EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

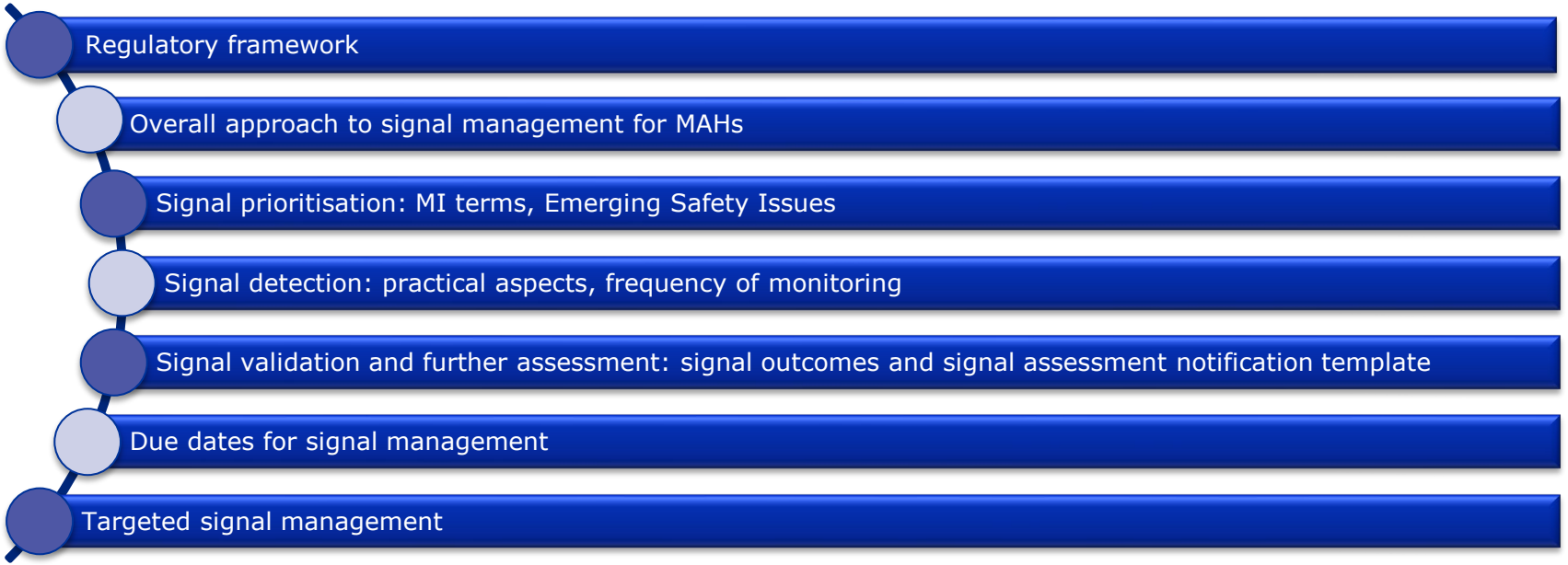
Union Pharmacovigilance Database: Webinar on Signal Detection and Analysis

Signal management following Veterinary Good Pharmacovigilance Practices

Presented by Daniel Zondag on 23 November 2021
Veterinary Risk and Surveillance Service

An agency of the European Union

Content Summary



Not in the scope in this training

- Technical submission of signals in the Union Pharmacovigilance Database
- Follow through of the regulatory procedures for relevant variations and post-surveillance

