Standard operating procedure

Title: Co-ordination of pre-approval inspections in the context of plasma master file certification		
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1. Purpose

This SOP describes the process for co-ordinating pre-approval inspections of the blood establishments in which collection, testing, processing, look back, storage and distribution is carried out under the Plasma Master File (PMF) certification system. These inspections are coordinated by the P-CI-MQC section.

2. Scope

This SOP applies to P-CI-MQC and H-QM-BIO sections.

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

Major update of the process. Update to reflect the new organisational names in the Agency, the new corporate identity and editorial updates of the procedure and flow-chart.

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:

- Template 1: Factors to be considered by EMA in determining an inspection proposal to the co-ordinator.

- Template 2: GMP inspection request.

- Template 3: Inspection announcement letter to applicant/PMF holder.

- Template 4: Inspection announcement letter to inspectorate.

- Template 6: Inspection report quality review and instruction for payment order generation.

- Template 7: Inspection outcome letter to applicant/PMF holder.

- Template 8: Inspection outcome letter to PMF co-ordinators.

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:

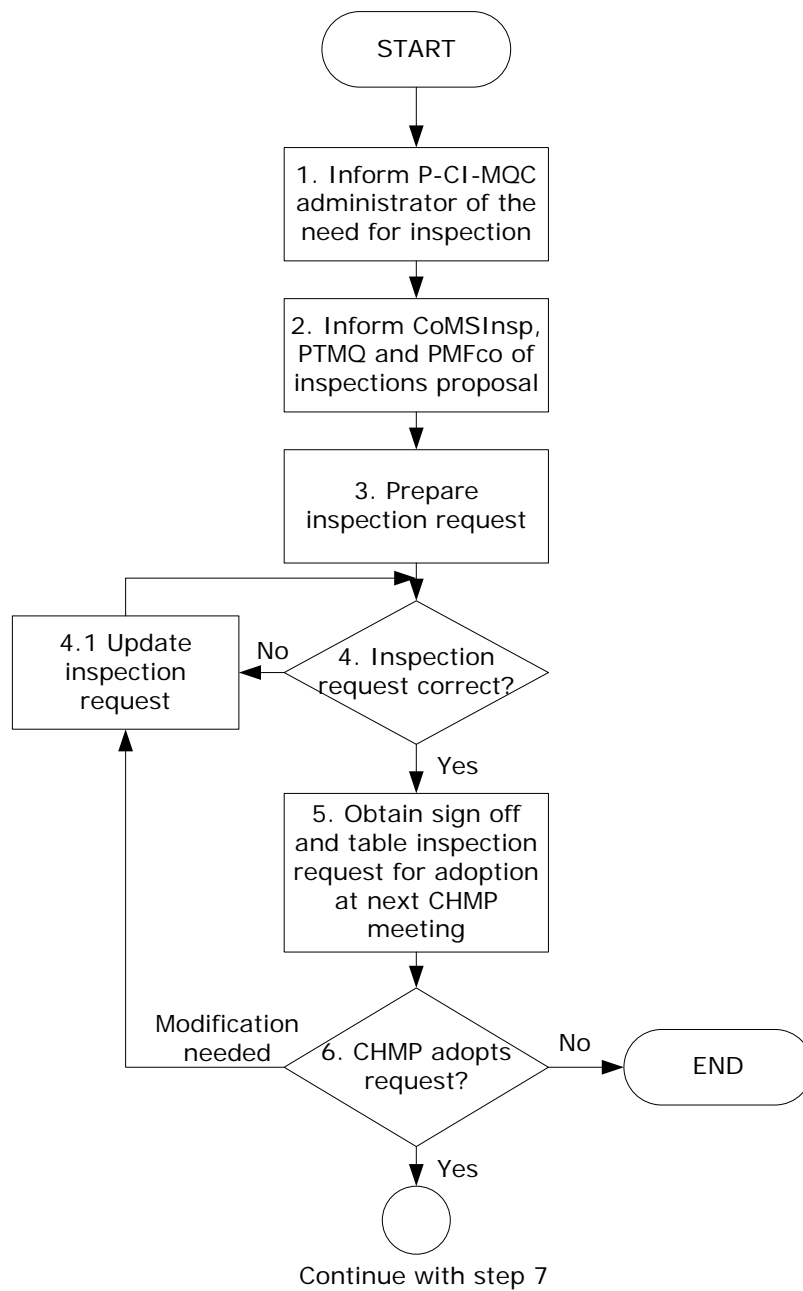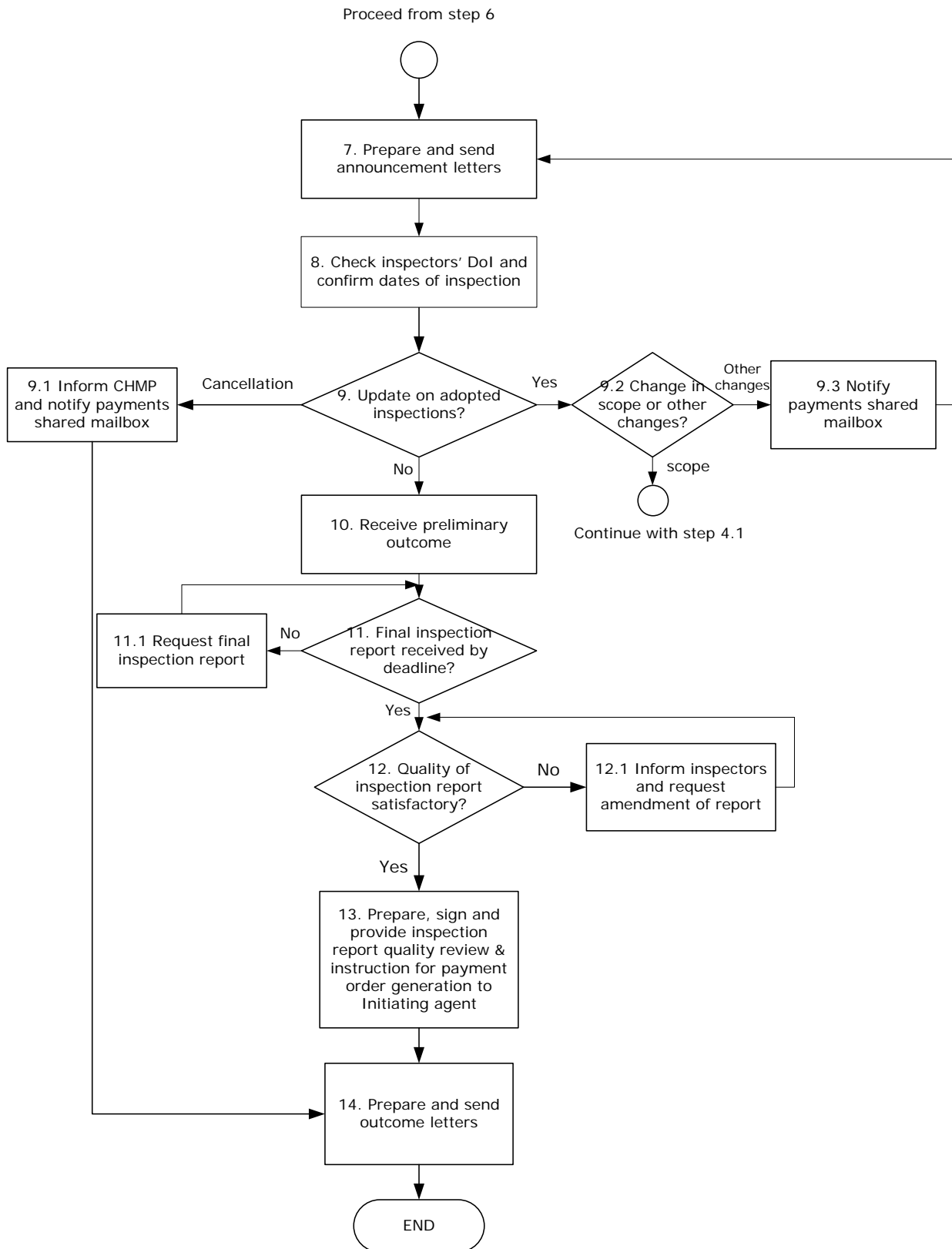- Template 9: GMP inspection contract.

