

Title: Procedure for Co-ordinating pre-authorisation GMP and product/process related inspections		Document no.: SOP/INSP/2003
Applies to: Inspections Sector		Effective Date: 15-AUG-2004
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Signature: Signature on file	Signature: Signature on file	Signature: Signature on file
Date: 19/07/2004	Date: 19/07/2004	Date: 21/07/2004

1. Purpose

To describe the procedure for co-ordinating GMP and product/process related inspections of the manufacturing sites proposed in human and veterinary applications for marketing authorisations under the centralised system.

2. Scope

This SOP applies to all GMP inspections and product/process related inspections that may be requested by the CxMP during the pre-authorisation phase of an application for a medicinal product under the centralised system.

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 post-authorisation inspections for variations or routine re-inspections.

3. Responsibilities

Completion, issue and update of this SOP GMP managers, Inspections Sector.
 Approval Head of Inspections Sector.
 Authorisation Head of Veterinary Medicines and Inspections Unit.
 Implementation GMP managers, Inspection Sector.

The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section 7.

4. Forms needed for this SOP

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

- Form 4.1: Checklist on validation
- Form 4.2: GMP compliance fax:
- Form 4.3: Draft GMP Inspection requests
 - a. Human
 - b. Veterinary
- Form 4.4: Fax to Rapporteur/Co-Rapporteur
- Form 4.5: Example of Human contract in English
- Form 4.6: Letter to inspecting authorities to initiate inspection
- Form 4.7: Letter to applicant to initiate inspection
- Form 4.8: Check-list on validation inspection reports
- Form 4.9: Payment order form
- Form 4.10: Letter to applicant on probable inspection in 3rd countries
- Form 4.11: Letter to Rap/CoRap confirming the outcome of the inspection
- Form 4.12: Form for multiproduct inspections in 3rd countries

5. Related documents

- The rules governing medicinal products in the European Union, Volume 2A “Notice to Applicants”. Chapter 4, Pre-authorisation inspections (page 61-63):
<http://dg3.eudra.org/eudralex/vol-2/A/pdfs-en/cap4aen.pdf>
- EMEA Pre-submission Guidance for Users of the Centralised Procedure.
 - GMP-inspections during the assessment of the application:
<http://www.eudra.org/gendocs/presub/q28.html>
 - What is the fee for a GMP Inspection?:
<http://www.eudra.org/gendocs/presub/q12.html>
- 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.
- SOP on GMP inspection coordination for variations.
- SOP on GMP re-inspection coordination.
- Policy on financial transactions and payments for GMP inspections of multiproduct manufacturers under the centralised procedure.
- Rules for the implementation of Council Regulation (EC) 297/95 on fees payable to the EMEA.

6. Definitions

- *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**¹ 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.
- *Inspection Report*: Report prepared by the official representing the Competent Authority stating whether the company inspected in general complies with the Community GMP principles and/or the product and process related issues arising from the assessment of the application.
- *Supervisory Authority*: Competent authority of the Member State in which the product is either manufactured or imported, controlled and released for sale within the European Economic Area (EEA), as defined in Articles 18 and 43 of Regulation 726/2004.
- *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*: Where the Supervisory Authority is unable to verify the GMP status of any third country manufacturer(s) they may request another EU/EEA Competent Authority to carry out an inspection, which is defined as the Replacement Competent Authority.
- *Leading inspector*: Inspector responsible for communication with the IS (when there is more than one inspector (from the same or different competent authorities), they should reach an agreement which one takes the responsibility to communicate with the IS)

Abbreviations:

CxMP = CPMP and/or CVMP

IS = Inspections Sector

PM = Project Manager

PTL = Product Team Leader

R/CoR = Rapporteur/Co-Rapporteur

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

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

Applicant/MAH = Applicant or holder of a marketing authorisation

1 *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.

