

Title: Coordination of pre-approval GxP Inspections		
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Lead Author	Approver	Effective Date: 16-MAY-07
Name: Francisco Peñaranda	Name: Emer Cooke	Review Date: 16-MAY-10
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## 1. Purpose

This SOP describes the processes used for Inspection Co-ordination in the routine review of applications, preparation and processing of inspection requests, and co-ordination and reporting of inspections in human and veterinary, when appropriate, applications for marketing authorisations under the centralised procedure.

It interfaces with procedures and guidance documents prepared by the GMP and GCP Inspection Services groups where appropriate and for practical purposes may overlap with these in some areas. It also interfaces with the human SOP-H-3009 (Validation of new applications for marketing authorisations, applications for extensions and Article 58 opinions) and veterinary SOP-V-4013 (Submission of an Application for the Granting of a Community Marketing Authorisation).

## 2. Scope

This SOP applies to all pre-approval inspections that may be requested by the CxMP during the evaluation phase of an application for a medicinal product under the centralised system. It therefore covers GMP, GCP and GLP inspections, which are referred in this SOP as “GxP inspections”.

This SOP also applies to pre-approval Sampling & Testing.

This SOP does not apply to either exceptional inspections requested in connection with a Rapid Alert / Recall / Quality Defect (see SOP-INSP-007 for Rapid Alert inspections) or GMP/GCP post-authorisation inspections for variations or routine re-inspections.

## 3. Responsibilities

It is the responsibility of the Head of Unit/Sector to ensure that this procedure is adhered to within their own Unit/Sector. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of “**9. Procedure**”.

## 4. Changes since last revision

Extensive revision to rewrite SOP. As part of process improvement, streamlining and continuous improvement exercises, this SOP has been developed to harmonise practices across all types of inspections.

The previous SOPs for the coordination of GMP inspections (SOP-INSP-2003), GCP (SOP-INSP-2004) and GLP (SOP-INSP-2008) have been extensively modified and integrated in this single SOP.

## 5. Documents needed for this SOP

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

### 1. GMP forms:

- GMP-1: GMP validation form
- GMP-2: GMP compliance fax
- GMP-3: E-mail on recommended GMP Inspection(s)
- GMP-4: GMP Inspection Request Form
  - a. Human
  - b. Veterinary
- GMP-5: Fax to Rapporteur/Co-Rapporteur
- GMP-6: GMP Inspection Contract
- GMP-7: Letter Announcement to Reporting Inspectorate with Contract
- GMP-8: Letter Announcement to Applicant
- GMP-9: GMP Inspection Report Review Checklist
- GMP-10: GMP Inspection Payment Order
- GMP-11: Letter to applicant on probable inspection in 3<sup>rd</sup> countries
- GMP-12: Circulation of Final SIR to Rapporteur and Co-Rapporteur – Cover letter
- GMP-13: Letter to applicant informing on the outcome of the inspection
- GMP-14: Form for multiproduct inspections in 3<sup>rd</sup> countries

### 2. GCP forms:

- GCP-1: GCP Validation form
- GCP-2: Addendum to the GCP Validation Form
- GCP-3: GCP Inspection Request Form
- GCP-4: Announcement of GCP inspection to applicant – Fax Cover
- GCP-5: Announcement of GCP inspection to applicant – Letter
- GCP-6: GCP Inspection Contract
- GCP-7: Fax Cover to Reporting Inspectorate
- GCP-8: Letter Announcement to Reporting Inspectorate with Contract
- GCP-9: Attachment covers
- GCP-10: List of contact persons for the Inspection
- GCP-11: Assignment letter to Participating Inspectorate
- GCP-12: GCP Inspection Report Review Checklist
- GCP-13: Template cover letter to R-Co-R and CHMP with final IIR and IRs
- GCP-14: GCP Inspection Payment Order
- GCP-15: Memo to initiate payment

### 3. GLP forms:

- GLP-1. GLP Inspection Request Template
- GLP-2. Letter to rapporteur with outcome of inspection
- GLP-3. Template GLP Contract in English
- GLP-4. Letter to monitoring authorities to initiate inspection
- GLP-5. Announcement of GLP inspection to applicant (Orphan)
- GLP-6. Announcement of GLP inspection to applicant (non-Orphan)
- GLP-7. Check-list on validation inspection reports
- GLP-8. Payment order form