6. Related documents

- EU Legislation – EudraLex. Volume 1 - Pharmaceutical Legislation Medicinal Products for Human Use. Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC: European Commission > DG Health & Consumers > Public health > News and updates on pharmaceuticals > Eudralex > Vol 1: Legislation Human.

- EU Legislation – EudraLex. Volume 4 - Good manufacturing practice (GMP) Guidelines. Annex 14 - Manufacture of Products derived from Human Blood or Human Plasma: European Commission > DG Health & Consumers > Public health > News and updates on pharmaceuticals > Eudralex Vol 4: GMP Human & Veterinary.

- Guideline on Requirements for Plasma Master File (PMF) Certification: EMA public website > Home > Regulatory > Human medicines > Scientific guidelines > Biologicals > Drug substance - Plasma master file.

- Ph.Eur. monograph on Human Plasma for Fractionation.

- 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.

7. Definitions

- Blood establishment   any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks

- CHMP   Committee for Medicinal Products for Human Use

  CoMSInsp   Co-ordinator MS's Inspectorate (relevant Inspectorate of the Member State acting as co-ordinator during the procedure)

- H-QM-BIO   Biologicals section in the Quality of Medicines sector in the Human Medicines Development and Evaluation unit

- NCA   National Competent Authority

- P-CI   Inspection and Compliance sector in the Patient Health Protection unit

- P-CI-MQC   Manufacturing and Quality Compliance section in the Inspection and Compliance sector in the Patient Health Protection unit

- PMF   Plasma Master File

- PMFco   Plasma Master File co-ordinator

- PTMQ   Quality Product Team Member

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

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                          │    START    │
                          ╰─────────────╯
                                 │
                                 ▼
                    ┌─────────────────────────┐
                    │ 1. Inform P-CI-MQC       │
                    │ administrator of the     │
                    │ need for inspection      │
                    └─────────────────────────┘
                                 │
                                 ▼
                    ┌─────────────────────────┐
                    │ 2. Inform CoMSInsp,      │
                    │ PTMQ and PMFco of        │
                    │ inspections proposal     │
                    └─────────────────────────┘
                                 │
                                 ▼
                    ┌─────────────────────────┐
                    │ 3. Prepare               │
                    │ inspection request       │
                    └─────────────────────────┘
                                 │
    ┌──────────────┐     No      ▼
    │ 4.1 Update   │◄────────◇ 4. Inspection ◇
    │ inspection   │         ◇ request correct? ◇
    │ request      │             │
    └──────────────┘             │ Yes
           ▲                      ▼
           │          ┌─────────────────────────┐
           │          │ 5. Obtain sign off       │
           │          │ and table inspection     │
           │          │ request for adoption     │
           │          │ at next CHMP             │
           │          │ meeting                  │
           │          └─────────────────────────┘
           │                      │
  Modification                    ▼                No
     needed      ◇ 6. CHMP adopts ◇ ──────────► ╭─────────╮
           └─────◇   request?    ◇              │   END   │
                                 │              ╰─────────╯
                                 │ Yes
                                 ▼
                               ╭───╮
                               │   │
                               ╰───╯
                       Continue with step 7
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Proceed from step 6

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7. Prepare and send
announcement letters
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8. Check inspectors' DoI and
confirm dates of inspection
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9.1 Inform CHMP and notify payments shared mailbox ← Cancellation — ◇ 9. Update on adopted inspections? ◇ — Yes → ◇ 9.2 Change in scope or other changes? ◇ — Other changes → 9.3 Notify payments shared mailbox

No ↓ (from 9. Update on adopted inspections?)

scope ↓

○

Continue with step 4.1

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10. Receive preliminary
outcome
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11.1 Request final inspection report ← No — ◇ 11. Final inspection report received by deadline? ◇

Yes ↓

◇ 12. Quality of inspection report satisfactory? ◇ — No → 12.1 Inform inspectors and request amendment of report

Yes ↓

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13. Prepare, sign and
provide inspection
report quality review &
instruction for payment
order generation to
Initiating agent
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14. Prepare and send
outcome letters
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(END)

