



Title: Coordination of GCP Inspection Services		Document no.: SOP/INSP/2004
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Date: 10/8/05	Date: 15/8/05	Date: 15/8/05

1. Purpose

This SOP describes the processes used by GCP Inspection Co-ordination in the routine review of applications, preparation and processing of inspection requests, and co-ordination and reporting of inspections. It interfaces with procedures and guidance documents prepared by the GCP Inspection Services group where appropriate and for practical purposes may overlap with these in some areas. It also interfaces with the SOP-H-3009: Standard Operating Procedure on Validation of new applications for marketing authorisations.

2. Scope

The scope is to cover all general activities of GCP Inspection Co-ordination services not already covered by more general Inspection Sector SOPs or those of other Sectors/Units or the Agency. Among these activities are included not only the coordination of GCP inspections but also PhV inspections. The procedure also encompasses activities undertaken with the CHMP, assessors and inspectors. In addition aspects of the procedures directly interface with the applicant.

3. Responsibilities

It is the responsibility of the Inspections Sector Head to ensure that this procedure is adhered to within his/her own sector. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of the procedure in chapter 7. Approximate procedure timelines are also identified.

4. Forms needed for this SOP

All forms needed for this SOP can be found under the following folder:

Form 4.1: *Template Transmission slip*

Validation

- Form 4.2: *GCP Validation Form*
Form 4.3: *Addendum to the GCP Validation Form*
Form 4.4: *Application Review*

Inspection request

- Form 4.5: *GCP Inspection Request Form*
Form 4.6: *Pharmacovigilance – GCP inspection request form*

Inspection Announcement to applicant

- Form 4.7: *Announcement of GCP inspection to applicant -Fax Cover*
Form 4.8: *Announcement of GCP inspection to applicant - Letter*

Inspection announcement to Reporting Inspectorate

- Form 4.9: *Fax Cover to Reporting inspectorate*
Form 4.10: *Letter Announcement to Reporting inspectorate with contract*
Form 4.11: *Attachment covers*
Form 4.12: *List of contact persons for the inspection*
Form 4.13: *GCP Inspection Contract*
Form 4.14: *Assignment letter to participating inspectorate*
Form 4.15: *Letter on Notification of Inspection to 3rd countries inspectorates*

Review and circulation of IRs/Initiation of payments

- Form 4.16: *GCP Inspection report review checklist*
Form 4.17: *GCP Inspection Payment Order*
Form 4.18: *Memo to initiate payment*
Form 4.19: *Circulation of final IIR and SIRs to Rapporteur and Co-Rapporteur – Cover letter*
Form 4.20: *GCP Inspection Spreadsheet*

5. Related documents

- The rules governing medicinal products in the European Union, Volume 2A “Notice to Applicants”. Chapter 4, Pre-authorisation inspections (GCP inspections).
- EMEA Pre-submission Guidance for Users of the Centralised Procedure.
- SOP-H-MTR/15589: Standard Operating Procedure on Pre-submission Meetings.
- SOP-H-3009: Standard Operating Procedure on Validation of new applications for marketing authorisations.
- Internal Standard Operating Procedure on Processing of Financial Documents for GMP, GCP, GLP Inspections, SOP/INS/2005.
- Procedure for co-ordinating pre-authorisation GCP Inspections during assessment of applications submitted to the EMEA INS/GCP/1
- Procedure for preparation of reports on pre-authorisation GCP inspections during assessment of applications submitted to the EMEA INS/GCP/4
- Policy on financial transactions and payments for GCP inspections requested in order to complete the assessment of applications under the centralised procedure