## 6. Related documents

- Regulation (EEC) No 726/2004 of the European Parliament and of the Council laying down Community Procedures for the authorisation and supervision of medicinal products for human and veterinary use and establish a European Medicines Agency Articles 8, 19, 57(i).
- Directive 2001/82/EC on the Community code relating to veterinary medicinal products as amended.
- Directive 2001/83/EC on the Community code relating to medicinal products for human use as amended.
- Directive 2004/10/EC on the Principles of GLP.
- Directive 2004/9/EC on the inspection and verification of GLP.
- Council Regulation 297/95 (as amended) Financial Regulation Applicable to the Budget of the European Medicines Agency.
- Rules for the implementation of Council Regulation (EC) 297/95 on fees payable to the EMEA.
- The rules governing medicinal products in the European Union, Volume 2A “Notice to Applicants”. Chapter 4, Pre-authorisation inspections.
- EMEA Pre-submission Guidance for Users of the Centralised Procedure.
- SOP-H-3009: Validation of new applications for marketing authorisations, applications for extensions and Article 58 opinions.
- SOP-V-4013: Submission of an Application for the Granting of a Community Marketing Authorisation.
- SOP-INSP-2005: Standard Operating Procedure on Processing of Financial Documents for GMP, GCP and GLP inspections.
- SOP-INSP-2006: Standard Operating Procedure on Processing Inspection Contracts for GMP, GCP and GLP inspections
- INS/GCP/1: Procedure for co-ordination pre-authorisation GCP inspections during assessment of application submitted to the EMEA.
- INS/GCP/4: Procedure for preparation of reports on pre-authorisations GCP inspections during assessment of applications submitted to the EMEA.

## 7. Definitions

### a. GMP specific

- **GMP Inspection:** on-Site assessment of the compliance with the Community GMP principles performed by officials of Community Competent Authorities or authorities found equivalent under a Mutual Recognition Agreement.
  - A **general GMP Inspection**<sup>1</sup> covering general GMP aspects should be carried out before a Manufacturing Authorisation is granted, in accordance with Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC, and periodically afterwards as required.
  - An inspection is **product- or process- related** when it is requested to assess specific issues related to the assessment of an application/variation (focused on the adherence by the manufacturer to the requirements of the marketing authorisation of a medicinal product and on the manufacture and documentation related to the product or to a specific manufacturing process) or other aspect of the manufacturing process.

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<sup>1</sup> *Site outside the EEA:* a general GMP inspection is requested if the site is not under EEA supervision or has not been inspected by any EEA-Inspection Services for the last 2-3 years, unless there is an operative Mutual Recognition Agreement between the EEA and the country where the product is manufactured, and hence a GMP certificate or inspection report is available from the third party.

*Site located in the EEA:* the Supervisory Authority of the Member State on a routine basis inspects this site for GMP purposes. An inspection is requested only if there are specific issues connected with assessment of the application.

- **Lead Supervisory Authority:** Supervisory Authority responsible for communication with the IS (If there is more than one Supervisory Authority, they should reach an agreement which one takes the responsibility for organising, planning and reporting the inspection(s)).
- **Replacement Competent Authority:** When the Supervisory Authority is not able to inspect in a third country, the Rapporteur and the Supervisory Authority together designate another competent authority as the “Replacement Competent Authority” for the inspection. The “Replacement Competent Authority” will then carry out the inspection as the “lead Supervisory Authority”.
- **Summary Inspection Report (SIR):** for each GMP 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.
- **Supervisory Authority:** competent authority of the Member State in which the product is either manufactured or imported for sale within the European Economic Area (EEA), as defined in Articles 18 and 43 of Council Regulation 726/2004.

#### **b. GCP specific**

- **GCP 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.
- **Integrated Inspection Report (IIR):** for each GCP inspection request made by the CHMP one Integrated Inspection Report is prepared. 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 IRs 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 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 and IR.

#### **c. GLP specific**

- **GLP Inspection:** On-Site assessment of the compliance with the OECD GLP principles as adopted by the Community, performed by officials of Community Competent Authorities or authorities found equivalent under a Mutual Recognition Agreement. The inspection referred to in this SOP is typically a **study related** audit which is performed when it is requested to assess in retrospect specific issues related to the assessment of Module II and III of an application (focused on the adherence of the study to the requirements of the marketing authorisation of a medicinal product and on the process and documentation related to the product or to a specific study) or other aspect of the study. Exceptionally a

**general GLP Inspection** covering general GLP compliance could be carried out in accordance with Directive 2004/10/EC and Directive 2004/9/EC.

- **GLP Inspection Report:** Report prepared by the official representing the Competent Authority stating whether the test facility inspected in general complies with the Community GLP principles and/or covers the study related issues arising from the assessment of the application.
- **GLP monitoring authority:** Competent authority of the Member State in which the test facility is located. For test facilities in 3<sup>rd</sup> countries or OECD countries outside the EU the CxMP will nominate authorities in its inspection request if necessary.

#### d. General GXP Definitions

- **Lead Inspector:** (**Note:** *In the case of GMP/GLP inspections, the Reporting Inspector is always the Lead Inspector*) the Inspector who has the following duties for the GxP 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, where appropriate.
- **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.
- **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 (Co)Rap and the CxMP. 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 GxP inspection
  - the Reporting Inspector may also be the Lead Inspector (see below) for one or more sites.
- **Reporting Inspectorate:** the Inspectorate from an EU/EEA country requested and accepting to designate the Reporting Inspector.