Regulatory Framework

EU Veterinary Medicines Legislation

- Regulation EU 2019/06
- Commission Implementing Regulation EU 2021/1281

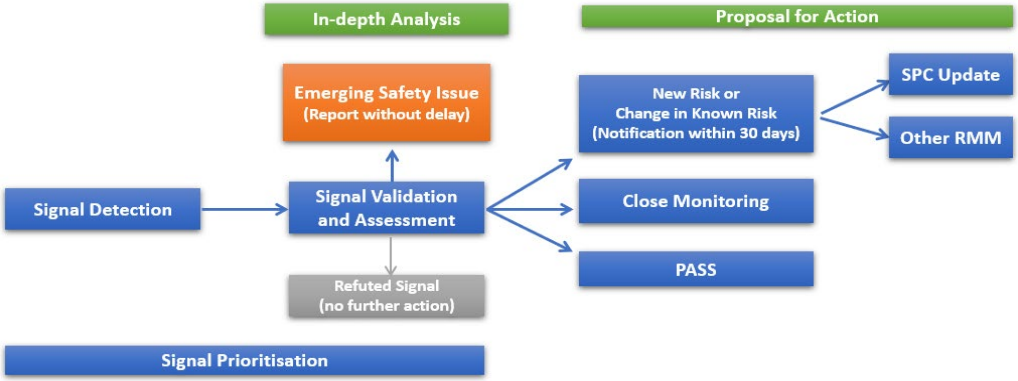
Regulation 2019/06

- Signal management process is the "**gold standard**" for determining whether there are any changes to the benefit-risk balance of veterinary medicinal products
- MAHs shall carry out signal management process for their veterinary medicinal products
- The Agency to develop **good pharmacovigilance guidance**, adopted by the Commission and marketing authorisation holders should comply with these

> '***Signal management process***' *means a process for performing active surveillance of pharmacovigilance data for veterinary medicinal products in order to assess the pharmacovigilance data and determine whether there is any change to the benefit-risk balance of those veterinary medicinal products, with a view to detecting risks to animal or public health or protection of the environment.*

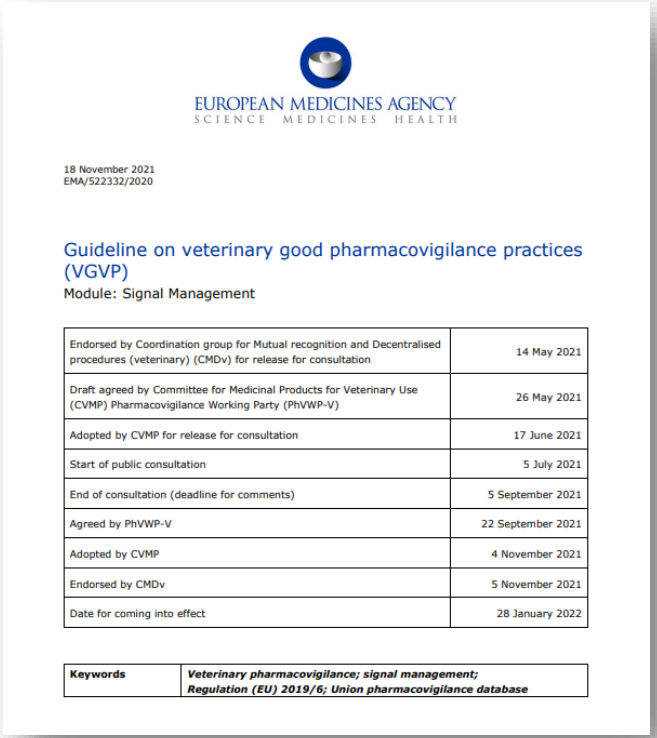
Commission Implementing Act EU 2021/1281

- Signal management process should enable continuous monitoring of the B/R balance
- The signal management process shall consist of at least pharmacovigilance processes of signal **detection**, **prioritisation**, **validation**, **assessment** and **documentation of outcome**



Signal Management Guideline

- Veterinary good pharmacovigilance practices (VGVP) on Signal Management
- Provides general methodological principles, describes the roles, responsibilities and procedural aspects
- Published on the EMA website
- Date for coming into effect **28th January 2022**
- Glossary for definitions



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18 November 2021
EMA/522332/2020

Guideline on veterinary good pharmacovigilance practices (VGVP)
Module: Signal Management

Endorsed by Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMDv) for release for consultation	14 May 2021
Draft agreed by Committee for Medicinal Products for Veterinary Use (CVMP) Pharmacovigilance Working Party (PhVWP-V)	26 May 2021
Adopted by CVMP for release for consultation	17 June 2021
Start of public consultation	5 July 2021
End of consultation (deadline for comments)	5 September 2021
Agreed by PhVWP-V	22 September 2021
Adopted by CVMP	4 November 2021
Endorsed by CMDv	5 November 2021
Date for coming into effect	28 January 2022