6. Definitions

- **Inspection:** the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect.
- **Reporting Inspectorate:** The Inspectorate from an EU/EEA State requested and accepting to designate the Reporting Inspector.
- **Reporting Inspector:** The Inspector designated by the Reporting Inspectorate to co-ordinate the preparation of the inspection, the conduct of the inspection and the activities of the inspectors. The Reporting inspector has the following general duties:
 - co-ordinating the
 - preparation of the inspection
 - practicalities of the inspection (with the inspectors and the sponsor/applicant)
 - conduct of the inspection
 - preparation of the reports by the inspectors involved
 - checking that the timelines for the inspection are kept
 - writing and co-signing the Integrated Inspection Report (IIR)
 - acting as the main communication point between the inspection team and the EMEA Inspection Sector. The Reporting Inspector and the EMEA Inspection Sector are responsible for the communication between the inspectorates and inspectors involved, the Rapporteur/Co-Rapporteur and the CPMP. The system of communication should however be flexible and there can be direct communication between the involved parties, including the assessors, where this is more practical
 - management of the live central archive related to the GCP inspection
 - the Reporting Inspector may also be the Lead Inspector (see below) for one or more sites.
- **Lead Inspector:** The Inspector who has the following duties for the GCP inspection of at least one inspection site:
 - evaluation of the feasibility of the inspection as requested and discussion with the Reporting Inspector
 - organisation of the practicalities of the inspection with the inspectee,
 - leading the conduct of the inspection on site,
 - communication between the inspectee and the Reporting Inspector/EMEA Inspection Sector. The system of communication should however be flexible and there can be direct communication between the involved parties where this is more practical
 - writing and signing the Inspection Report
 - writing and signing the Summary Inspection Report
 - reviewing and co-signing the Integrated Inspection Report.
- **Inspection Report:** An Inspection Report (IR) is prepared for each site inspected. It is written by the Lead Inspector and signed by the Lead Inspector and other inspectors as required by local legal requirements and SOPs
- **Summary Inspection Report (SIR):** For each Inspection Report, a Summary Inspection Report is prepared. The SIR is in English, contains a summary of deviations from regulatory requirements and other relevant observations. It focuses on major and critical findings, relevant to the scope of the requested inspection. It is written by the Lead Inspector and signed by the Lead Inspector and other participating inspectors. Each inspector should nominate a proxy who may sign on their behalf, if they are not available when the report needs to be signed off. Signature may be obtained by fax and originals mailed to the Lead inspector. It is

transmitted to the EMEA and to the Reporting Inspector. If the IR is in English, no SIR is needed but the IR should fulfil the needs of the SIR and IR in one document.

- ***Integrated Inspection Report (IIR)***: For each GCP inspection request made by the CPMP one Integrated Inspection Report is prepared (EMEA/INS/GCP/4). This report is in English, and summarises the critical and major findings of the inspection of all sites involved. The report contains an evaluation of the quality of the data submitted and of the compliance with the principles of GCP based on the findings from all inspected sites. It is written and signed by the Reporting Inspector, and reviewed and signed by the Lead Inspectors. The SIRs are attached to the IIR as appendices. Each inspector should nominate a proxy who may sign on their behalf or agree with the Reporting Inspector that the latter may sign on their behalf, if they are not available when the report needs to be signed. Signature may be obtained by fax, and the originals mailed to the Reporting Inspector. Where there is only one site inspected the IIR, SIR and IR can be one document provided that they are in English and provided that a summary of the findings and conclusion is given – the report should fulfil the objectives of the IIR/SIR and IR.

Abbreviations:

AS= Assessment Report

CHMP= Committee of Medicinal Products for Human Use

CTs= Clinical Trials

GCP= Good Clinical Practice

HoS= Head of sector

IIR = Integrated Inspection Report

IR = Inspection Report

Ireq=Inspection Request

IS = Inspections Sector

MAA= Marketing Authorization Application

PhV= Pharmacovigilance

PTL = Product Team Leader

S&E PTM= Safety and Efficacy Product Team Member

SIR = Summary Inspection Report

7. Procedure

Step	Action	Responsibility
1.0 (day –180)	Pre-submission Meeting	
1.1	Pre-submission meetings are arranged by the CIG before submission of an application. The CIG will set an appropriate date for the pre-submission meeting to all participants.	CIG Administrative assistant
1.2	The CIG circulates all relevant documents to the EMEA attendees in preparation for the meeting in advance.	CIG Administrative assistant
1.3	The IS representative is invited to attend the meeting when there are specific questions for GCP Inspections described in the "Pre-Submission Meeting Request Form". It may be appropriate that the IS representative attend only a specific part of the meeting. This decision is taken by the representative concerned after a review of the proposed agenda. If the IS representative attends the meeting or even if he/she is invited but cannot attend the meeting, then go to step 1.4.	IS GCP coordinator
1.4	Once the applicant has submitted to the PTL the minutes of the pre-submission meeting, he/she ensures that minutes are circulated to the IS representatives. Any comment should be forwarded according to the deadline established by the PTL. If the position or guidance on a particular issue has changed in the interim, the new information should be clearly identified as a "Post-Meeting Note". The same applies if the IS representative was invited to the meeting but unable to attend it.	PTL/IS GCP coordinator
2.0 (day –10, 0)	Validation of the application by Inspections Sector	
2.1	The CIG Administrative assistant distributes a copy of the Module I to IS GCP coordinator for validation at the latest on the day 1 of receipt.	CIG Administrative assistant
2.2	The IS GCP coordinator generally carries out the GCP inspection validation within 5 working days but always within the 10 days validation period. The validation is performed by following the points of a GCP validation form " <i>Validation Form EMEA-INS-GCP-118-04</i> ".	IS GCP coordinator

Step	Action	Responsibility
2.3	The IS GCP coordinator fills in the GCP validation form, recording the GCP validation result and the additional documentation to be provided by the applicant. This form is sent to the CIG administrative assistant, who originally sent the Module I.	IS GCP coordinator
2.4	If the IS GCP coordinator requires additional data, information or clarification to complete its validation of the dossier, the CIG administrative assistant contact the applicant through a letter, requesting data within a specific time limit. In this case, the validation can only be completed after receipt and verification of the information submitted. Additional information, which is not critical for the GCP validation but needed for the preparation of a potential inspection, will be requested in the same letter and should be provided by the applicant within the deadline specified by the IS GCP coordinator (usually within 30 days from the start of the procedure).	Administrative assistant
2.5	IS GCP coordinator reviews the response within 2 working days to ensure that the deficiencies have been solved and will inform the CIG administrative assistant if the conclusion is satisfactory or not. The IS GCP coordinator will follow up with the PTL that the applicant provides the additional information mentioned in step 2.4, which is not critical for the validation but needed in case an inspection is requested. The IS GCP coordinator will review this information and will inform the PTL if the information provided is acceptable or additional information is required.	IS GCP coordinator/PTL
2.6	The IS GCP coordinator completes the addendum to the GCP validation form “ <i>Addendum to the GCP Validation Form</i> ” and files it appended to the signed GCP validation form in the IS record of GCP review of applications. The excel spreadsheet on application review will be also updated “ <i>Application Review</i> ”.	IS GCP coordinator
2.7	If all parties come to a positive conclusion the overall outcome of the validation is positive. If anyone of the members of the validation team has come to a negative conclusion the overall outcome is negative. In both cases the applicant will be informed in writing If the validation was positive go to step 3.0.	CIG Administrative assistant
3.0 (day +1,+70)	Generation of a random inspection proposal	
3.1	Identify potential applications for inspection based on criteria for Random inspection	IS GCP Coordinator
3.2	Identify potential clinical trials and sites for inspection	IS GCP Coordinator
3.3	Agree the proposal with the S&E PTM	S&E PTM and IS GCP coordinator
3.4	Propose the potential inspection to the Rapporteur / Co-rapporteur and the respective inspectorates	S&E PTM and IS GCP coordinator
3.5	Prepare the inspection request, “ <i>GCP Inspection Request Form</i> ”, and review with the Rapporteur / Co-rapporteur and the respective inspectorates	S&E PTM and IS GCP coordinator
3.6	Agree the inspection request – the inspection request is then	Rapporteur, Co-Rapporteur and