Abbreviations (in alphabetic order):

**AA** = Administrative assistant in charge of “Veterinary Medicines and Inspections” administration of budget lines

**Applicant/MAH** = Applicant or holder of a marketing authorisation

**AR** = Assessment Report

**CHMP** = Committee for Medicinal Product for Human Use

**CIG** = Central Information Group (or equivalent in the Veterinary Unit)

**(Co)Rap** = Rapporteur and/or Co-Rapporteur

**CTs** = Clinical Trials

**CVMP** = Committee for Medicinal Product for Veterinary Use

**CxMP** = CHMP and/or CVMP

**GCP** = Good Clinical Practices

**GLP** = Good Laboratory Practices

**GMP** = Good Manufacturing Practices

**GxP** = GCP, GLP and GMP

**HoS** = Head of Sector

**IIR** = Integrated Inspection Report

**IR** = Inspection Report

**IREQ** = Inspection Request

**IS** = Inspections Sector

**MAA** = Marketing Authorisation Application

**OECD** = Organisation for Economic Co-operation and Development

**PhV** = Pharmacovigilance

**PM** = Project Manager

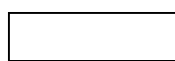
**PTL** = Product Team Leader (or equivalent in the Veterinary Unit)

**S&E PTM** = Safety and Efficacy, Product Team Member

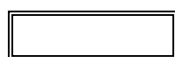
**SIR** = Summary Inspection Report

## 8. Process Map(s)/ Flow Chart(s)

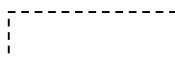
Below is an explanation of the various formatting conventions employed in the following flow-chart:



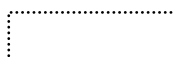
A line box is used when referencing to all types of inspections (GMP, GCP and GLP) or more than one.



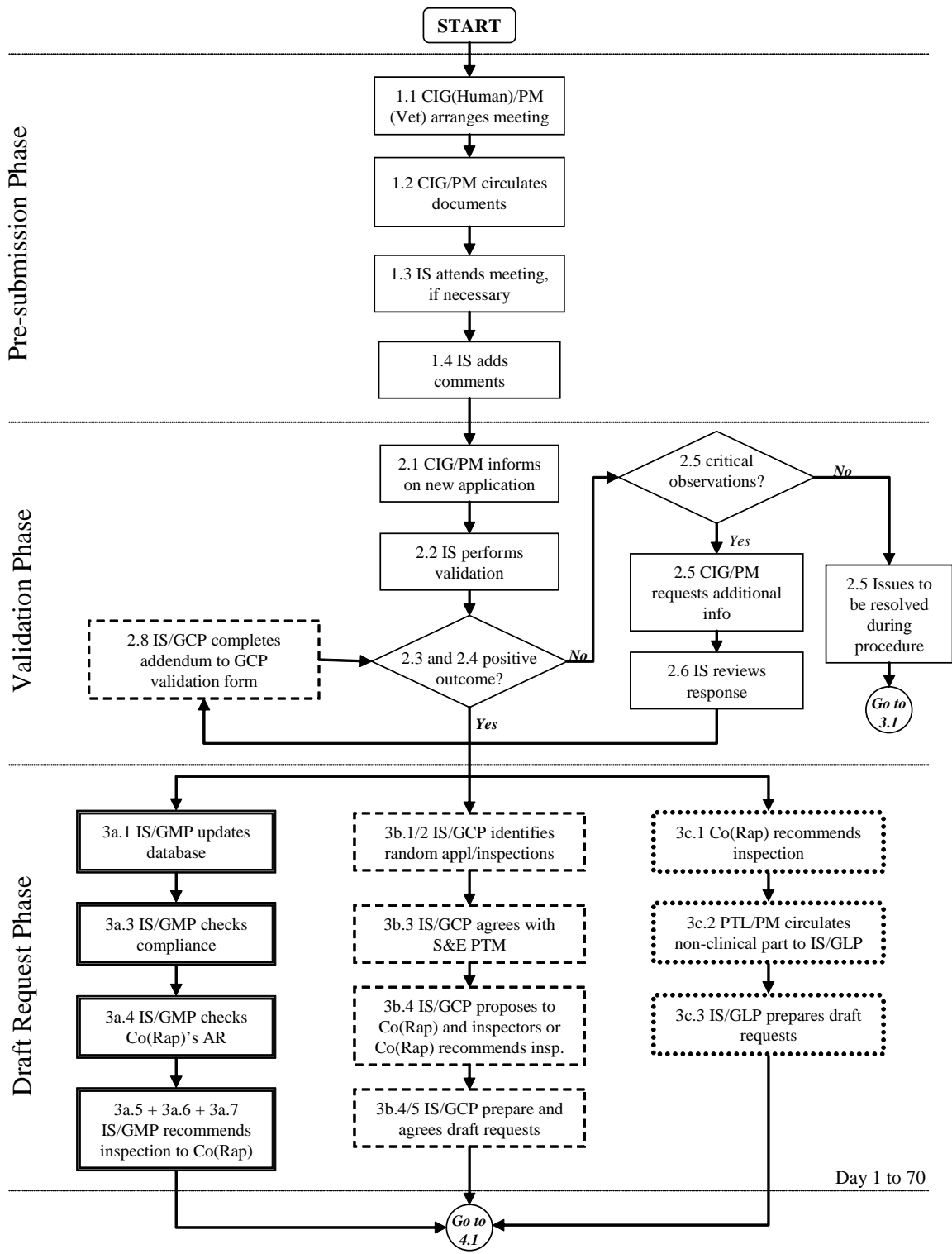
A double line box is used when referencing to only GMP inspections



