EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Standard operating procedure

Title: Co-ordination of GMP/GDP inspections		
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1. Purpose

This SOP describes how GMP and GDP inspections are coordinated by the P-CI-MQC section for human and veterinary medicinal products under the centralised procedure or in the context of a referral procedure.

This SOP covers:

- All GMP inspections requested by the CHMP/CVMP during the evaluation phase of initial applications for marketing authorisation, line extensions, type II variations and article 58 applications.
- All GMP inspections requested in accordance with the annual GMP re-inspection programme.
- All for-cause GMP inspections requested in connection with:
  - quality defects affecting centrally authorised medicinal products;
  - annual sampling and testing programmes;
  - referral procedures.
- All for-cause active substance GDP inspections.

GMP inspections in the context of Plasma Master File and Vaccines Antigen Master File certification are covered in separate procedures: SOP/INSP/2009 and SOP/INSP/2012, respectively.

2. Scope

This SOP applies to P-CI-MQC section only.

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3. Responsibilities

It is the responsibility of the Section Head to ensure that this procedure is adhered to within his/her own section. The responsibility for the execution of a particular part of this procedure is identified in the right-hand column of section 9.

4. Changes since last revision

New SOP superseding the GMP section of SOP/INSP/2019 Coordination of pre-approval GxP Inspections and widening the purpose of SOP to cover all types of GMP inspections. Addition of GDP inspections. Introduction of Corporate GxP.

5. Documents needed for this SOP

The templates needed for this SOP are located on the X drive under: X:\Templates\Others\Compliance and Inspection\GMP\Inspection Coordination or in Corporate GxP:

- Template 1: Email to (co)-rapporteurs on recommended GMP inspections (only on X drive).
- Template 2: GMP inspection request.
- Template 3: Inspection announcement letter to applicant/MAH.
- Template 4: Inspection announcement letter to inspectorate.
- Template 5: Email on negative validation of inspectors (only in Corporate GxP).
- Template 6: Inspection report quality review and instruction for payment order generation (only on X drive).
- Template 7: Inspection outcome letter to applicant/MAH.
- Template 8: Inspection outcome letter to (co)-rapporteurs.

The templates for the contracts with the EU NCAs are located on the X drive under: X:\Templates\Others\Compliance and Inspection\GMP\GMP inspection CONTRACT – Human/Vet:

- Template 9: GMP inspection contract.

6. Related documents

- EU Legislation – EudraLex. Volume 2A - Procedures for marketing authorisation. Chapter 4 - Centralised Procedure: European Commission > DG Health & Consumers > Public health > News and updates on pharmaceuticals > Eudralex > Vol 2: Notice to Applicants Human.
- EU Legislation – EudraLex. Volume 6A - Procedures for marketing authorisation. Chapter 4 - Centralised Procedure: European Commission > DG Health & Consumers > Public health > News and updates on pharmaceuticals > Eudralex > Veterinary use.
- Compilation of Community procedures on inspections and exchange of information: EMA Public website > Home > Regulatory > Human medicines/Veterinary medicines > Inspections > GMP/GDP compliance > Community procedures.
- Corporate GxP manual.

- SOP/EMA/0040 Evaluation of conflicts of interests of experts for involvement in EMA activities.
- SOP/INSP/2005 Processing of financial transactions for inspections.
- SOP/PDM/1004 Core master files of medicinal products for human and veterinary use following the centralised procedure.
- Core Master File – Compliance and Inspection. Doc. Ref.: EMA/641169/2010.
- WIN/INSP/2043 Calculation of fees for GMP and product related inspections.
- WIN/INSP/2046 Preparation of the annual GMP re-inspection programme.
- WIN/INSP/2047 Inspection of quality control facilities located in 3rd countries.