Step	Action	Responsibility
	processed as for all inspection requests (see 4.0)	HoS IS
4.0 (day +70,+120)	Processing a GCP inspection request	
4.1	Propose a GCP inspection via process 3.0 (above) or Rapporteur-Co-Rapporteur/EMEA/Inspectorates propose an inspection	Proposer of inspection
4.2	Contact EMEA GCP IS coordinator whenever there is a discussion on the need of a GCP inspection at CHMP or communication from Rapporteur-Co-Rapporteur regarding a GCP inspection (including any draft AR, etc.). The PTL will forward the Day 70 ARs to the IS GCP Coordinator in all cases.	Proposer of inspection/PTL
4.3	Prepare draft inspection request based on information provided by the proposer and gathered from the application, use the form “ <i>GCP Inspection Request Form</i> ”	IS GCP Coordinator
4.4	Identify the reporting inspectorate and lead inspectorates, to be confirmed based on sites finally selected	IS GCP Coordinator
4.5	Send the draft inspection request to the Rapporteur/Co-Rapporteur, EMEA S&E PTM, and the involved inspectorates for comments	IS GCP Coordinator
4.6	Finalise the inspection request and obtain the signatures of the Rapporteur, Co-Rapporteur, IS HoS or designee (IS GCP Coordinator)	IS GCP Coordinator
4.7	Circulate the GCP inspection request to the CHMP (IS GCP coordinator provides a copy of the inspection request to the CHMP secretariat who circulate the document and enter it on the CHMP agenda)	IS GCP Coordinator/CHMP Secretariat
4.8	CHMP adopts request – proceed, CHMP rejects request then modify if appropriate or request remains rejected If the ireq is adopted go to step 5.0. If requested to be modified go back to step 4.6. If rejected, end.	CHMP
5.0 (day +120 + 5 days)	Initiation of a GCP Inspection	
5.1	Inform applicant of the adoption of the GCP inspection request within 5 working days of the CHMP meeting at which it was adopted, using the “ <i>Announcement of GCP inspection to applicant</i> ”. IS GCP Coordinator will update the GCP inspection spread excel sheet and will file the inspection request	IS GCP Coordinator
5.2	Obtain contract number from the IS gestionnaire	IS GCP Coordinator
5.3	Prepare the contract for the Reporting Inspectorate and obtain necessary EMEA signatures “ <i>GCP Inspection Contract</i> ”	IS GCP Coordinator
5.4	Send the contract along with a copy of the inspection request and announcement letter to the applicant, to the Reporting Inspectorate for signature within 5 working days of the adoption of the inspection request (one copy for their file and one to be returned to EMEA IS) “ <i>Letter Announcement to Reporting inspectorate with contract</i> ”. Notify also to other inspectorates involved	IS GCP Coordinator