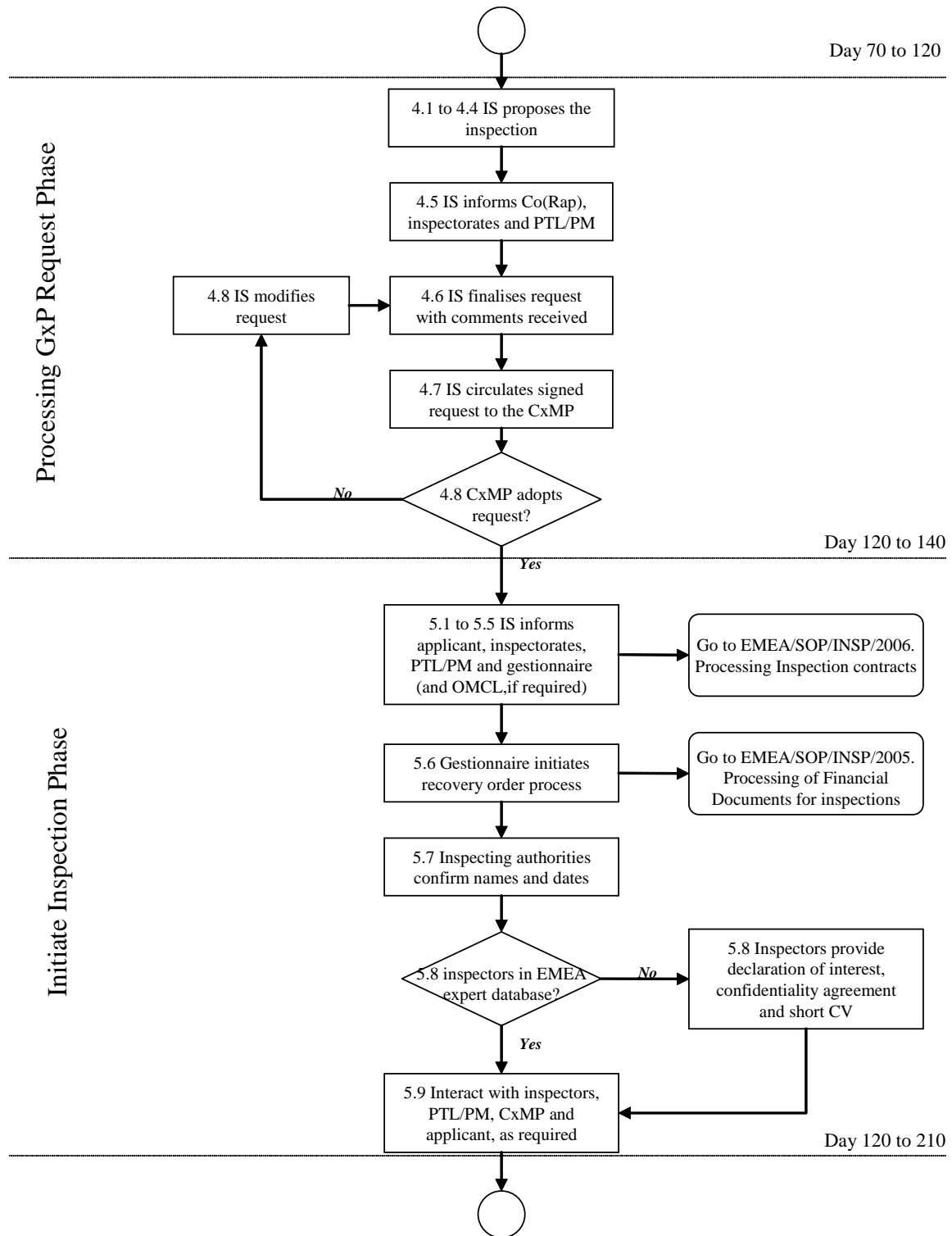
A dashed box is used when referencing to only GCP inspections