7. Procedure

Step ²	Action	Responsibility
1.0 (day –120)	Pre-submission Meeting	
1.1	Pre-submission meetings are arranged by either the Human or Veterinary Units before submission of an application. The CIG or PM/PTL, where relevant, sets an appropriate date for the pre-submission meeting to all participants.	Project Manager
1.2	The GIG circulates all relevant documents to the EMEA attendees in preparation for the meeting at the latest ten working dates in advance.	Project Manager
1.3	The person from the IS attends the meeting to reply to any specific questions on the coordination of GMP 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.	GMP managers
1.4	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. Any comment should be forwarded to the PM/PTL within six working days. 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"	GMP managers
2.0 (day –10)	Validation of the application by Inspections Sector	
2.1 (day –8)	The CIG distributes a copy of the Part IA and Annexes to IS for validation at the latest on the day 2 of receipt.	CIG
2.2 (day –6)	The IS carries out the inspection validation within 2 working days. The validation aspects are performed by following the points of a checklist for validation (see form 4.1).	GMP managers
2.3 (day –6)	The conclusion of the validation by the IS is either satisfactory or unsatisfactory. If the completed form is not available before the deadline of application validation, it means that the conclusion is satisfactory.	GMP managers
2.4 (day –6)	The IS provides the validation form to the CIG, who originally sent the Part IA. The inspection sector confirms the result and any deficiencies/observations in the inspection validation form that need to be rectified by the applicant.	GMP managers
2.5 (day –5)	If IS requires additional data, information or clarification to complete its validation of the dossier, the CIG contacts the applicant requesting data within a specific time limit. In this case, the validation can only be completed after receipt and verification of the information submitted.	CIG
2.6 (day –4)	IS reviews the response within 2 working days to ensure that the deficiencies have been solved and the inspection validation can be completed. If the completed form is not available before this deadline, it means that the conclusion is satisfactory.	GMP managers

² The days included in this column are the latest ones.

Step²	Action	Responsibility
2.7 (day -1)	Where all parties came to a positive conclusion the overall outcome of the validation is positive. If any of the members of the validation team has come to a negative conclusion the overall outcome is negative.	CIG
2.8 (day 0)	Once validated, it is normally not permitted to add a new site or to change the steps of manufacture/release during the 210-day procedure, unless a major problem occurred with the originally proposed manufacturing site and the change is assessed and accepted by the Rapporteur/Co-Rapporteur. Any additional site should be submitted as a variation after the granting of the marketing authorisation, if needed.	GMP managers Applicant
3.0	Submission and GMP compliance	
3.1 (day +10)	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. PTL should inform immediately the IS 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 Rapporteur/Co-Rapporteur, the PM/PTL, the inspection team and the applicant.	GMP managers PTL
3.2 (day +20)	Once the application is received, the IS determines 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. The IS asks the concerned supervisory authority(ies) and 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 fax format (see form 4.2). This concerns finished product manufacturing, packaging, diluent, batch release and biological active ingredient sites.	GMP managers
4.0	Preparation of GMP Inspection Request	
4.1 (day + 30)	Once the status of compliance has been clarified for all manufacturing sites described in point 3.2, the IS submits a recommendation (see form 4.3) on the need for carrying out an inspection and/or sampling & testing (see step 5). This form is sent directly to the Rapporteur and Co-Rapporteur for comments (see form 4.4) and a copy is distributed to the PM/PTL.	GMP managers