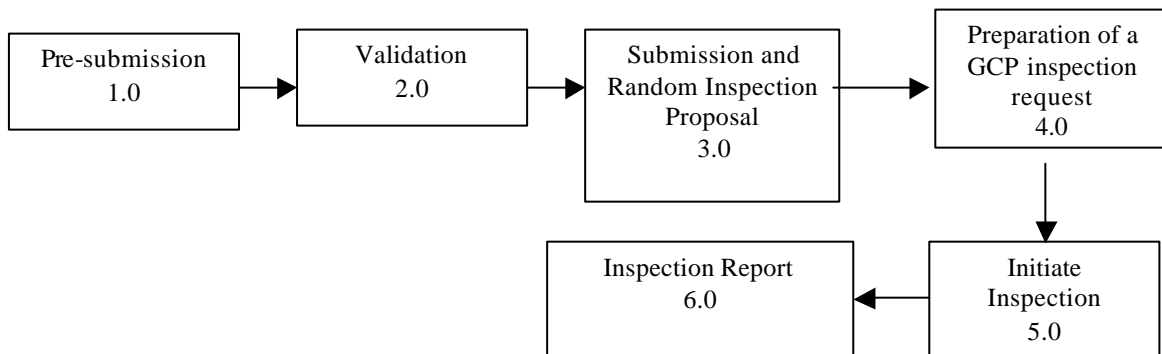
Step	Action	Responsibility
	<i>"Assignment letter to participating inspectorate"</i> .	
5.5	Send a copy of the letter mentioned in step 5.4 to the IS gestionnaire in order he/she initiates the recovery order process	IS GCP Coordinator
5.6	For a 3 rd country inspection, the IS GCP Coordinator will inform the local authorities or inspectorates about the proposed inspection <i>"Letter on Notification of Inspection to 3rd countries inspectorates"</i>	
5.7	Interact with inspectorates, EMEA PTM/PTL and with Rapporteur/Co-Rapporteur as required during the process	IS GCP Coordinator
6.0 (day +120, +150)	Inspection Reports	
6.1	Receive final Integrated Inspection Report and attachments (Summary Inspection Reports) and review using <i>"GCP Inspection report review checklist"</i> If the report is acceptable go to step 6.3. If not, go to 6.2	IS GCP Coordinator
6.2	Notify the Reporting Inspectorate if there are any items requiring clarification or if the report has been rejected – in which case take steps to obtain a satisfactory report in the required timeframe	IS GCP Coordinator
6.3	Distribute final Integrated Inspection Report and attachments to the S&E PTM, the PTL, the Rapporteur/Co-Rapporteur and to the CHMP (as needed). Once it is distributed, it should be sent to the applicant (EMEA IS reserves the right to advise the CHMP that a particular IIR is not distributed to the applicant eg. in case this might prejudice any enforcement or other actions arising)	IS GCP Coordinator
6.4	Complete the payment order form <i>"GCP Inspection Payment Order"</i> and forward it to the gestionnaire with a memorandum indicating the payment to be given in accordance with the "Policy on financial transactions and payments for GCP inspections requested in order to complete the assessment of applications under the centralised procedure" <i>"Memo to initiate payment"</i>	IS GCP Coordinator
6.5	Update the GCP inspection excel spreadsheet <i>"GCP Inspection excel spreadsheet"</i>	IS GCP Coordinator
6.6	Follow-up any actions arising from the inspection in conjunction with the PTM/PTL, Rapporteur/Co-Rapporteur and the inspectors	S&E PTM and IS GCP coordinator
7.0	Post-authorisation inspections In case of a conditional marketing authorisation or an authorisation under 'exceptional circumstances', the data submitted as a result of the specific obligations/follow-up measures, may give rise to the need for an inspection to verify compliance with GCP Principles. Similarly, other information received post-authorisation (e.g. in relation to safety updates, extensions etc...) may trigger a GCP inspection request. In all these cases the inspections are recommended to the CHMP following this SOP in accordance with the timelines appropriate to the circumstances.	

8. Records

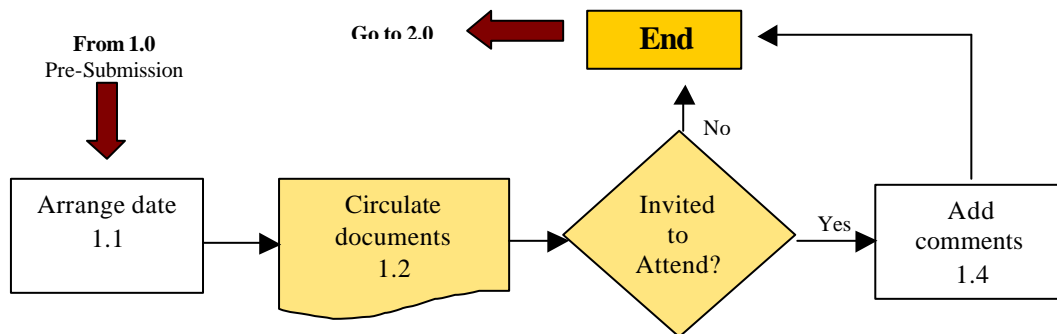
The EMEA inspection sector keeps a record of the GCP reviews of applications. The EMEA inspection sector keeps a file for each separate inspection request generated by CHMP, identified by the application number and also by an inspection number (EMEA/INS/GCP/YYYY/#). This file contains the related inspection request, contract, relevant correspondence and inspection reports. For each product involved a sub-folder “GCP” is created under “Inspections” for copies of electronic documents.