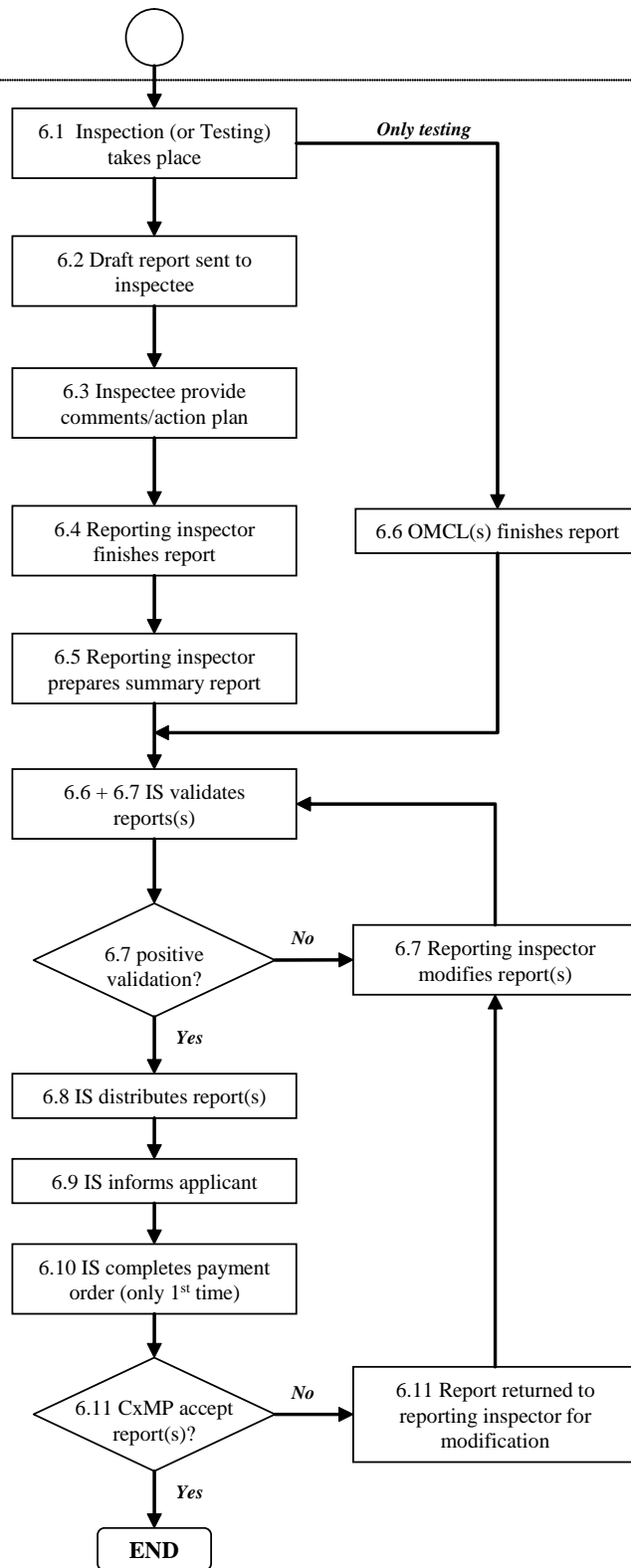
A dotted box is used when referencing to only GLP inspections



Day 1 to 70



Finalisation of report Phase



## 9. Procedure

Step <sup>2</sup>	Action	Responsibility
<b>1.0</b> (day approx. -180)	<b>Pre-submission Meeting</b>	
<b>1.1</b>	Pre-submission meetings are arranged by either the Human or Veterinary Units before submission of an application or scientific advice. An IS GxP coordinator(s) is invited, if appropriate.	CIG/PM <sup>3</sup>
<b>1.2</b>	The CIG circulates all relevant documents to the EMEA attendees in preparation for the meeting at the latest ten working days in advance.	CIG/PM
<b>1.3</b>	The person(s) from the IS attends the meeting to reply to any specific questions on the coordination of GxP 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. However, this decision may only be taken with the agreement of the representative concerned after a review of the proposed agenda.	IS GxP coordinator
<b>1.4</b>	Once the applicant has submitted to the PM/PTL the draft minutes of the pre-submission meeting, he/she ensures that minutes are circulated to IS GxP coordinator(s). Any comment should be forwarded to the PM/PTL 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(s) was invited to the meeting but unable to attend it.	IS GxP coordinator
<b>2.0</b> (day -10 to 0)	<b>Validation of the application by Inspections Sector</b>	
<b>2.1</b>	The CIG administrative assistance sends an e-mail informing the PTL/PM on: <ul style="list-style-type: none"> <li>the availability of the dossier in the validation room</li> <li>the location of the full electronic dossier on the EMEA server</li> <li>the timetable for validation (e.g. deadline for sending out the letter to company in case of validation issues and start of evaluation procedure)</li> </ul> The CIG administrative assistance distributes the relevant information to IS for validation at the latest on the day 1 of receipt.	CIG
<b>2.2</b>	The IS carries out the inspection validation within the 7 days deadline and identifies any difficulties or issues, which would prevent a positive validation of the dossier. The validation is performed by following the points of GxP validation forms (see forms GMP-1 and GCP-1).	IS GxP coordinators
<b>2.3</b>	The inspection sector confirms in the inspection validation form the result and any observations that need to be rectified by the applicant. The inspection validation form is sent to the CIG.	IS GxP coordinators

<sup>2</sup> The days included in this column are the latest ones.

<sup>3</sup> CIG for human medicinal products or PM for veterinary medicinal products.

