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Information note on GMP inspections carried out by Anses-Anmv outside France

1. SUBJECT MATTER

The purpose of this document, for the benefit of stakeholders, is to describe the procedures for carrying out Good Manufacturing Practices (GMP) inspections conducted by Anses-ANMV outside the French territory as part of its annual inspection programme or at the request of the EMA. It also defines the process whereby the sites directly or indirectly affected by these inspections, hereinafter referred to as beneficiaries, contribute financially to the cost of the inspection.

2. DEFINITION

TERM	DEFINITION
MA	MARKETING AUTHORISATION
ANSES-ANMV	NATIONAL AGENCY FOR VETERINARY MEDICINAL PRODUCTS
MRA	MUTUAL RECOGNITION AGREEMENT
BENEFICIARY	HOLDER OF THE MA, IMPORTING SITE, OTHER ORGANISATION RESIDING IN THE EU OR AT LEAST, THIS SITE INSPECTED
GMP	EUROPEAN GOOD MANUFACTURING PRACTICES
EMA	EUROPEAN MEDICINE AGENCY
EU	EUROPEAN UNION
UINSP	INSPECTION UNIT

3. FIELD OF APPLICATION

This document applies to all GMP inspections carried out by the Anses-ANMV inspectors outside France.

4. APPLICATION MODALITIES

This document shall apply from 1st February 2021.

5. CONTACTS

INSPECTION UNIT

Head of Inspection Unit: Grégory Verdier, gregory.verdier@anses.fr

Inspection unit: Insp@anses.fr

SERVICE IN CHARGE OF THE MOVEMENT

General Affairs Service: Saf.fougeres@anses.fr

6. GMP INSPECTION PROCESS

6.1. INITIATION OF INSPECTION

In EU, the competent national authorities, including Anses-ANMV, are responsible for inspecting manufacturing sites located on their own territory. For its part, the EMA has a coordinating role for GMP inspections of medicinal products manufacturing sites whose marketing authorisation in the EU is submitted via the centralised procedure.

Manufacturing sites outside the EU are generally inspected by the competent national authority of the Member State in which the EU importer is located, unless a Mutual Recognition Agreement (MRA) is in place between the EU and the country concerned. If an MRA applies, the authorities shall rely on their respective inspections.

If the products are imported directly into more than one Member State from a manufacturing site outside the EU, there may be several competent national authorities responsible for inspecting them. In this case, the EMA shall facilitate cooperation between the authorities concerned in monitoring the site.

The competent authorities of the EU shall provide for routine inspections using a risk-based approach or in the event of suspicion of non-compliance. Each year, the EMA and Anses-ANMV develop their own routine sites inspection program to be certified in accordance with GMP. At the same time, some companies may contact Anses-ANMV to apply for GMP certification for new manufacturing sites in third countries or for an extension of its GMP certificate to new processes, new activities, new dosage forms or new products.

6.2. PRE-INSPECTION PHASE

In the case of medicinal products whose marketing authorisation in the EU is submitted via the centralised procedure, when the Committee for Medicinal Products for Veterinary Use (CVMP) requests Anses-ANMV for an inspection of the manufacturing facilities of that medicinal product, an inspection announcement letter shall be sent by the EMA to the holder of that medicinal product. In parallel, the latter is responsible for informing the manufacturing site concerned.

During the pre-inspection phase, the Anses-ANMV inspectors who have been assigned to an inspection of a manufacturing site outside the EU shall contact the beneficiary's representative located in Europe (i.e. MAH, EU importing site or other organisation residing in the EU) and/or the representative of the inspected site for the organisation of the inspection, where known.

Once they have agreed on the dates, duration and scope of inspection, an official inspection notice shall be sent by Anses-ANMV to the site concerned by the inspection. This notice shall specify the person responsible for the mission and, if applicable, the associated inspector(s), the inspection dates and the scope of the inspection.