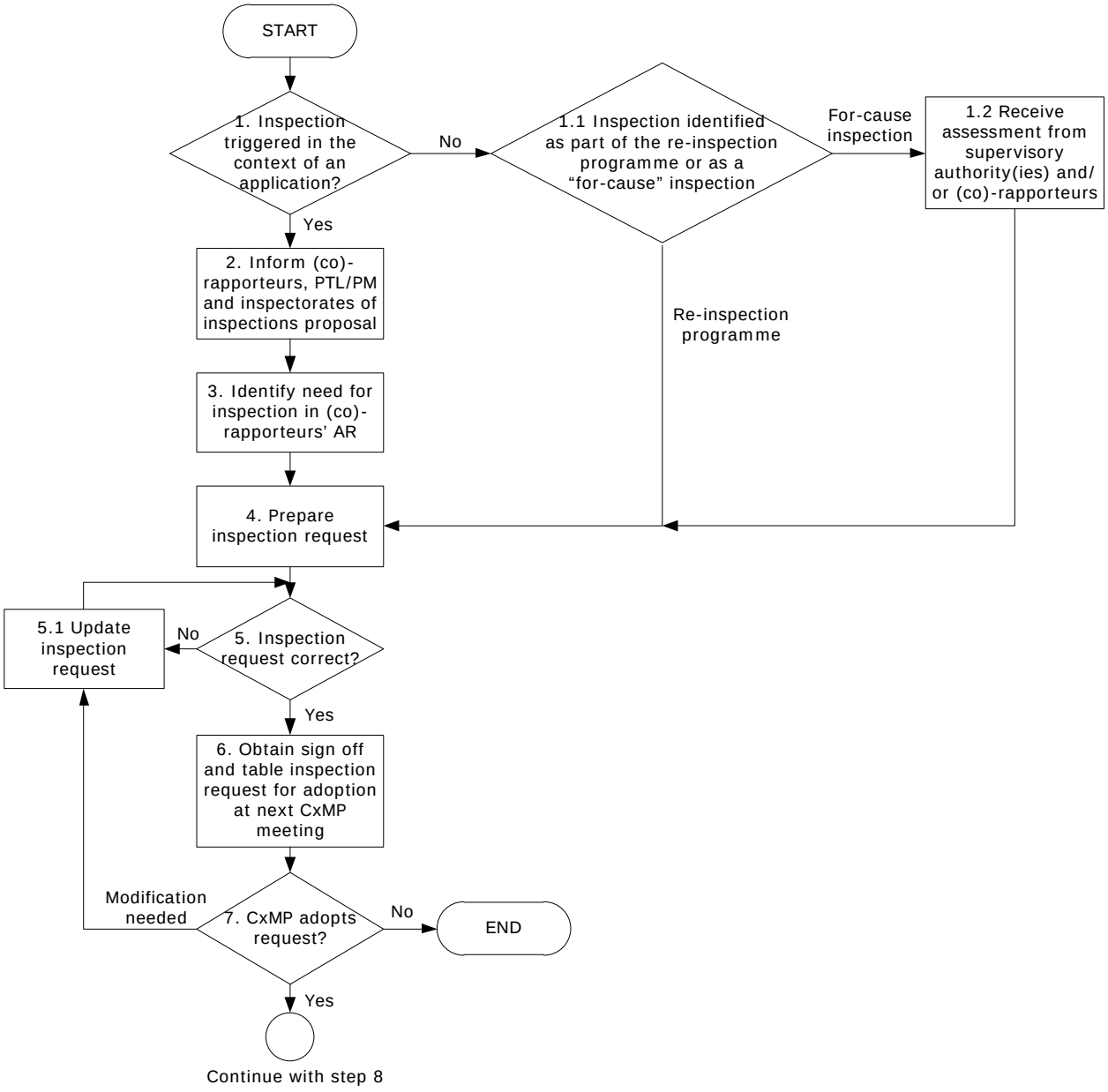
7. Definitions

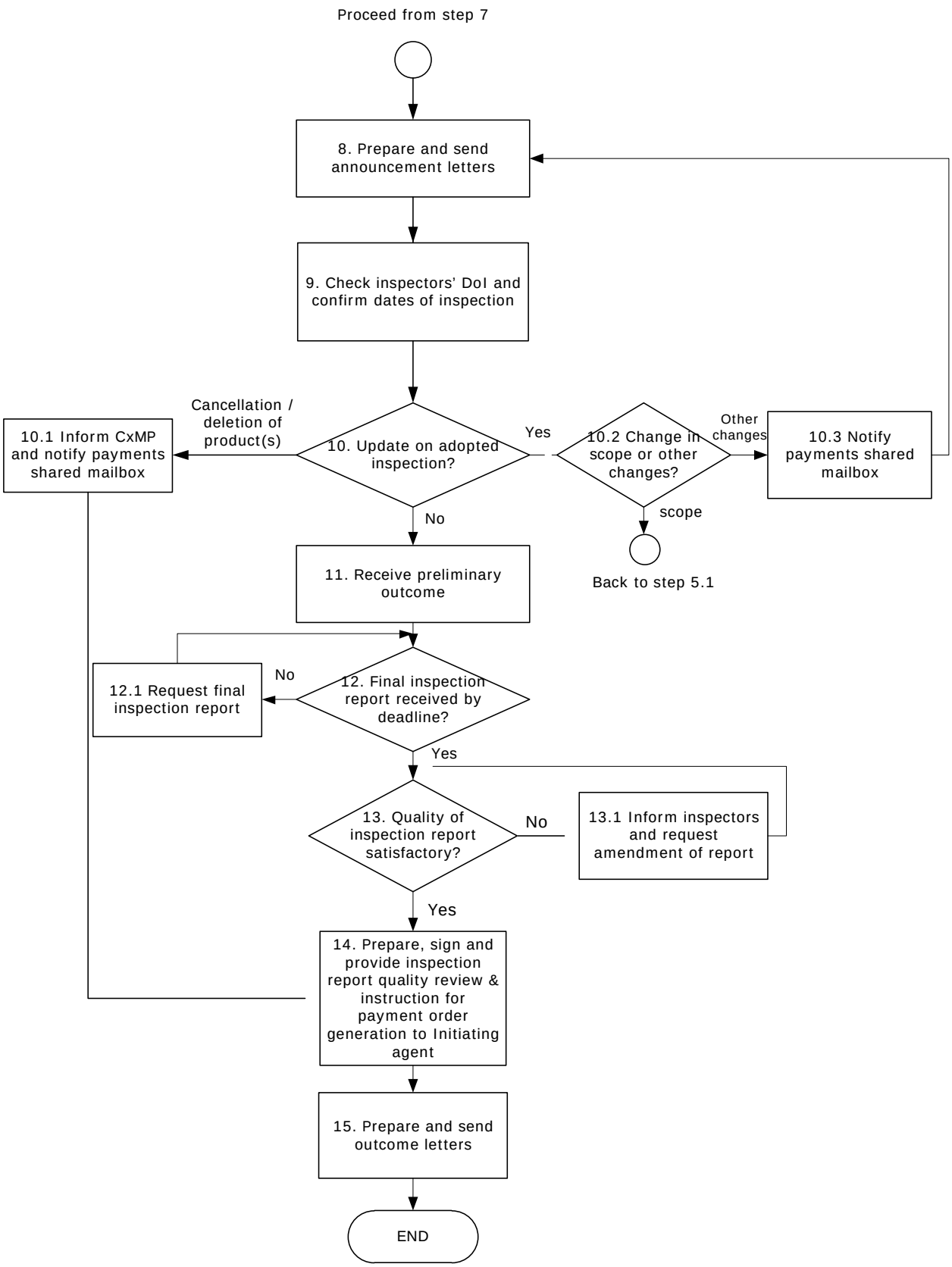
- **GMP inspection**: on-site assessment of the compliance with the EU GMP principles performed by officials of EU competent authorities or authorities found equivalent under a mutual recognition agreement.

Abbreviations

AR	Assessment report
AS	Active substance
CHMP	Committee for Medicinal Products for Human use
CMF	Core Master File
CVMP	Committee for Medicinal Products for Veterinary use
CxMP	Committee for Medicinal Products for Human/Veterinary use
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
P-CI-MQC	Manufacturing and Quality Compliance section in the Inspection and Compliance sector in the Patient Health Protection unit
PM	Project Manager
PSM	Product Shared Mailbox
PTL	Product Team Leader
PTM	Product Team Member
SIAMED	Sistema de Información Automatizada sobre Medicamentos, which is a model system for computer-assisted drug registration that enables the EMA to track its core processes and retrieve key registration data
ToD	Table of decisions

8. Process map(s) / flow chart(s)




Proceed from step 7
8. Prepare and send announcement letters
9. Check inspectors' DoI and confirm dates of inspection
10. Update on adopted inspection?
Cancellation / deletion of product(s)
10.1 Inform CxMP and notify payments shared mailbox
Yes
10.2 Change in scope or other changes?
Other changes
10.3 Notify payments shared mailbox
scope
Back to step 5.1
No
11. Receive preliminary outcome
12. Final inspection report received by deadline?
No
12.1 Request final inspection report
Yes
13. Quality of inspection report satisfactory?
No
13.1 Inform inspectors and request amendment of report
Yes
14. Prepare, sign and provide inspection report quality review & instruction for payment order generation to Initiating agent
15. Prepare and send outcome letters
END