<b>Step<sup>2</sup></b>	<b>Action</b>	<b>Responsibility</b>
2.4	It may be necessary to consult with the PTL/PM (and potentially with other members of the product team) to discuss validation findings, based on the completed checklists.	IS GxP coordinators
2.5	The CIG prepares a letter requesting additional information based on the completed validation checklists and the outcome of the validation meeting.  Additional information, which is not critical for the validation but needed, will be requested in the same letter and should be provided by the applicant within the deadline specified (e.g. for certain GxP issues for the preparation of a potential inspection, usually within 30 days from the start of the procedure).	CIG
2.6	IS reviews the response within 2 working days to ensure that the deficiencies have been solved and the inspection validation can be completed.  The IS GXP coordinator will follow up with the PTL that the applicant provides the additional information mentioned in step 2.5, which is not critical for the validation but needed in case an inspection is requested. The IS GxP coordinator will review this information and will inform the PTL if the information provided is acceptable or additional information is required	IS GxP coordinators
2.7	Consult with the PTL/PM, or set-up an ad hoc validation meeting with the product team, as appropriate, to discuss if the additional information provided by the applicant is satisfactory.	CIG
2.8	The IS GCP coordinator completes the addendum to the GCP validation form (see form GCP-2) and appends it to the GCP validation form kept in the IS record of GCP review of applications. The application review database is further updated.	IS GCP coordinator
<b>3a.0</b> (day +14 to 70)	<b>(Only GMP) Generation of an Inspection and Sampling and Testing proposal</b>	
3a.1	On confirmation that the clock for the assessment of the application has started, the IS updates the GMP database and plans the timetable for the GMP related activities described below.	GMP secretaries
3a.2	PM/PTL should inform immediately the IS GMP coordinator in the case of a marketing application that is given or is planned to be given an “accelerated” assessment. In the case of a marketing application that is given an “accelerated” assessment the time allowed for reporting and finalising the inspection may need to be reduced significantly. In these exceptional circumstances the timetable for reporting the inspection will be agreed for each application with the (Co)Rap, the PM/PTL, the inspection team and the applicant.	PM/PTL
3a.3	Once the application is received, the IS determines, if relevant, whether or not the manufacturing, control, batch release and importation site(s) concerned have already been inspected, by whom, and if satisfactory inspection reports are available.  If necessary, the IS asks the concerned supervisory authority(ies) and/or MRA partners to confirm in writing the GMP compliance and date of last inspection of the sites detailed in the Part IA of the application using the standardised format (see form GMP-2).	IS GMP coordinators
3a.4	The IS GMP coordinator checks in the Day 70 ARs whether they recommend a product-related inspection.	IS GMP coordinator

<b>Step<sup>2</sup></b>	<b>Action</b>	<b>Responsibility</b>
<b>3a.5</b>	Once the status of compliance has been clarified for all manufacturing sites described in point 3a.3 and the (Co)Rap assessment report has been reviewed, the IS submits to the (Co)Rap a recommendation by email (see form GMP-3) on the need for carrying out an inspection.  The information is distributed to the PM/PTL and Supervisory Authority(ies).	IS GMP coordinators
<b>3a.6</b>	When more than one Supervisory Authority is involved <sup>4</sup> in the recommended inspections described in step 3a5, they should reach an agreement regarding which authority will take the leading role.	Supervisory Authorities
<b>3a.7</b>	Agree the draft inspection request by all parties (i.e. (Co)Rap, Supervisory Authority(ies) and PTL/PM). The inspection request is then processed as for all inspection requests (go to step 4.0)	(Co)Rap, Supervisory Authority(ies) and PM/PTL
<b>3b.0</b> (day +1 to +70)	<b>(Only GCP) Generation of a routine random inspection proposal</b>	
<b>3b.1</b>	Identify potential applications for inspection based on criteria for routine random inspection	IS GCP Coordinator
<b>3b.2</b>	Identify potential clinical trials and sites for inspection	IS GCP Coordinator
<b>3b.3</b>	Agree the proposal with the S&E PTM	S&E PTM and IS GCP coordinator
<b>3b.4</b>	Propose the potential inspection to the (Co)Rap and the respective inspectorates  or  S&E PTM checks in the (Co)Rap assessment report whether they recommend a GCP inspection and informs the IS.	S&E PTM and IS GCP coordinator
<b>3b.5</b>	Prepare the inspection request, (see form GCP-3), and review with the (Co)Rap and the respective inspectorates	S&E PTM and IS GCP coordinator
<b>3b.6</b>	Agree the draft inspection request – the inspection request is then processed as for all inspection requests (see step 4.0)	Rapporteur, Co-Rapporteur and HoS IS

<sup>4</sup> The composition of the inspection team for multiproduct inspections should be established taking into consideration the procedure described in the point 2.5 of the SOP for routine re-inspections.