At the same time, the inspection team prepares the logistic aspects of the inspection (see 7) and asks the inspected site representative to provide the necessary documentation for the preparation of the inspection. The list of items to be transmitted includes, but may not be limited to:

- the updated Site Master File;
- a list of the site procedures for the activities involved in the inspection;
- the plans of the areas to be inspected;
- the list of veterinary medicinal products marketed in the EU covered by the inspection indicating the type of authorisation procedure in the EU (i.e. centralised, decentralised, mutual recognition, national);
- A flow chart explaining the physical route taken by veterinary medicinal products marketed in the EU (samples and finished products) covered by the inspection from the manufacturing site to the importing site in the EU, indicating the site(s) in charge of quality control and the type(s) of transport used;
- An organisation chart showing all the sites involved in the manufacturing, control and import processes of veterinary medicinal products marketed in the EU covered by the inspection with details of the import stages such as:
    - steps for samples and batch, if different,
    - type of transport to the EU,
    - transport conditions to the EU,
    - site(s) in charge of quality controls, retention samples, storage and distribution, and release for the EU market
- where applicable, Part II of the MA file of the medicinal product(s) concerned by the inspection;

6.3. ON-SITE INSPECTION PHASE

The on-site inspection generally consists of 3 phases:

- Opening meeting:
    - On this occasion, inspectors meet with the management, the qualified person of the institution or his representative, and generally the staff in key positions.

- The purpose of this meeting is to:
  - present inspectors and persons inspected,
  - recall the purpose of the inspection and the standard(s),
  - provide an overview of the forecast plan and inspection methodology,
  - present the organisation chart of the establishment,
  - identify key documents to be presented during the inspection,
  - describe the major changes that have occurred since the previous inspection, if any, as well as the expected short-term changes, to obtain from the qualified person the report of any significant quality problems encountered by the establishment,
  - make an appointment at the place and time of the closing meeting.

- During the Inspection:
  - the inspection team will interview the personnel involved in the manufacturing operations and review documents related to the activities covered by the inspection,
  - The inspection team will perform on-site visits that could include the entire establishment or related to any process involved in the production, supply and distribution of veterinary medicinal products marketed in the EU covered by the inspection, including:
    - manufacturing areas,
    - quality control laboratories (QC),
    - the management of stocks,
    - sampling, storage areas and return areas,
    - monitoring of the manufacturing environment (t° C, pressure…),
    - validation and qualification operations,
    - purchasing and sales functions,
    - contractual arrangements (transport, QC…),
    - self-inspection, internal audit and external audit (planning, reports…).
  - The inspection team may request additional documents and samples during the inspection. It may also change the focus of the inspection if they suspect serious non-compliance.

- Closing meeting
  - It includes:
    - A time in the absence of company representatives, allowing inspectors to share views, to finalise the various observations and to assess the l level of compliance of the establishment with GMPs.
    - A summary, including a description of the deficiencies to the European GMPs, which will be included in the inspection report, which is presented to the company's representatives (qualified person, management, people in key positions, technical supervision).

6.4. POST-INSPECTION PHASE

After the inspection closing meeting, usually within 3-4 weeks, a preliminary inspection report in English is sent to the inspected site containing the deficiencies found.

Deficiencies from inspections are classified in the inspection report in 3-levels in accordance with the European document EMA compilation of community procedures on inspections and exchange of information:

- Critical deviation:

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal or of a falsified product. Any intentional fraud and a combination of several "major" deficiencies that may together represent a critical deficiency.

- Major deviation:

This is a non-critical defect that:

- has produced or may produce a product, which does not comply with its marketing authorisation;
- indicates a major deviation from EU Good Manufacturing Practice;
- (within EU) which indicates a major deviation from the terms of the manufacturing authorisation;
- which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfil his legal duties;
- a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such;
-

- Other discrepancy:

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice. (A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical)..

The persons involved in the inspected site respond to the deviations identified by the inspection team by post and/or digital by detailing the proposed preventive and corrective actions and the projected dates on which these actions will be completed for each deviation.

Upon receipt, the inspection team will review the responses proposed by the site. If the responses appear satisfactory, a favourable conclusion will be given to the final report by the inspectors and the management of Anses-ANMV will be able to issue a GMP certificate which will be transmitted together with the final inspection report.

If a response is deemed unacceptable and the proposed new preventive and corrective actions are unsatisfactory, this may lead to an inability to conclude on GMP site compliance.

7. INSPECTION COSTS

This section presents the different costs associated with a GMP inspection conducted by Anses-ANMV.
These costs include:

- The fee for the inspection itself, which varies according to the type of inspection and its sponsor;
- Ancillary costs such as:
    - Transportation costs;
    - Travel preparation expenses: fees for obtaining passport, visa, special administrative authorisation, vaccination, prophylaxis…
    - The cost of meals;
    - Housing costs;
    - Translation costs (if necessary).