Keywords	***Veterinary pharmacovigilance; signal management; Regulation (EU) 2019/6; Union pharmacovigilance database***

Overall approach to signal management

Overall approach to signal management by MAHs

- Signal management is a **continuous** process throughout the product life-cycle
  - MAHs are expected to continuously monitor the safety of their products
  - Continuous monitoring of the Union Pharmacovigilance Database
  - Risk-based approach
- Transition from time-based into a **data-driven** pharmacovigilance system
- **Flexibility** and sound **scientific** and **clinical judgement** should always be applied

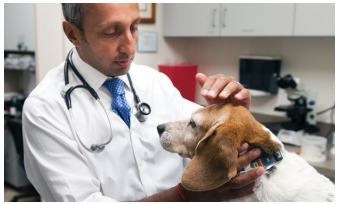
Overall approach to signal management by MAHs

*A **signal** is defined as information that arises from one or multiple sources, including observations and experiments, which **suggests** a potentially **new** causal association, or a new aspect of a known causal association between an intervention and an **adverse event** or a set of related adverse events, that is judged likely to justify further **investigation** of possible causality (Article 1(c) of the Implementing Act)*

- The focus should be on identifying **new** information
- A signal is an hypothesis; it does not always translate into a definitive causal association
- Not all signals represent risks or require further regulatory actions

Overall approach to signal management by MAHs

Sources of information in signal management



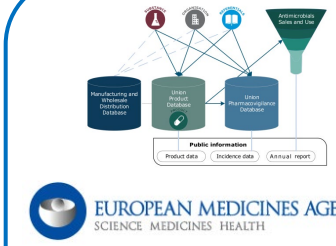
Clinical trials

Scientific literature

Pharmacovigilance Signal Management

Non-clinical trial data

Post-marketing surveillance studies



Union Pharmacovigilance Database

Overall approach to signal management by MAHs

Limitations of spontaneous reporting

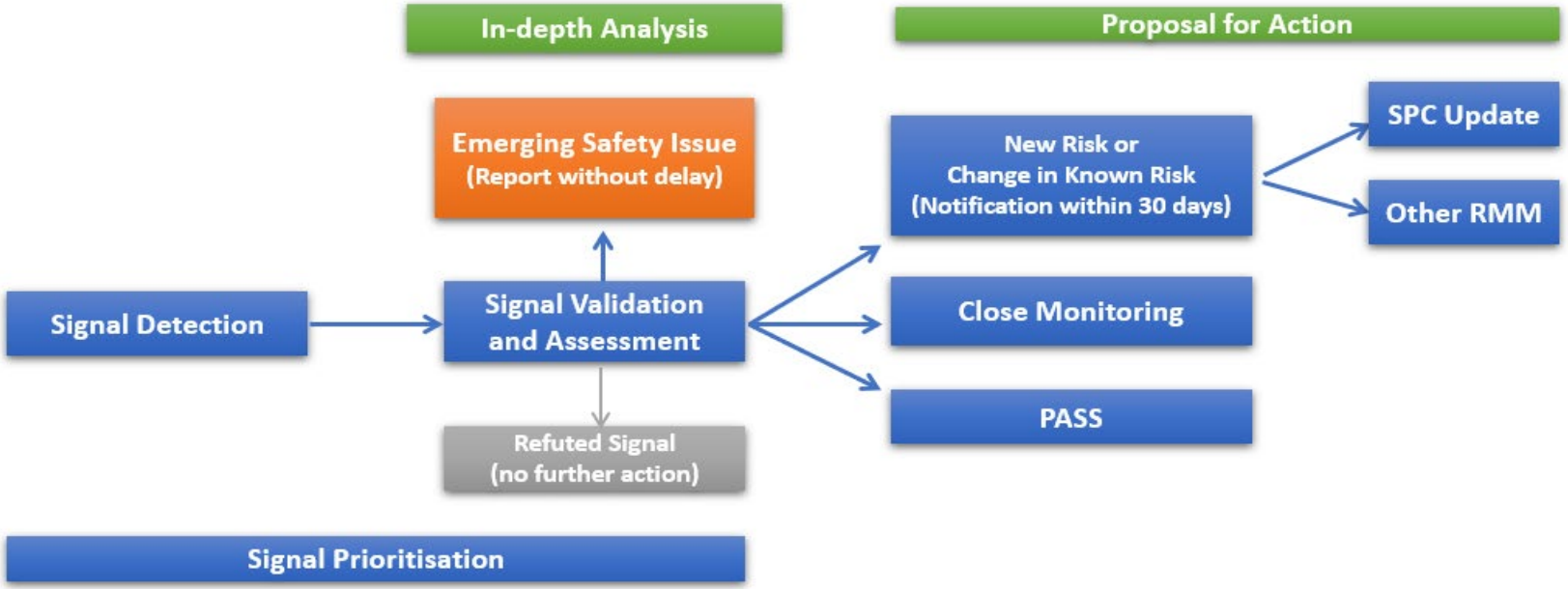
- **Under-reporting** and **reporting bias** (reporting is voluntary and may be influenced by external factors which might influence rate and quality of reporting)
- **Data quality** and **missing data** (not allowing proper evaluation or identification of risk factors)
- No accurate drug **exposure data**
- **Confounding by indication**
- **Confounders**
- **Duplicate** reporting