Step ²	Action	Responsibility
4.2 (day + 60)	<p>Where a satisfactory report is not available for a third country site, the IS contacts the Rapporteur and Co-Rapporteur with a recommendation to inspect the manufacturing site. A copy is distributed to the PM/PTL</p> <p>The IS coordinator sends a letter (see form 4.10) to the applicant with preliminary information on the potential inspection in the concerned third country site(s) and for confirmation of the following points: site address, billing address, flow chart of the manufacturing process at the site concerned, applicant contact point and eligibility to request the inspection fee to be waived for orphan medicines. The letter will inform the applicant of the financial consequences if the inspection is adopted by the CxMP (see step 4.7) on day 90 or 120.</p>	GMP managers Applicant
4.3 (day + 60)	The letter referred to in step 4.2 is also sent to the Supervisory Authority(ies) ³ to facilitate the planning of any potential inspection likely to be requested by the CxMP in third countries.	GMP managers
4.4 (day +85)	The Supervisory Authority should inform the EMEA of any actual or probable difficulty in meeting the timetable deadlines or if they are unable to perform the inspection and finalise the report within the evaluation of the dossier. In this situations, a Replacement Competent Authority may be recommended by the Supervisory Authority ⁴ . This information should be notified as soon as possible in order to discuss it before the request is adopted by the CxMP.	Supervisory Authorities
4.5 (day +85)	<p>In the case of multiproduct inspections, the lead Supervisory Authority should inform the EMEA, before the adoption of the inspection by the CxMP, about the total fee to be paid by the applicants/MAHs, taking into account the envisaged number of hours, number of inspectors, size of the site and category of products to be covered. They should justify if more than one single fee is applicable, using the form 4.12. If the completed form is not available before the adoption of the inspection, it means that a single fee will be applied.</p> <p>When more than one Supervisory Authority is involved⁵, they should reach an agreement regarding which authority will take the leading role (responsible for organising, signing contracts, planning and reporting the inspection). The lead Supervisory Authority should specify the composition of the inspection team using the form 4.12.</p>	Supervisory Authorities
4.6 (day +90)	In the case of a Product related inspection, the Rapporteur/CoRapporteur 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. A copy of the document is distributed to the PM/PTL.	Rapp/CoRapp
4.7 (day +120)	The IS circulates to the CxMP during its plenary meeting the final GMP Inspection Request recommended by the Rapporteur and Co-Rapporteur. A copy of the document is distributed to the PM/PTL.	GMP managers
4.8 (day +120)	The CxMP adopts, rejects or postpones the recommended request.	CxMP

³ See question 5 of “Questions and answers on GMP inspection coordination”.

⁴ See question 4 of “Questions and answers on GMP inspection coordination”.

⁵ 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.

Step²	Action	Responsibility
4.9 (day +125)	If the CxMP confirms that no Inspection or Sampling and Testing is necessary, the IS updates the GMP database.	GMP managers
4.9 (day +125)	If the CxMP adopts ⁶ the request recommending an inspection the IS carries out the following tasks: preparation of payment order, preparation of contract(s) and initiation of the inspection(s).	GMP managers
5.0	Pre-authorisation Sampling and Testing	
5.1 (day + 120)	No samples of the proposed medicinal product are required at time of submission of the application. The recommendation for formal sampling and testing request is included in the draft GMP Inspection Request form and is processed at the same time.	GMP managers
5.2 (day +120)	The Rapporteur/CoRapporteur should provide a justification, specify a test protocol (type of samples, number of samples, number of batches) and agree with the EMEA, which OMCL carries out the required testing.	Rapp/CoRap
5.3 (day +125)	If the CxMP adopts the request recommending the sampling and testing to be carried out, then the IS inform the concerned Official Medicines Control Laboratory(ies) (OMCL), EDQM and the applicant. No contract or payment order is required (see step 6)	GMP managers
5.4 (day +180)	The results of the tests are reported by the OMCL directly to the GMP manager, who will forward them to the Rapporteur/CoRapporteur, EDQM and PM/PTL for consideration in finalising the CxMP assessment report. A copy of the report is distributed to the PM/PTL	OMCL and GMP managers
6.0	Initiation of a GMP Inspection and/or Sampling and Testing	
6.1 (day + 125)	The IS prepares the contract (see form 4.5) in the language of the Supervisory Authority, which should be signed by the EMEA Executive Director or another authorised person (Head of Sector, Head of Unit) and attaches a timetable to the contracts.	GMP managers
6.2 (day + 125)	The IS sends to the Supervisory Authority(ies), inspectors involved and the applicant all the relevant information in order to initiate the inspection ⁷ , giving details of the inspection team and asking for the inspection fees to be paid. This information is contained in two standard letters (see forms 4.6 and 4.7).	GMP managers
6.3 (day + 125)	The IS informs the AA in order to initiate the preparation of recovery order, commitment and invoice for product applications where the CxMP has requested an inspection. The IS provides to the AA a copy of adopted inspection request, contract and letter to applicant.	GMP managers
6.4 (day + 150)	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. The IS then updates the timetable with the dates and inspectors as provided.	Inspecting authorities

⁶ See question 12 of “Questions and answers on GMP inspection coordination”.