7.1. RATES FOR INSPECTIONS

7.1.1. Rates according to sponsors

7.1.1.1. The EMA is the sponsor of the inspection:

In the context of a GMP inspection carried out at the request of the EMA and concerning one or more veterinary medicinal products benefiting from a centralised marketing authorisation procedure, the inspection fees shall be fixed and levied by the EMA, which contractually pays a share of the inspection fee to the Anses-ANMV.
The Anses-ANMV will not charge for the provision of inspection with the exception of the associated costs associated with this inspection in accordance with European procedures.

7.1.1.2. Anses-ANMV is the sponsor of the inspection:

As part of a GMP inspection conducted at the request of the Anses-ANMV outside France, the delivery of the inspection is invoiced in proportion to the number of days of inspection and the number of inspector(s) required for on-site inspection in accordance with the scale fixed by decision of the Director General of the Anses and the associated costs. The inspection period is a multiple of 1/2 day, any half-day started is charged.
The possible participation of observers, inspectors in training or supervisors, at the request of the Anses-ANMV, shall not be included in the number of inspector(s) required for the inspection.

7.1.2. Rates by type of inspection

The applicable rates for the various inspections commissioned by the EMA in accordance with Regulation 297/95 are regularly reviewed and publicly available on the EMA website (www.ema.europa.eu).

The schedule fixed by decision of the Director General of the Anses for inspections commissioned by Anses-ANMV is published in the annual catalogue of Anses tariffs accessible on the Anses website (www.anses.fr).

7.2. PAYMENT OF THE ASSOCIATED COSTS OF THE INSPECTION

Regardless of the sponsor for the inspection (EMA or Anses-ANMV), the costs associated with the inspection shall be borne by the beneficiary (i.e. MAH, EU importing site, other organisation residing in the EU or at least the inspected site) in their entirety.
The costs associated with the participation of observers, inspectors in training or supervisors, at the request of the Anses-ANMV, shall not be borne by the beneficiary.

7.2.1. Pre-inspection phase

Prior to the inspection, the inspector(s) concerned shall contact the beneficiary's representative located in Europe and, in a second step, the representative of the inspected site for the organisation of the inspection. The recipient shall forward to the inspection prior to the inspection the contact information of his or her designated organisation or organisation that will be responsible for the payment of the inspection costs and confirms that the inspection will bear all the costs incurred for the inspection as described below (Annex1).

- Transport:
  Travel arrangements include both ground and air transportation.

  After agreement on the inspection dates, inspectors shall communicate to the beneficiary the point of departure and the date of departure to be taken into account for the establishment of the travel itinerary. The transport is normally handled from the personal or professional address of the inspectors, unless specifically specified.

  Inspectors shall provide the beneficiary with an appropriate travel itinerary using the application form for a transport ticket in Annex *2*. The beneficiary may submit a counter-proposal if it has a definite advantage in terms of travel or transit time.

  The travel itinerary shall be drawn up on the basis of the following criteria:
  - Air transport:
    - The flight itinerary normally provides the shortest travel time and distance from the point of departure indicated by the inspectors to the point of arrival and without transit, if applicable. If transit is necessary due to the unavailability of direct routes, details of the transit areas and the duration of the transit are specified;
    - Unless specifically indicated by the inspectors, the preferential airline is Air France;
    - For a travel section of 4 hours or more without stopover or for an intercontinental journey, the selected flight class is the business class, with, if possible, a flexible fare structure allowing a change in flight date or time without any penalty or charge. In other cases, the flight class is Premium Economy with the same flexibility conditions;

- Land transport:
    - Train: train journeys are made in first class and on the most direct and shortest itinerary between the point of departure indicated by the inspectors and the point of arrival and without transit, if applicable. If transit is necessary due to the unavailability of direct routes, details of the transit areas and the duration of the transit are specified;
    - Other:
        - The beneficiary is also requested to organise and cover the costs of transferring inspectors between the hotel and the airport, as well as between the hotel and the inspection site during the entire inspection mission.
        - Taxi/public transport between the point of departure and the airport/station is supported by the beneficiary. If advanced by the inspectors, they will be reimbursed by the beneficiary to Anses ANMV at the end of the inspection upon presentation of an invoice/receipt. (see. 7.2.3)
        - Private car travel expenses by inspectors are reimbursed at the same fare as a second-class train ticket. If the itinerary is not served by a train, the costs of travelling by private car are reimbursed at the rate of EUR 0.29/Km for vehicles of 5 hp and less, EUR 0.37/Km for vehicles of 6 and 7 hp and EUR0.41/Km for vehicles of 8 hp or more. Any parking costs over the duration of the mission will be borne at the actual costs. They will be refunded by the beneficiary to Anses-ANMV at the end of the inspection upon presentation of an invoice/receipt.(see 7.2.3)

