1 publication.
2 nd	31/Jan/2018	3.3 Quality Aspects: Renumbering of questions 1 to 6 to 3.3.1 to 3.3.6.	Renumbering was made due to the document layout change.
2 nd	31/Jan/2018	3.3 Quality Aspects: Question 3.3.5: the answer was updated.	The answer was updated to reflect the changes of the 2nd edition of the Quality data submission manual regarding the investigational products
2 nd	31/Jan/2018	3.3. Quality Aspects: Addition of Questions 3.3.7 to 3.3.14.	Inclusion of the Questions made after v1 publication.
2 nd	31/Jan/2018	3.4. Importation: Renumbering of questions 1 to 4 of version 1 to 3.4.1 to 3.4.4.	Renumbering was made due to the document layout change.
2 nd	31/Jan/2018	3.4. Importation: Question 1: addition of the sentence "This form must be amended to the clinical trial request approved by RDC 39/2008 and not to the DDCM request." in the answer.	Inclusion of the sentence to clarify where the form must be amended.
2 nd	31/Jan/2018	3.4. Importation: Addition of questions 3.4.5 to	Inclusion of the Questions made after v1 publication.

? QUESTIONS & ANSWERS

Edition	Date	Change	Justification
		3.4.8.	
2 nd	31/Jan/2018	3.5. Deadlines: Renumbering of questions 1 to 5 to 3.5.1 to 3.5.5.	Renumbering was made due to the document layout change.
2 nd	31/Jan/2018	3.5. Deadlines: Question 3.5.3: the answer was updated	Due to the creation of a specific subject code, the answer was updated.
2 nd	31/Jan/2018	3.5. Deadlines: Addition of Questions 3.5.6 to 3.5.9.	Inclusion of the Questions made after v1 publication.
2 nd	31/Jan/2018	3.6. Reports: Renumbering of questions 1 to 6 to 3.6.1 to 3.6.6.	Renumbering was made due to the document layout change.
2 nd	31/Jan/2018	3.6. Reports: Addition of Questions 3.6.7 to 3.6.9.	Inclusion of the Questions made after v1 publication.
2 nd	31/Jan/2018	3.7. Adverse Events: Renumbering of questions 1 to 4 to 3.7.1 to 3.7.4.	Renumbering was made due to the document layout change.
2 nd	31/Jan/2018	3.7. Adverse Events: Question 3.7.2: the following sentence was added to the answer: <i>The 1st edition of the manual for adverse event notification and safety monitoring in clinical trials is available at Anvisa's website. <u>This manual is in final review phase and will be published soon.</u></i>	The answer was updated, after the publication of the manual for adverse event notification and safety monitoring in clinical trials.
2 nd	31/Jan/2018	3.7. Adverse Events: Addition of Questions 3.7.5 to 3.7.7.	Inclusion of the Questions made after v1 publication.
2 nd	31/Jan/2018	3.10. Miscellaneous: Renumbering of questions 1 to 3 to 3.10.1 to 3.10.3	Renumbering was made due to the document layout change.
2 nd	31/Jan/2018	3.10. Miscellaneous: Addition of Questions 3.10.4 to 3.10.12.	Inclusion of the Questions made after v1 publication.
2 nd	31/Jan/2018	Minor changes in the whole text, with no substantial change of its content.	Review for orthographic, grammar or formatting corrections, or to bring more clarity to the text, with no substantial change of its content.

7. ATTACHMENTS

7.1. ATTACHMENT 1 – Organization of DDCM's electronic file

General Folders:

Name

-  01 DDCM Request Form
-  02 Proof of Payment
-  03 Development Plan
-  04 Investigator's Brochure
-  05 Summary of Safety Aspects
-  06 Development Interruption
-  07 Investigational Medicine Dossier

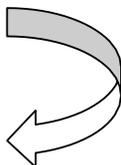
Note: Other folders can be created if they do not fit into any of the 7 previous topics

Sub-folders – Example:

-  Investigational medicine dossier

Name

-  07a API or Active Substance
-  07b Investigational Medicine
-  07c Placebo
-  07d Modified Comparator
-  07e TSE
-  07f Label
-  07g Critical analysis – non-clinical
-  07h Critical analysis – clinical



Documents in each folder – Example:



Formatado: Fonte: 10 pt, Inglês (Estados Unidos)