9. Process Map(s)/ Flow Chart(s)

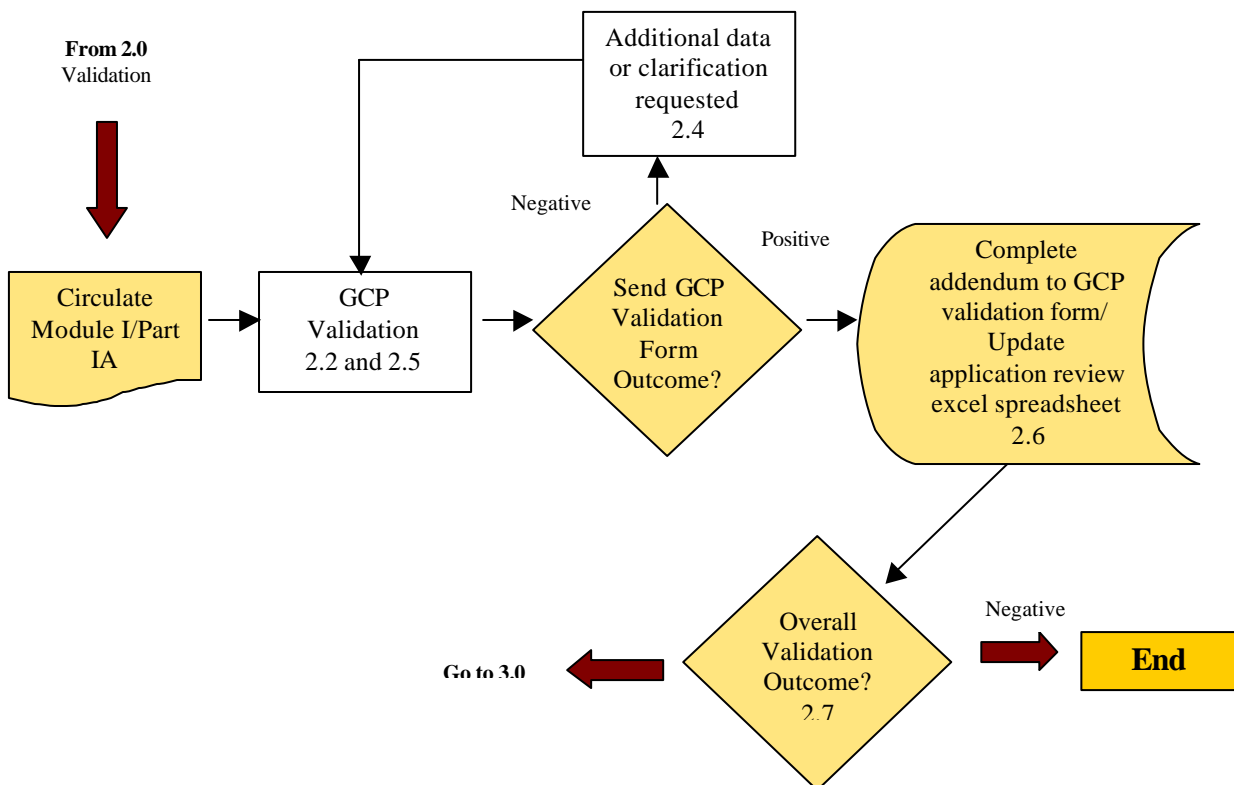
Level 1



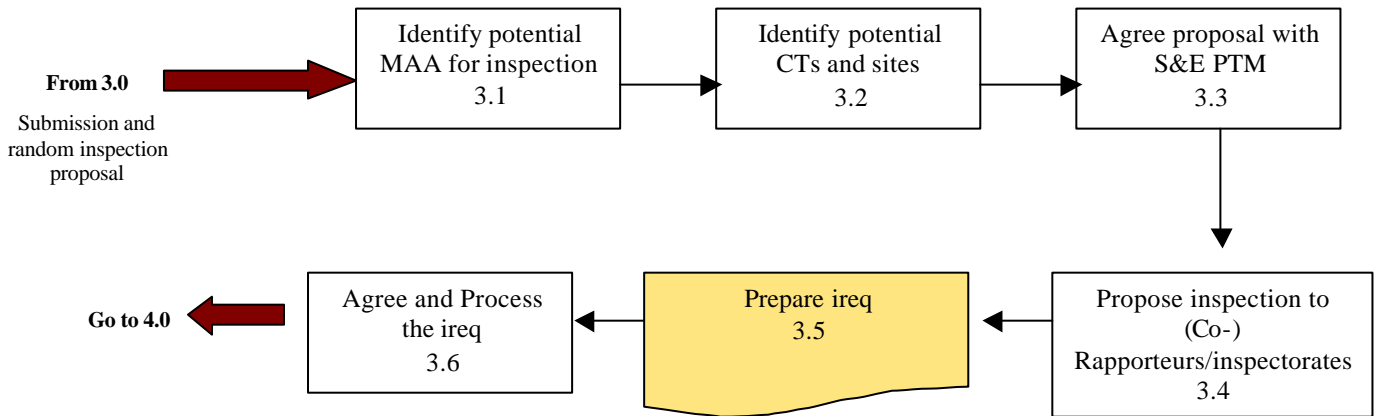