<b>3c.0</b>	<b>(Only GLP) Preparation of a triggered inspection proposal<sup>5</sup></b>	
<b>3c.1</b>	The Rapporteur/Co-Rapporteur evaluates the statements on GLP compliance provided in the application, the scientific content, the results of the Inspections Sector GLP compliance check and utilising the annex “FACTORS TO BE CONSIDERED BY EMEA & RAPPORTEUR IN DETERMINING AN INSPECTION PROPOSAL TO THE CxMP” considers if an audit is necessary.  A standard statement concerning the GLP status of the studies is included in the day-70 assessment report	(Co)Rap
<b>3c.2</b>	The non-clinical part of the assessment report should be circulated to the GLP manager in the inspections sector for action or filing of relevant pages.	PTL/PM
<b>3c.3</b>	If GLP audits are requested, inspections sector will finalise the inspection request for adoption at day 90 or 120 <sup>6</sup> .	IS GLP coordinator
<b>4.0</b> (day +70 to +120)	<b>Processing of GxP Inspection Request</b>	
4.1	Propose a GxP inspection via process 3a, 3b and 3c (above) or (Co)Rap/EMEA/Inspectorates propose an inspection	Proposer of inspection
4.2	Contact EMEA IS GxP coordinator whenever there is a discussion on the need of a GxP inspection at CxMP or communication from (Co)Rap regarding a GxP inspection (including any draft AR, etc).  The IS GxP coordinator checks in the Day 70 ARs whether they recommend inspection(s).  In the case of a GMP Product related inspection, the (Co)Rap should make a separate annex to the quality assessment report to list issues which, in the opinion of the assessor, should be addressed during an inspection visit. This separate annex should be provided directly to the GMP coordinator. In addition, GMP managers check the Assessment Report in order to verify that inspections issues have been raised.  The (Co)Rap should also include in the Assessment Report a justification for sampling and testing. They should specify the test protocol (type of samples, number of samples, number of batches) and agree with the EMEA, which OMCL carries out the required testing.	Proposer of inspection
4.3	Prepare draft inspection request based on information provided by the proposer and gathered from the application, use the forms GMP-4 and/or GCP-3 and/or GLP-1.	IS GxP Coordinator
4.4	Identify the reporting inspectorate (only for GCP inspections) and lead inspectorates, to be confirmed based on sites finally selected.	IS GxP Coordinator

<sup>5</sup> In the exceptional case of establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin the time schedule will be adapted to the initial evaluation: Within 90 days of receipt of a valid application the inspection request will be adopted and transmitted with the list of questions. The report of the audit will be available before the consolidated response and the start of the 30 day final evaluation

<sup>6</sup> In the case of a marketing application that is given an “accelerated” assessment, the time allowed for reporting and finalising the inspection may need to be reduced significantly. In these circumstances the timetable for carrying out and reporting the inspection will be agreed for each application with the Rapporteur/Co-Rapporteur, the EMEA, the inspection team, the applicant and the test facility.

4.5	Send the draft inspection request to the (Co)Rap, EMEA S&E PTM (GCP & GLP inspection), PTL and the involved inspectorates for final comments. In the case of GMP inspections, use the form GMP-5 along with the draft GMP inspection request.	IS GxP Coordinator
4.6	Finalise the inspection request and obtain the signature of the IS HoS or designee.	IS GxP Coordinator
4.7	Circulate the GxP inspection request to the CxMP for formal adoption. IS GxP coordinator provides a copy of the inspection request to the CxMP secretariat, who circulate the document and enter it on the CxMP agenda.	IS GxP Coordinator/Cx MP Secretariat
4.8	CxMP adopts request – proceed to step 5.0 CxMP rejects request - modify if appropriate (then go back to step 4.6) or request remains rejected (then end of process)	CxMP
<b>5.0</b> (day +120 to +140)	<b>Initiation of a GxP Inspection</b>	
5.1	Inform applicant of the adoption of the GxP inspection request within 10 working days of the CxMP meeting at which it was adopted, using the forms GMP-8 and/or GCP-4/5 and/or GLP5/6. IS GxP coordinators updates GxP databases, if available, and file the inspection request	IS GxP Coordinator
5.2	If the CxMP adopts the GMP request recommending sampling and testing to be carried out, then the IS GMP coordinator informs the concerned Official Medicines Control Laboratory(ies) (OMCL) and the applicant. No contract or payment order is required.	IS GMP Coordinator
5.3	Obtain contract number from the AA	AA
5.4	Prepare the contract, following the SOP-INSP-2006, for the Inspectorates involved and obtain necessary EMEA signatures, using the forms GMP-6 and/or GCP-6 and/or GLP-3.	IS GxP Coordinator
5.5	Send the contract along with a copy of the inspection request and announcement letter to the applicant, to the involved Inspectorates for signature within 10 working days of the adoption of the inspection request (one copy for their files and one to be returned to the EMEA IS), using the forms GMP-7 and/or GCP-7 and GCP-11 to 10 and/or GLP-4	IS GxP Coordinator
5.6	Send a copy of the letter mentioned in step 5.5 to the AA in order to initiate the recovery order process using the SOP-INSP-2005 (Processing Financial Documents for inspections)	IS GxP Coordinator
5.7	The inspecting organisation(s) will confirm the name of the inspectors (and leading inspector, if necessary) and the proposed dates of inspection to the IS using the standard faxes attached in the letter to inspecting authorities (forms GMP-7 and/or GLP 4) or by email in the case of the GCP inspections.  This information should be sent to the IS GxP coordinator as soon as available and at the latest one week before the inspection takes place.	Inspecting authorities
5.8	IS checks if the inspectors nominated are in the EMEA expert database. If not, IS must obtain the following information before the inspection takes place: declaration of interest, confidentiality agreement and short CV.	IS GxP Coordinator