⁷ In the case that a pre-approval inspection is combined with a routine re-inspection or an inspection triggered by a variation, the procedure will be determined by the by the procedure requiring the shortest timetable.

Step²	Action	Responsibility
7.0	Inspection reports	
7.1 (day + 150)	The leading inspector sends the list of deficiencies to the IS and the preliminary outcome of the inspection report using the standard fax attached in the letter to inspecting authorities (see page 5 of Form 4.6).	Leading inspector
7.2 (day + 150)	At the same time, the draft inspection report is sent by the inspectors to the management of the site or company with a request on remedial actions to be provided within 15 (calendar) days or receipt.	Leading inspector
7.3 (day + 165)	The company has 15 days to give comments on the report. This period of time may be extended if the deadline for reporting allows it. If a response is not received within the agreed time the inspectors should record the absence of a reply. The timing of any discussions with the company or the provision of additional information that could be extended beyond the deadline for reporting will be agreed and communicated to the Rapporteur / Co-Rapporteur and the EMEA taking account of the overall timetable adopted for completion of the assessment of the application.	Company inspected
7.4 (day + 180)	On receipt of comments on the draft report from the manufacturer, the report should be finalised by the author(s) taking account, as necessary of the comments received.	Inspecting authorities
7.5 (day + 180)	When the report is complete the author(s) should prepare a summary of the inspection report for circulation to the CxMP or other competent authority that request it. This summary will follow the format established, which is included in the letter to inspecting authorities (see form 4.6), and should contain an overall conclusion as to whether or not the manufacturer is acceptable for the proposed activities. The report has to be sent to the IS by the day 180 at the latest.	Inspecting authorities
7.6 (day + 180)	The outcome of GMP or Product- or process- related inspection is either positive (with follow-up) or negative.	Supervisory Authority
7.7 (day + 185)	The IS will check inspection reports received for adherence to the established guideline and overall quality. Reports that are found to be deficient, incomplete or below the required scientific standard will be returned to the authorities who were responsible for their preparation 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 taking into account the overall timetable adopted for completion of the assessment of the application. The IS will use for this purpose a checklist on validation Inspection Reports (see form 4.8).	GMP managers
7.8 (day + 185)	If the quality of the report is positive, then, the Summary of the inspection report is circulated to the Rapporteur/CoRapporteur and PM/PTL with a letter containing an overall conclusion as to whether or not the manufacturer is acceptable (see form 4.11).	GMP managers
7.9 (day + 185)	On completion and after endorsement by the CxMP, property and liability in the inspection report is transferred to the EMEA. The EMEA may make available the report upon request of another EEA Competent Authority.	GMP managers

Step²	Action	Responsibility
7.10 (day + 185)	The IS informs the applicant on the overall conclusion of the inspection report and any other comments raised by the CxMP, using the letter sent to the Rapporteur/CoRapporteur on step 7.8. The letter does not ⁸ include the summary report.	GMP managers
7.11 (day + 185)	The IS prepares the payment order using the standardised form (see form 4.9). The form should be signed by the Head of Inspections Sector. IS attaches a copy of the summary report and validation checklist described in point 7.7 along with the payment order. 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 authorities that were responsible for their preparation, with a written explanation of the reasons for non-acceptance and proposed deadline for revision or other remedial action. This deadline for re-submission of the report will be set by the EMEA taking account of the overall timetable adopted for completion of the assessment of the application. In exceptional circumstances and on the recommendation of the CxMP, the EMEA may breach the contract and cancel any corresponding payment	GMP managers
7.12 (day + 210)	If the applicant's comments on major deficiencies stating that the site is not in GMP compliance or operations are not carried out in accordance with the application, then, it is referred to the scientific committee. In this case the CxMP may reach a negative opinion on the basis of the inspection report.	CxMP
7.13 (day + 220)	IS updates the GMP database and relevant status lists (e.g. third country inspections, CxMP ongoing applications).	GMP managers