Level 2: Pre-Submission



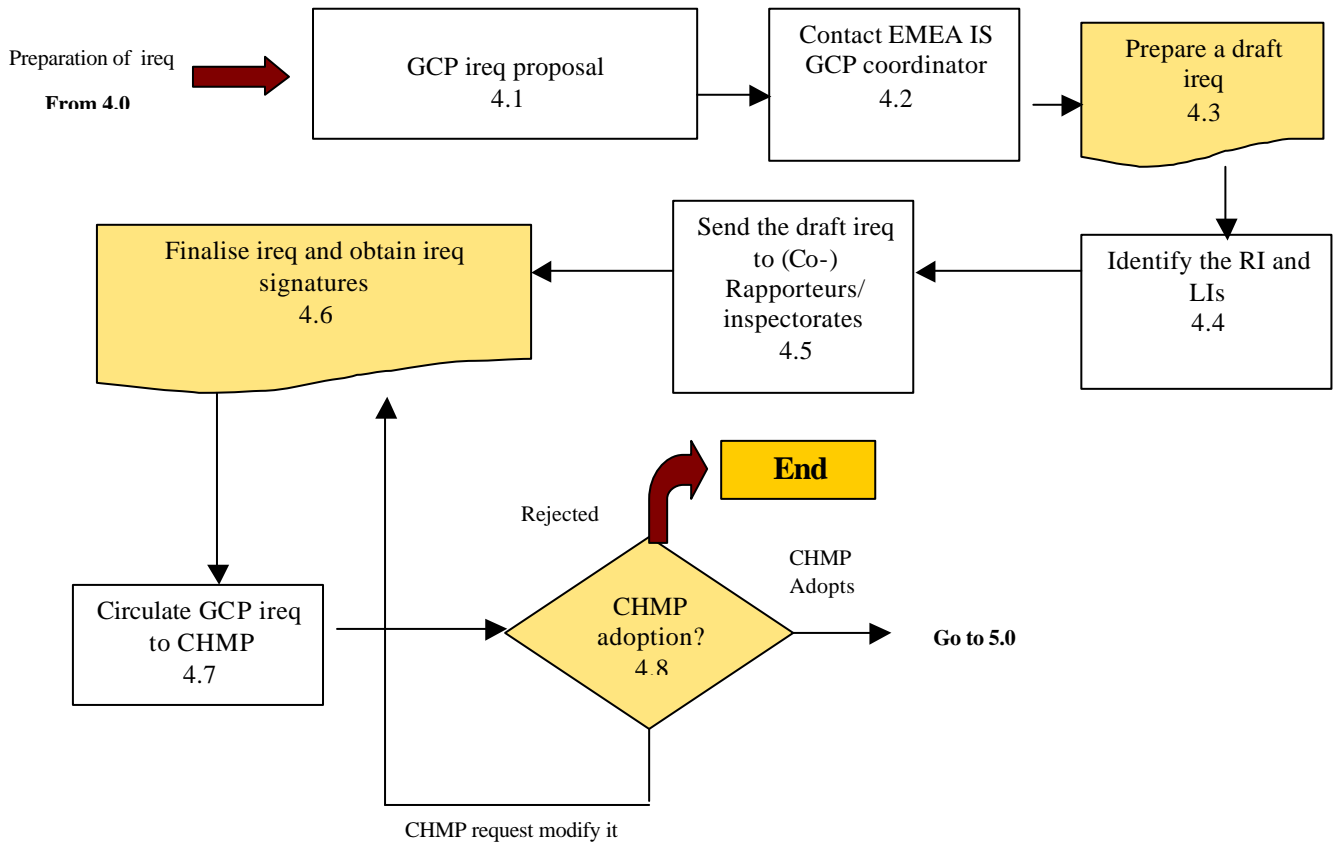
Level 2: Validation



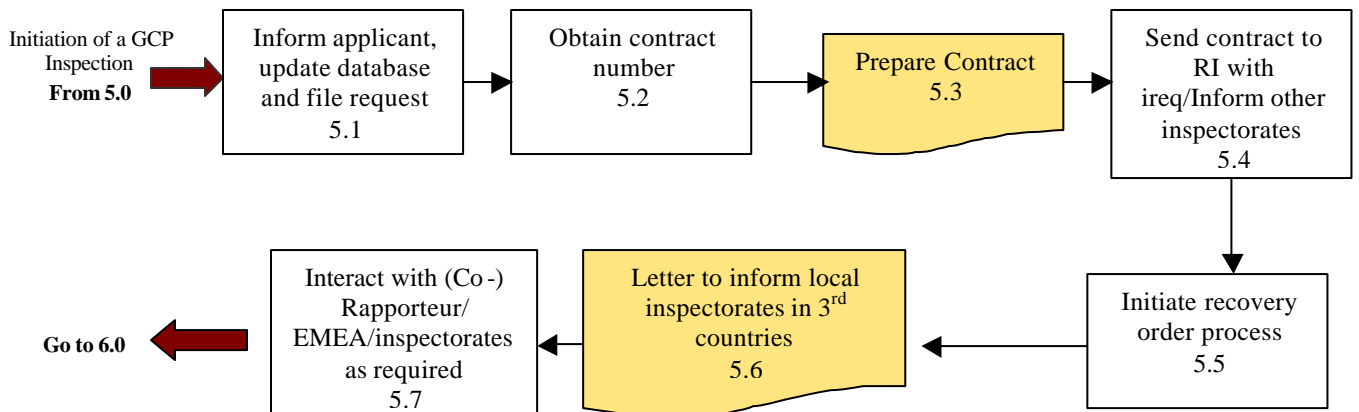
Level 2: Submission and Random inspection proposal



Level 2: GCP Inspection Request



Level 2: Initiation of a GCP Inspection



Level 2: Inspections Reports