Overall approach to signal management by MAHs

- Frequencies of ADRs can be estimated when **clinical trial data** is available.
- Frequencies of ADRs observed in clinical trials **should not be replaced** by frequency estimations based on spontaneous data.
- Only in cases when there is **evidence** suggesting an increase in frequency of known ADRs, consideration should be given open a signal and revise the frequency in product information.

Signal Prioritisation

Signal Prioritisation



Signal Prioritisation

- **Continuous activity** performed throughout the whole signal management process, from signal detection to signal assessment (not a single step)
- Prioritisation means using specific criteria to focus on (potential) signals which require **more urgent attention** because they have a potential significant impact on the B/R or high impact on animal or public health
- Focus **available resources** on the most important issues
- **Different values** to be taken into account depending on the step

Medically Important terms for Signal Prioritisation

Medically Important (MI) terms *are VeDDRA Preferred Terms (PT) that identify serious medical concepts that are often casually associated with drugs across multiple pharmacological/therapeutic classes and should automatically be prioritised.*

- To be used by EMA, Member States and MAHs for prioritisation
- MI terms deserve special attention, even in the absence of any statistical disproportionality measure (e.g. ROR)
- Species specific: some PTs are only medically important in some species
- Any events occurring in human should be considered an MI term
- Lack of expected efficacy, especially for products used in anaesthesia, should be prioritised
- List is not definitive

Medically Important terms

MI VeDDRA term	Species #
Any event	Human
Abdominal pain	Horse
Abomasitis	Ruminant, Camelid
Abortion	All
Acute mastitis	Ruminant, Camelid, Horse
Aggression	All
Anaphylaxis	All
Anorexia	Horse
Apnoea	All
Ataxia	Horse
Bee systemic disorders NOS*	Bee
Birth defect	All
Blindness	All
Bone marrow hypoplasia	All
Cardiac arrest	All
Cardiac insufficiency	All
Circulatory shock	All
Coagulopathy	All
Collapse NOS*	All
Coma	All
Convulsion	All
Deafness	All
Death	All
Diabetes mellitus	All
Disseminated intravascular coagulation	All
Dyspnoea	All
Epileptic seizure	All
Fish asphyxia	Fish
Fish body deformity	Fish
Haemolytic anaemia	All
Haemorrhagic gastroenteritis	All
Heart block	All
Hepatic failure	All
Hypersensitivity reaction	All
Hypocalcaemic condition	Ruminant, Camelid
Hypomagnesaemic condition	Ruminant, Camelid
Impaired hearing	All
Impaired vision	All
Immune mediated thrombocytopenia	All
Increased coagulation time	All
Ketosis	Ruminant, Camelid
Laminitis	Horse
Loss of consciousness	All
Lying down	Horse, Ruminant, Pig, Camelid
Metastatic neoplasia	All
Metritis	Horse, Ruminant, Camelid
Moribund	All
Multi-organ failure NOS*	All
Myoglobinuria (Horses only)	Horse
Paralysis	All
Paresis	All
Perinatal mortality	All
Recumbency	Horse, Ruminant, Pig, Camelid
Renal insufficiency	All
Reticulitis	Ruminant, Camelid
Stillbirth	All
Suspected infectious agent transmission	All
Thrombocytopenia	All