8. Records

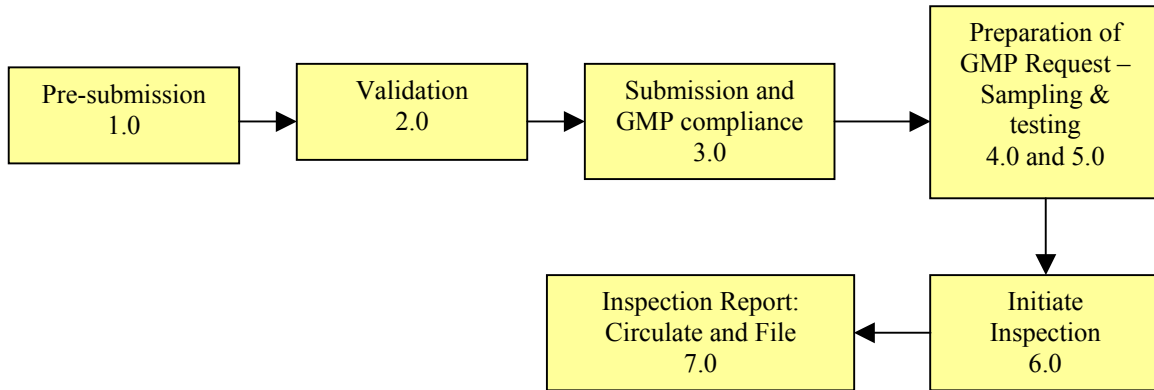
When completed, approved and numbered, the retention of the hardcopy of this SOP and storage and archiving according to EMEA-SOP-T-1000 and EMEA-SOP-T-1050 will be responsibility of the Veterinary and Inspections Unit.

All completed forms and other records relating to the operation of this procedure will be collected by the Scientific Administrators (GMP managers) who are responsible for maintaining the files containing the original documents for GMP inspections for the products concerned.

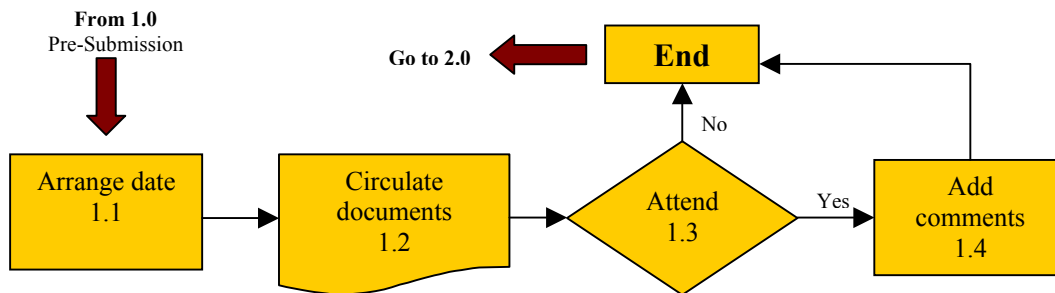
9. Process Map(s)/ Flow Chart(s)

⁸ See questions 14 and 15 of "Questions and answers on GMP inspection coordination".