9. Procedure

Step	Action	Responsibility
1. (before day 30)	Inform P-CI-MQC administrator that the need for inspection has been identified by the co-ordinators using the template 1 during the assessment of the PMF.	PTMQ
2. (day – 35)	Contact the CoMSInsp to alert them that an inspection request is likely to be adopted by the CHMP at the day 30 (at the latest) of the procedure. Copy this information to the PMF co-ordinators and PTMQ. In parallel, contact the applicant to discuss on the potential inspections recommended and fees related.	Administrator
Preparation of the inspection request		
3.	Inform CHMP's secretariat of the blood establishments and related PMF applications to be requested for inspection 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. Prepare draft inspection request 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.	Assistant
4.	Are the inspection request details correct? If yes, give "go ahead" to assistant and go to step 5. If no, go to step 4.1. *Note: This step represents the <u>operational initiation</u> in the inspection co-ordination process.*	Administrator
4.1	Update inspection request and continue with step 4.	Assistant
5.	Sign inspection request. *Note: This step represents the <u>operational verification</u> in the inspection co-ordination process.*	Section Head
	Scan signed copy of the request and save it in DREAM.	Assistant
	Table inspection request for adoption at the next CHMP meeting.	
6.	Is the inspection request adopted by CHMP? If yes, 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 7. If no, the procedure ends. If a modification is needed, go to step 4.1.	Administrator
Preparation of announcement letters		
7.	Prepare inspection announcement letters to applicant/PMF holder and inspectorates using templates 3: *Inspection announcement*	Assistant

Step	Action	Responsibility
	letter to applicant /PMF holder and 4: *Inspection announcement letter to inspectorate.* Print letters and obtain signature from appointed administrator. Scan, save in DREAM and send out signed announcement letters using Eudralink within 10 working days after adoption of inspection by CHMP. 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 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 P-CI 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 CHMP meeting, check CHMP's ToD for adopted inspections against scanned copies of requests. In case there are any mistakes in the ToD, inform CHMP secretariat by the specified deadline.	Administrator
8.	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, inform the relevant inspectorate(s)/inspector(s). Confirm dates of inspection with NCA as needed.	Administrator
9.	Are updates received after adoption of inspection? If no, go to step 10. If the inspection is cancelled (e.g. due to withdrawal of the PMF application), go to step 9.1. If there are any other changes, go to step 9.2.	Administrator
9.1	Inform CHMP and notify payments shared mailbox (Inspection_Payment@ema.europa.eu). Continue with step 13 if necessary (i.e. if fees apply after cancellation, the relevant instruction for payment order generation needs to be prepared).	Administrator
9.2	Does the change relate to the scope of the inspection request (e.g. addition or deletion of blood establishments)? If yes, notify payments shared mailbox (Inspection_Payment@ema.europa.eu) and continue with step 4.1. If no (change relates to the Inspectorates involved (e.g. number,	Administrator

Step	Action	Responsibility
	member state…) or to the date of inspection, go to step 9.3.	
9.3	If the update involves a change in the inspectorates: - notify payments shared mailbox (Inspection_Payment@ema.europa.eu); - inform previous inspectorate and - continue with step 7 (i.e.: update and send out amended inspection announcement letters to applicant/PMF holder 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 (Inspection_Payment@ema.europa.eu).	Administrator
Validation of inspection report		
10.	Receive preliminary outcome and prepare for appropriate actions if necessary.	Administrator
11.	Is final inspection report received by deadline? If yes, go to step 12. If no, go to step 11.1. *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 exceptional circumstances, late reports can lead to difficulties with financial procedures.*	Administrator
11.1	Contact inspectors to request final inspection report and continue with step 11.	Administrator
12.	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 13. If no, go to step 12.1.	Administrator
12.1	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 P-CI-MQC Section Head/P-CI Head of Sector.*	Administrator
13.	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	Administrator

Step	Action	Responsibility
	DREAM under *Cabinets/04. Inspections/4. GMP/Planning and reporting/GMP inspections coordination.*	
Preparation of outcome letters		
14.	Prepare inspection outcome letters to applicant/PMF holder and PMFCo using templates 7: *Inspection outcome letter to applicant/PMF holder* and 8: *Inspection outcome letter to PMF co-ordinators*, as appropriate. Print letters and obtain signature from appointed administrator. Scan, save in DREAM and send out signed outcome letters using Eudralink 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.*	Assistant

10. Records

Electronic copies of all records generated using the templates referred to in this SOP are saved in DREAM under *Cabinets/01. Evaluation of Medicine/PMF - VAMF/PMF.*