9. Procedure

Step	Action	Responsibility
1.	Is an inspection triggered in the context of an initial marketing authorisation application, line extension, type II variation or article 58 application taking account of *EU Legislation – EudraLex. Procedures for marketing authorisation. Chapter 4 - Centralised Procedure*? If yes, go to step 2. If no, go to step 1.1.	Administrator
1.1	Is an inspection identified as part of the GMP re-inspection programme (see WIN/INSP/2046) or as a "for-cause" inspection? For re-inspections, go to step 4. For "for-cause" inspections, go to step 1.2.	Administrator
1.2.	Receive assessment report from supervisory authority(ies) and/or appointed (co)-rapporteurs and liaise with them (CC PTL/PM) in order to finalise inspection details. Continue with step 4.	Administrator
2.	Identify (co)-rapporteurs' AR due date in Siamed II. Before AR due date, send an e-mail to the appointed (co)-rapporteurs for the product in question (CC the PSM and the product's PTL/PM*)* informing them about the inspections identified in step 1. To write this e-mail, use template 1: *Email to (co)-rapporteurs on recommended GMP inspections*. Identify lead and supporting inspectorate by checking the country(ies) where the batch release site is(are) located. Send an e-mail to the contact person of the appointed inspectorate(s) providing specific details of the inspection to be conducted (i.e. name and address of the site, activities carried out and deadline for reporting).	Administrator
3.	Receive (co)-rapporteur's AR from PTL/PM and identify need for inspection.	Administrator
Preparation of inspection request		
4.	• For <u>human medicinal products</u>, inform CHMP's secretariat of the sites and related products to be inspected at the next CHMP meeting no later than Thursday noon before the CHMP meeting week so that the inspection requests can be included in the meeting's agenda. • For <u>veterinary medicinal products</u>, update agenda latest by 3rd mailing of next CVMP meeting. Prepare draft inspection request in Corporate GxP, if possible. If the inspection request cannot be prepared in Corporate GxP,	Assistant

Step	Action	Responsibility
	prepare it using template 2: *GMP inspection request*, save it in DREAM and print out a copy. While preparing the request, ask administrator to determine number of fees applicable, in accordance with WIN/INSP/2043.	
5.	Are the inspection request details correct? If yes, click on "generate request reference number" (for Corporate GxP requests) or give "go ahead" to assistant (for manual requests) and go to step 6. If no, go to step 5.1. *Note: This step represents the operational initiation in the inspection co-ordination process.*	Administrator
5.1	Update inspection request and continue with step 5.	Assistant
6.	Sign off (electronic for Corporate GxP requests or signature for manual requests). *Note: This step represents the operational verification in the inspection co-ordination process.*	Section Head
	For Corporate GxP requests, save PDF document in DREAM, print and file it in the appropriate binder. For manual requests, scan signed copy of the request, save it in DREAM, print and file it in the appropriate binder. Table inspection request for adoption at the next CxMP meeting.	Assistant
7.	Is the inspection request adopted by CxMP? If yes, inform P-CI-MQC, update GMP inspection co-ordination spreadsheet located in DREAM under *Cabinets/04. Inspections/4. GMP/Planning and reporting/GMP inspections coordination* and go to step 8. If no, the procedure ends. If a modification is needed, go to step 5.1.	Administrator
Preparation of announcement letters		
8.	Prepare inspection announcement letters to applicant/MAH and inspectorates using Corporate GxP (for Corporate GxP requests) or templates 3: *Announcement letter to applicant/MAH* and 4: *Announcement letter to inspectorate* (for manual requests). Print letters and obtain signature from appointed GMP co-ordinator. Scan, save in DREAM and send out signed announcement letters using Corporate GxP (for Corporate GxP requests) or Eudralink (for manual requests) within 10 working days after adoption of inspection by CxMP. Provide original letter to lead inspectorate to Initiating agent according to step 1 of SOP/INSP/2005. If necessary (e.g. no framework contract between EMA and NCA is	Assistant