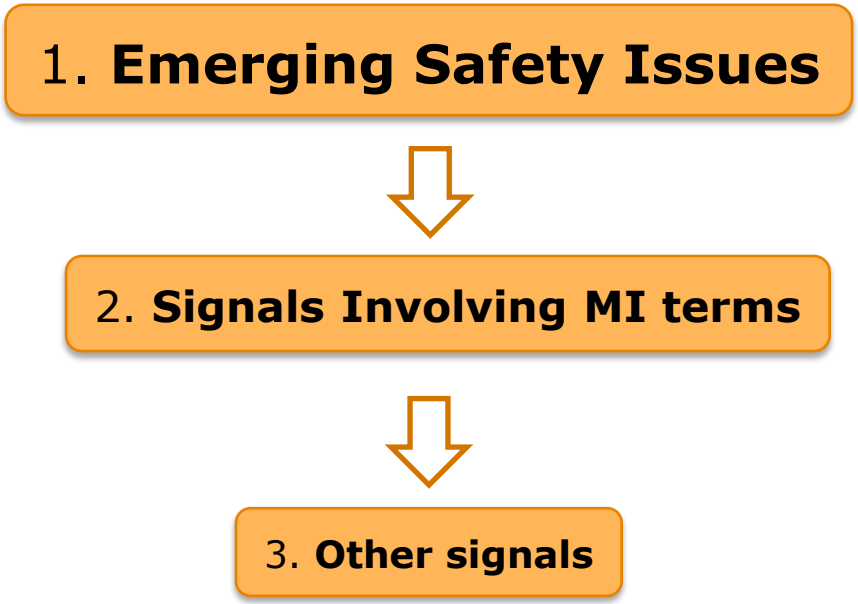
*NOS: Not otherwise specified.

Medically Important terms for Signal Prioritisation

In EudraVigilance:

- For signals involving **MI terms**, usually a minimum of **3 cumulative cases** are needed
- For signals involving any **other PT terms**, usually a minimum of **5 cumulative cases** are needed

Signal Prioritisation



- Reporting **without delay**, no later than **3 working days**
- Separate procedure involving Incident Review Group

- Always prioritised, even in the absence of statistical disproportionality
- **3 cases** are usually needed

- Other criteria relevant
- **5 cases** are usually needed

Emerging Safety Issues

"New information which might influence the assessment of the benefits and the risks of veterinary medicinal product according to Article 58(10) of Regulation (EU) 2019/6, and which may require ***urgent regulatory action and communication****, should be identified as an emerging safety issue. It should be reported to the relevant competent authority(ies), without delay and* ***no later than 3 working days*** *after identification of an emerging safety issue"*

Emerging Safety Issues

Examples

- **major safety issues** in context of ongoing/completed **studies**, e.g. unexpected increased rate of fatal or life-threatening AEs ;
- **major safety issues** from spontaneous reports or scientific literature, which may lead to **contraindication**, **restriction of use** of VMP or **withdrawal** from market;
- **major safety-related regulatory actions outside the EU**, e.g. restriction of use of VMP or its suspension