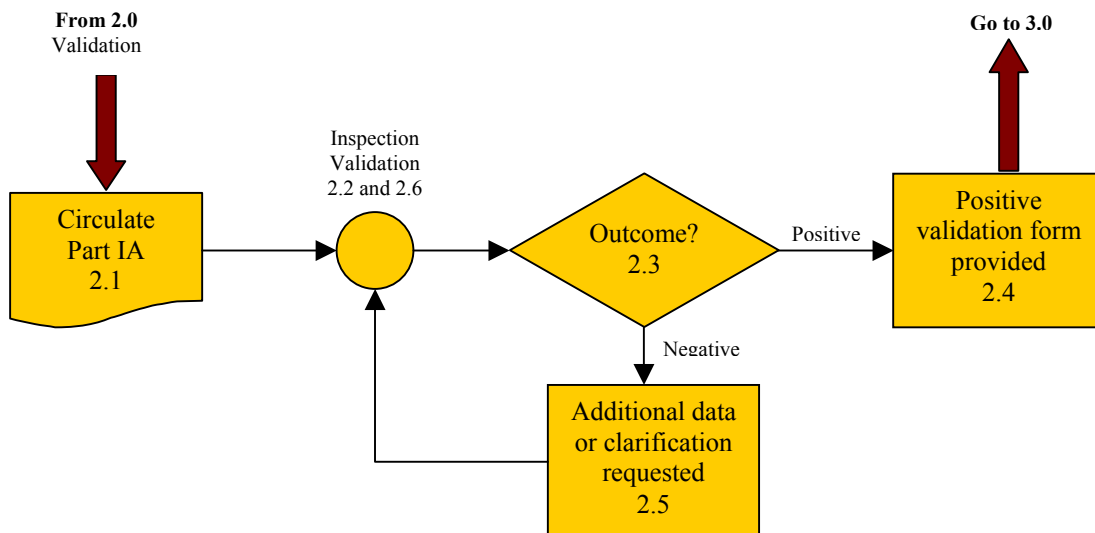
Level 1



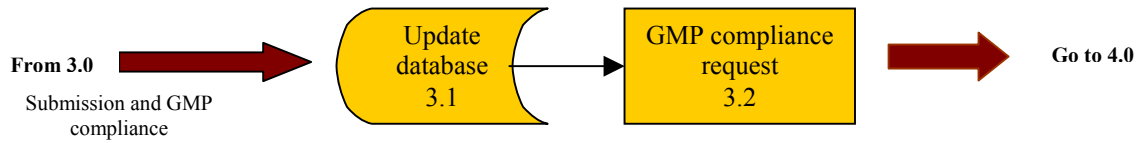
Level 2: Pre-Submission



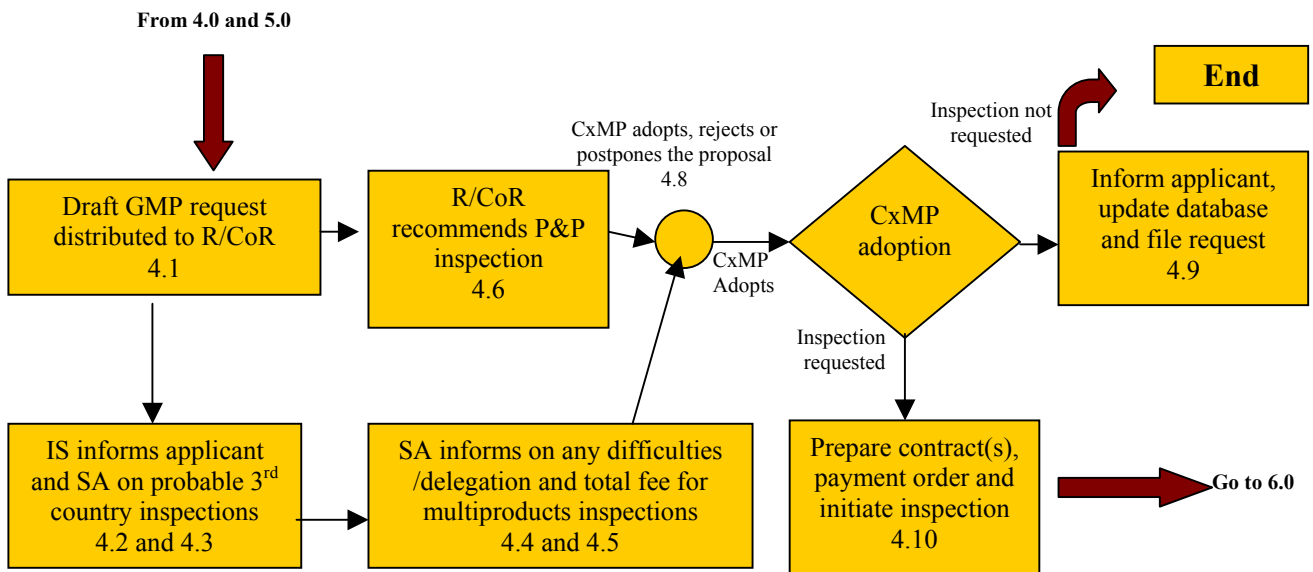
Level 2: Validation



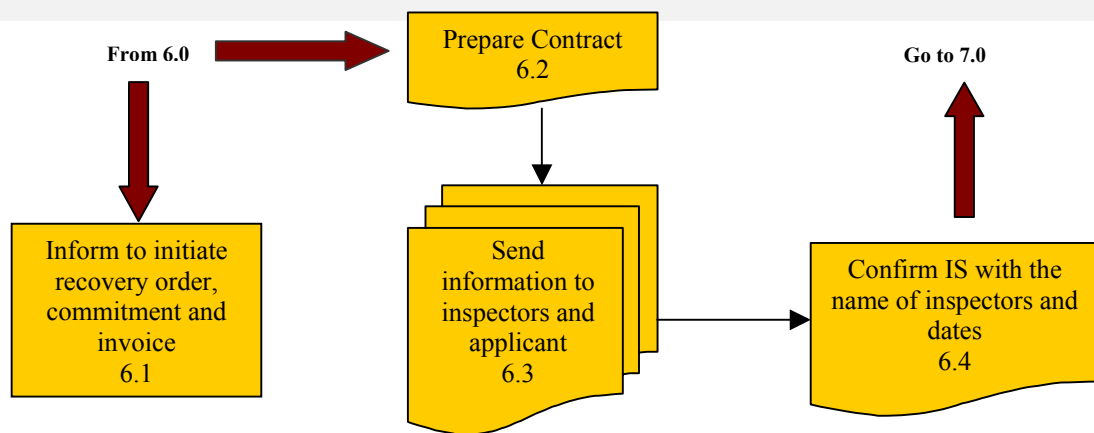
Level 2: Submission and GMP compliance



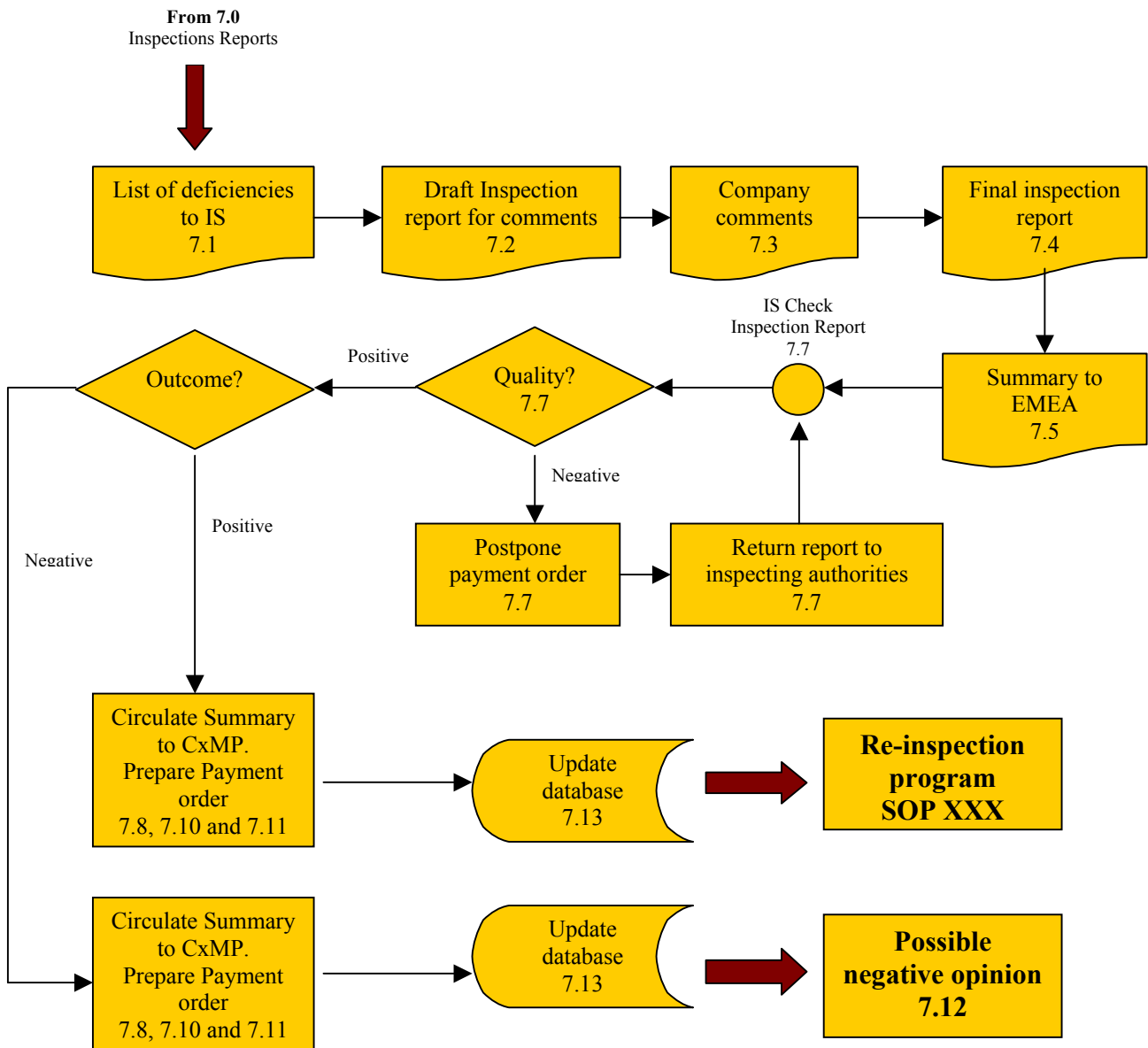
Level 2: GMP Inspection Request



Level 2: Initiation of a GMP Inspection and/or Sampling and Testing



Level 2: Inspections Reports



ANNEX 1 - DEADLINES

The deadlines described under chapter 7.0 correspond to those for pre-authorisation inspections. A summary of the equivalent deadlines for post-authorisation inspections is described in the following table:

Step	Action	Pre-authorisation	Post-authorisation	Re-inspections
		Applications	Variations Type II	
1.0	Pre-submission phase			
1.3	Start pre-submission meeting	-120	-60	-
2.0	Validation phase			
2.1	Validation start	-10	-10	-
2.6	Validation completed	0	0	-
3.0 to 7.0	Evaluation phase			
3.1	Start of evaluation & inspection	1	1	$150^9 + 550^{10} = 700^{11}$
4.1	Prepare draft request	60	5	760
4.4	Information on multiproduct inspections	85	-	780
6.1	Submit recommendations	120	60	790
6.4	Confirmation that the inspection has taken place	150	90	$150^{12} + 730^{13} = 880$
7.6	Receive final inspection report	180	110	940
7.8	Circulation to Rap/CoRap and PM/PTL	185	111	945
7.12	Final decision	210	120	970

⁹ Latest date to perform the inspection in the original application.

¹⁰ 1 year and half after the previous inspection.

¹¹ The following re-inspection is initiated the day 1250 ($700 + 550$) and so on.

¹² Latest date to perform the inspection in the original application.

¹³ Two years after the previous inspection.

ANNEX 2 - FlowChart for pre-authorisation inspections

See graphic attached

ANNEX 3 - Questions and answers on GMP inspection coordination

See document attached

ANNEX 4 – Delegation of responsibilities for GMP inspections for products covered under the Centralised Procedure

See document attached