5.9	Interact with inspectors, EMEA PTL/PM and with (Co)Rap, as required during the process	IS GxP Coordinator
<b>6.0</b> (day+120 to 210)	<b>Inspection reports<sup>7</sup></b>	
6.1	For GMP and GLP inspections, the lead inspector sends the list of deficiencies to the IS GMP or GLP coordinator, as appropriate, and the preliminary outcome of the inspection report using the standard fax attached in the letter to inspecting authorities (see Form GMP-7 and/or GLP-4).	GMP/GLP Lead inspector
6.2	At the same time, the GMP and/or GLP and/or GCP draft inspection report is sent by the lead inspector to the inspectee with a request for major factual errors, points of disagreement and/or on remedial actions to be provided within 15 calendar days of receipt.	GxP Lead inspector
6.3	The inspectee has 15 calendar days to give comments on the report. This period of time may be extended if the deadline for reporting allows it.	Inspectee
6.4	On receipt of comments on the draft report from inspectee, the report is finalised by the lead inspector.	GxP Lead Inspector
6.5	When the report is complete the lead inspector should prepare a summary of the inspection report for circulation to the (Co)Rap, the CxMP, if necessary, or other competent authority that may request it. This summary will follow the format established by the different GxP inspectors groups.	GMP/GLP Lead Inspector(ate)
6.6	In the case of pre-approval Sampling&Testing, the results of the tests are reported by the OMCL directly to the IS GMP coordinator, who will forward them to the (Co)Rap and PM/PTL for consideration in finalising the CxMP assessment report.	IS GMP coordinator
6.7	IS GxP coordinators receive final reports, summary reports, integrated reports and other attachments, and review using the checklists in forms GMP-9 and GCP-12 and GLP-7.  The IS GxP coordinator will check reports received for adherence to the established guidelines and overall quality. Reports that are found to be deficient, incomplete or below the required scientific standard will be returned to the Reporting Inspectorate (or Lead Inspectorate for GMP/GLP inspections) with a written explanation of the reasons for non-acceptance and proposed deadline for revision, for a re-inspection or other remedial action. This deadline for re-submission of the report will be set by the IS GxP coordinator taking into account the overall timetable adopted for completion of the assessment of the application.	IS GxP co-ordinator
6.8	IS GxP coordinators distribute final Inspection Report (GLP)/final Integrated Inspection Report (GCP)/Summary Report (GMP) and relevant attachments to the PTL/PM, the (Co)Rap and the CxMP (as needed), using the form GLP-2, GMP-12 and GCP-13, respectively. Eudralink messages may be used as an alternative.	IS GxP co-ordinator
6.9	Once the inspection reports are distributed according to step 6.8:	IS GxP co-

<sup>7</sup> At Day 120 there is a clock stop in order for the applicant to answer the list of questions from the CxMP. The clock will stop for one to six months depending on the time the company takes to answer the list. Day 150 therefore occurs a minimum of two months after the inspection request but in most cases around 4-7 months after the request. The Inspectorate may contact the applicant/MAH to adapt the inspection to the actual clock start.

	<ul style="list-style-type: none"> <li>• GMP/GLP: a letter should be sent to the applicant on the overall conclusion of the inspection report, using the form GMP-13 and/or GLP-9</li> <li>• GCP: the IIR 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, e.g. in case this might prejudice any enforcement or other actions arising)</li> </ul>	ordinator
6.10	Complete the payment order form (GMP-10 and/or GCP-14 and/or GLP-8) and forward it to the AA with a memorandum (form GCP 15) indicating the payment to be given in accordance with the “ <i>Rules for the implementation of Council Regulation (EC) 297/95 on fees payable to the EMEA</i> ”. In the case of GMP inspections, the payment order form should be accompanied by GMP-9 form and copy of the summary report.	IS GxP co-ordinator
6.11	<p>Where in the opinion of the CxMP the inspection report does not meet the expected quality requirements, the EMEA reserves the right to withhold payment until a report acceptable to the relevant CxMP has been provided. The inspection report will be returned to the Lead inspectorate or Reporting Inspectorate, where applicable, with a written explanation of the reasons for non-acceptance and proposed deadline for revision or other remedial action.</p> <p>This deadline for re-submission of the report will be set by the IS GxP coordinator taking account of the overall timetable adopted for completion of the assessment of the application.</p>	CxMP and IS GxP co-ordinator
6.12	In exceptional circumstances and on the recommendation of the CxMP, the EMEA may breach the contract and cancel any corresponding payment	CxMP and IS GxP co-ordinator
6.13	IS GxP coordinator updates the GxP database, if available.	IS GxP co-ordinator

## 10. Records

When completed, approved and numbered, the retention of the hardcopy of this SOP and storage and archiving according to EMEA-SOP-T-1000 and EMEA-SOP-T-1050 will be responsibility of the Veterinary and Inspections Unit.

All completed forms and other records relating to the operation of this procedure will be collected by the IS GxP coordinators, who are responsible for maintaining the files containing the original documents and relevant correspondence for GxP inspections for the products concerned.