Step	Action	Responsibility
	in place), prepare two copies of contract with NCA using template 9: *GMP inspection contract.* Save them in DREAM, print and provide them to the Head of Sector for signature. Send these contracts along with the paper copy of the letter to the relevant NCA by post. One of the two copies needs to be signed by the relevant NCA and sent back to the Agency. *Note: When saving signed announcement letters in DREAM, make sure they are marked as CMF. Also, mark adopted inspection request as CMF in accordance with SOP/PDM/1004.* After CxMP meeting, check CHMP's ToD (for human medicinal products) or CVMP's minutes (for veterinary medicinal products) for adopted inspections against paper copies of requests. In case there are any mistakes in the ToD or minutes, inform CHMP or CVMP secretariat by the specified deadline.	Administrator
9.	Check inspectors' declaration of interests in accordance with SOP/EMA/0040. In case the inspectors cannot participate in the inspection due to a conflict of interests, a notification will be sent to them (see template 5 for Corporate GxP requests). For manual requests, inform the relevant inspectorate(s)/inspector(s). Confirm dates of inspection with NCA as needed.	Administrator
10.	Are updates received after adoption of inspection? If no, go to step 11. If the inspection is cancelled (e.g. due to withdrawal of the application) or a product is deleted from the inspection request, go to step 10.1. If there are any other changes, go to step 10.2.	Administrator
10.1	Inform CxMP and notify payments shared mailbox (Inspection_Payment@ema.europa.eu). Continue with step 14 if necessary (i.e. if fees apply after cancellation/deletion, the relevant instruction for payment order generation needs to be prepared).	Administrator
10.2	Does the change relate to the scope of the inspection request (e.g. addition of products)? If yes, notify payments shared mailbox (Inspection_Payment@ema.europa.eu) and continue with step 5.1. If no (change relates to the Inspectorates involved (e.g. number, member state…) or to the date of inspection), go to step 10.3.	Administrator
10.3	If the update involves a change in the inspectorates: - notify payments shared mailbox (Inspection_Payment@ema.europa.eu); - inform previous inspectorate; - update Corporate GxP and - continue with step 8 (i.e. update and send out amended	Administrator

Step	Action	Responsibility
	inspection announcement letters to applicant/MAH and inspectorate). If the date of inspection changes before its proposed first day, no further action is required. However, if the date changes after the proposed first day of inspection, inform payments shared mailbox.	
Validation of inspection report		
11.	Receive preliminary outcome and prepare for appropriate actions if necessary.	Administrator
12.	Is final inspection report received by deadline? If yes, go to step 13. If no, go to step 12.1 *Note: It is especially important for pre-approval inspections to make sure that the report is received by the agreed deadline to avoid delays in the marketing authorisation procedure. In exceptional circumstances, late reports can lead to difficulties with financial procedures.*	Administrator
12.1	Contact inspectors to request final inspection report and continue with step 12.	Administrator
13.	Is the quality of the inspection report satisfactory (i.e. in accordance with template 6? The validation of the report should be performed within 15 working days from the day of receipt. If yes, go to step 14. If no, go to step 13.1.	Administrator
13.1	Inform inspectors, request amendment of the report and continue with step 13. *Note: In case the quality of the report does not satisfy the validation after having requested amendment to the concerned inspectors, P-CI-MQC may consider withholding the payment after consultation with the Section Head/Head of Sector.*	Administrator
14.	Prepare inspection report quality review and instruction for payment order generation by using template 6, print it out, sign and provide it to Initiating agent according to step 13 of SOP/INSP/2005. Update GMP inspection co-ordination spreadsheet located in DREAM under *Cabinets/04. Inspections/4. GMP/Planning and reporting/GMP inspections coordination.*	Administrator
Preparation of outcome letters		
15.	Prepare inspection outcome letters to applicant/MAH and (co)-rapporteurs using Corporate GxP or templates 7: *Inspection outcome letter to applicant/MAH* and 8: *Inspection outcome letter to (co)-rapporteurs*, as appropriate.	Assistant

Step	Action	Responsibility
	Print letters and obtain signature from appointed GMP co-ordinator. Scan, save in DREAM and send out signed outcome letters using Corporate GxP or Eudralink, as appropriate within 10 working days after validation of the inspection report. Also, save inspection report and inspection report quality review and instruction for payment order generation in DREAM. *Note: When saving signed outcome letters and the inspection report in DREAM, make sure they are marked as CMF, in accordance with SOP/PDM/1004.*	

10. Records

Electronic copies of all records generated using the templates referred to in this SOP are saved in DREAM under *Cabinet 4 > Manufacturers > Site folder > YYYY MM Inspection* except the inspection reports received from the GMP inspectors, which are saved under *Cabinet 4 > Manufacturers > Site folder > Compliance History*.