If meals are taken during the travel and are not paid directly by the beneficiary, they are then advanced by the inspectors and are reimbursed by the beneficiary to Anses-ANMV at the end of the inspection upon presentation of an invoice/receipt. .(see 7.2.3)

After agreement on routes, travel dates and times, means of transport (train and/or air tickets, airport/hotel/site journey) are organised, booked and paid by the beneficiary. Confirmation of the entire journey, including steps, shall be sent to the inspectors prior to the start of the trip. In principle, the inspectors or ANSES do not advance the transport costs.

- <u>Accommodation</u>:
  After agreement on the inspection dates, the beneficiary shall propose to the inspectors one or more suitable accommodations based on the following criteria:
    - The hotel category corresponds to an intermediate or higher class and the room category corresponds to at least one standard room. A description of the services and services offered by the hotel as well as the standard configuration and equipment of the room may be requested by the inspectors;
    - Accommodation must be located at a reasonable distance from the inspection site. The estimated time to reach the inspection site from the hotel at working hours should be indicated to the inspectors;
    - The stay at the hotel must start at least on the day of arrival of the inspectors, usually on the eve of the inspection and cover the entire duration of the inspection. When the inspection end schedules are not compatible with the

flight or train schedules for the return journey, then an additional night must be provided.

After agreement on the place of accommodation, the hotel room on site is booked and prepaid by the beneficiary. A confirmation is sent to the inspectors prior to the start of the trip.

- Other associated costs:
    - Visa fees or other administrative authorisations necessary for the travel of inspectors may be advanced by the inspectors and shall be reimbursed by the beneficiary to Anses ANMV at the end of the inspection upon presentation of an invoice/receipt.(see 7.2.3)
    - The inspectors shall be aware of the health precautions on the website of the Ministry of Foreign Affairs (www.diplomatie.gouv.fr/fr/conseils-aux-voyageur), which mentions specific indications concerning vaccinations or prophylaxis in order to visit the countries concerned by the inspection. In the event that inspectors wish to follow these recommendations, consultation with the attending physician and/or hospital centre, prior to the date of departure and any prophylactic treatment advanced by the inspectors shall be reimbursed by the beneficiary at the Anses ANMV at the end of the inspection upon presentation of an invoice/receipt. (see .7.2.3)
    - Assistance contract: Anses-ANMV has a contract of assistance covering its agents as part of their mission abroad.
    - Language and translation problems should not affect the outcome of the inspection. For this reason, in cases where it is not possible to complete the inspection in English or French in its entirety, the use of a professional translator (local language to English or French) should be considered. The costs associated with the use of a translator shall be borne by the beneficiary. Confirmation of the ability to carry out the inspection in one of the two languages shall be forwarded to the inspectors prior to the start of the trip. In addition, inspectors may at any time in the inspection process request the transmission of documents for examination or evidence assessment purposes. Any translation costs related to these requests will also be covered by the beneficiary.

7.2.2. On-site inspection phase

During the inspection, the following costs may be incurred:

- Meals:

If meals are not paid directly by the beneficiary, they are then advanced by the inspectors and are reimbursed by the beneficiary at the Anses-ANMV at the end of the inspection upon presentation of an invoice/receipt.

- Other associated costs:
    - In the event of extension of the duration of the mission due to unrelated force majeure (natural disaster, earthquake, flood, cancelled airline flight, strikes, etc.), all additional costs incurred by the inspectors (daily expenses, meals, accommodation) shall be reimbursed by the beneficiary to Anses ANMV at the end of the inspection upon presentation of an invoice/receipt.(see 7.2.3)

7.2.3. Post-inspection phase

Upon return from an inspection mission, each inspector shall prepare a summary of the costs of the inspection. This statement of costs together with the supporting documents is forwarded to the Anses-ANMV travel department, which verifies the completeness and accuracy of the file.

The dossier must contain:

- the original statement of costs completed by the inspector;
- original signed mission order;
- all the proofs of transport (tickets, tickets, taxi invoices, km travelled...) and meals (invoice, receipt);
- all supporting documents relating to possible ancillary costs: fees for obtaining a visa, passport as well as those generated by a medical examination or vaccination...

When a piece has been lost, the missionary has the opportunity to provide a certificate of the supporting honor.

Anses-ANMV's travel department reimburses the inspectors for mission expenses in accordance with the organisation note relating to the Anses' travel.

At the same time, the department establishes and transmits to the attention of the designated organisation (see 7.2.1) which will be responsible for the payment of the inspection costs:

- an invoice related to the costs of the inspection mission;
- a reference sheet of the organisation to be returned to Anses-ANVM for the first payment.

All supporting mission expenses are held by the department, a copy may be provided to the recipient upon request.

The invoice must be paid within one month of receipt by the designated organisation (see 7.2.1) which will be responsible for the payment of the inspection fees. In the event of difficulties or delays in the payment process, the beneficiary will inform the travel service as soon as possible.

It is recalled that non-payment of costs related to an inspection conducted by Anses-ANMV may result in a blockage in the GMP compliance decision-making process and in the issuance of a GMP certificate, if applicable.

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Annex1:

Information Sheet – European Organisation

Madam, sir,

In order to allow the billing of the fees related to an inspection carried out by the Anses-ANMV, thank you for completing this form and sending it to me by e-mail to saf.fougeres@anses.fr and insp@anses.fr .

INSPECTION **(To be completed by inspector)**
REFERENCE FOR INSPECTION:
SITE INSPECTION:
INSPECTION PREVISIONAL DATE:
INSPECTION COST COVERING ORGANISATION **(To be completed by recipient)**
NAME OR BUSINESS NAME (1):
TITLE (Mr., Mrs, Legal Status, etc.) (1):
SIRET (14 digits) (1):
EPA/NAF CODE (1):
INTRA-COMMUNITY VATCODE (1):
NAME OF CONTACT:
ADDRESS (1):
TELEPHONE N° (1):
FAX N°:
ELECTRONIC ADDRESS (1):
CERTIFICATE: **I, the undersigned, [FIRST NAME, NAME, QUALITY], certify that the costs associated with the inspection of [SITE NAME, CITY, COUNTRY] carried out by Anses-ANMV, which are invoiced under the conditions described in the information note published on the Anses website, will be borne by [NAME, ADDRESS OF ORGANISM].** **Do the ___/___/___** **Signature:**
COMMENT

(1) – Mandatory **information**

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Nos coordonnées bancaires
Our bank details

Si vous payez ***(If you pay)*** **:**

- **<u>Par virement</u>** ***(By wire transfer)*** **:**
  Veuillez utiliser le compte suivant *(Please use the following account)*

  IBAN : FR76 1007 1940 0000 0010 0043 619
  BIC/SWIFT : TRPUFRP1

  Adresse Banque *(bank address)* :
  DDFIP du Val de Marne
  1 place du général Billotte
  94040 Créteil Cedex - France

- **<u>Par chèque</u>** ***(By check)*** **:**
  veuillez adresser votre chèque à l'adresse suivante *(please send your check to the following address)*
  Anses
  Service comptabilité
  14 Rue Pierre et Marie Curie
  94700 Maisons-Alfort - France

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Identifiant nationale de compte bancaire - RIB				
Code banque	Code guichet	N° de compte	Clé RIB	Domiciliation
10071	94000	00001000436	19	TPCRETEIL

Identifiant international de compte bancaire - IBAN

IBAN (International Bank Account Number)							
							BIC (Bank Indentifier Code)
FR76	1007	1940	0000	0010	0043	619	TRPUFRP1

TITULAIRE DU COMPTE :

ANSES **M L'AGENT COMPTABLE**

Annex 2

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REQUEST FOR TRANSPORT
Inspection Outside France

Inspection					
Site inspection: (full address)					
Date:					
Inspection team					
Name:		**First name:**		**SNCF discount card number:**	
Passport No.:		**Date of issue:**		**Flying blue card number:**	
Name:		**First name:**		**SNCF discount card number:**	
Passport No.:		**Date of issue:**		**Flying blue card number:**	
Travel itinerary					
Place of departure:		**Exact location of the mission:**			

Journey Go				
Place of departure	**Date/Time of departure**	**Place of arrival**	**Date/Time of arrival**	**Flight/train number**
Journey Back				
Place of departure	**Date/Time of departure**	**Place of arrival**	**Date/Time of arrival**	**Flight/train number**
Comments				