Emerging Safety Issues

Cabergoline

- Use in dairy cows as an aid in abrupt drying-off by reducing milk production to: reduce milk leakage at drying off, reduce risk of new intramammary infections during the dry period, reduce discomfort.
- Serious adverse events reported in cows, including **recumbency** and **deaths**
- Within 24 hours of administering cabergoline
- In total, 71 reported deaths in cows
- Exact cause of AEs yet to be determined, evidence suggested they may be linked to cabergoline.
- Given number and severity of AEs following use of the medicine in healthy dairy cows, the CVMP concluded that the benefit-risk balance was negative
- **Marketing authorisation suspended** in the EU due to **risks outweighing benefits**
- Company suspended sales in the EU, CVMP recommended recall of cabergoline on the market

Emerging Safety Issues

BVD vaccine

- Inactivated vaccine for the immunisation of cattle at breeding age to prevent foetus against bovine viral diarrhoea virus (BVDV)
- Concerns raised regarding adverse event reports of **bovine neonatal pancytopenia** following use of the product in Germany
- Urgent procedure started to assess all data available from pharmacovigilance reports, epidemiological and laboratory studies
- CVMP concluded that although the aetiology of bovine neonatal pancytopenia had yet to be determined there was evidence to suggest that the vaccine may be associated with bovine neonatal pancytopenia and that **benefit-risk balance** was **unfavourable**
- CVMP recommended **suspension of the marketing authorisation**
- Batch recall was also recommended

Emerging Safety Issues

What should MAHs do when identifying an ESI?

- Create specific entry in relevant module of the Union Pharmacovigilance database
- Fill in and submit ESI notification form
- No later than 3 working days
- MAH should collaborate with EMA and NCAs in the assessment

What happens after EMA received an ESI notification?

- EMA will assess if the issue fulfils the definition of an ESI
- Incident Management Plan to be followed
- Further regulatory procedures might be started (e.g. referral)

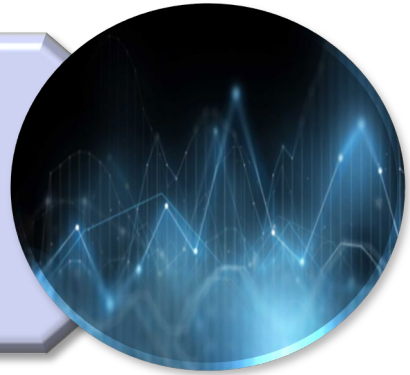
Signal Detection

Practical aspects of Signal Detection

- A signal in pharmacovigilance is more than just a statistical parameter that tells you that something is disproportionately reported in your database
- Statistical detection methods alone are not sufficient to detect signals in spontaneous reporting databases
- A combination of **quantitative** and **qualitative** methods is preferable
- If dataset is very small, there is no need to implement a quantitative method
  - Qualitative review complement simple metrics e.g. number of case reports
- Disproportionality methods such as the ROR can help identify certain events to investigate
- Signal of disproportionate reporting does not necessarily means a signal of suspect causality

Practical aspects of Signal Detection

Statistical analyses in signal detection should always be complemented by a qualitative review of the cases.



Practical aspects of signal detection

Screening and quantitative analyses should be performed at **Preferred Term (PT)** VeDDRA level

- There are no data to suggest that screening at higher aggregation levels (HLT or SOC level) would detect more signals or detect them at an earlier stage
- In exceptional cases, a group of adverse events might be associated and it might be justified to analyse several PTs together

** Good signal detection practices: Evidence from IMI PROTECT. Drug Saf 2016.*

Practical aspects of Signal Detection

- Focus on **new** information coming
- No obligation to assess historical data

- ➢ No need to start looking for potential signals of adverse events in the database for which no new cases (after January 2022) have been reported
- ➢ However, if a new signal is detected, based on new reported cases, a cumulative review including all available cases in the Union pharmacovigilance database should be performed

How to decide on the frequency of monitoring

*Marketing authorisation holders shall perform signal management using a **risk-based approach** and monitor the data with a **frequency proportionate to the identified risk**. The risk-based approach shall take into account the following topics: **type of product**, length of **time on the market** and **stability of the pharmacovigilance profile**, **identified** and **potential risks** and the **need for additional information**. The risk-based approach shall be applied to determine the methodology, extent and frequency of the signal management process and the rationale shall be documented.*

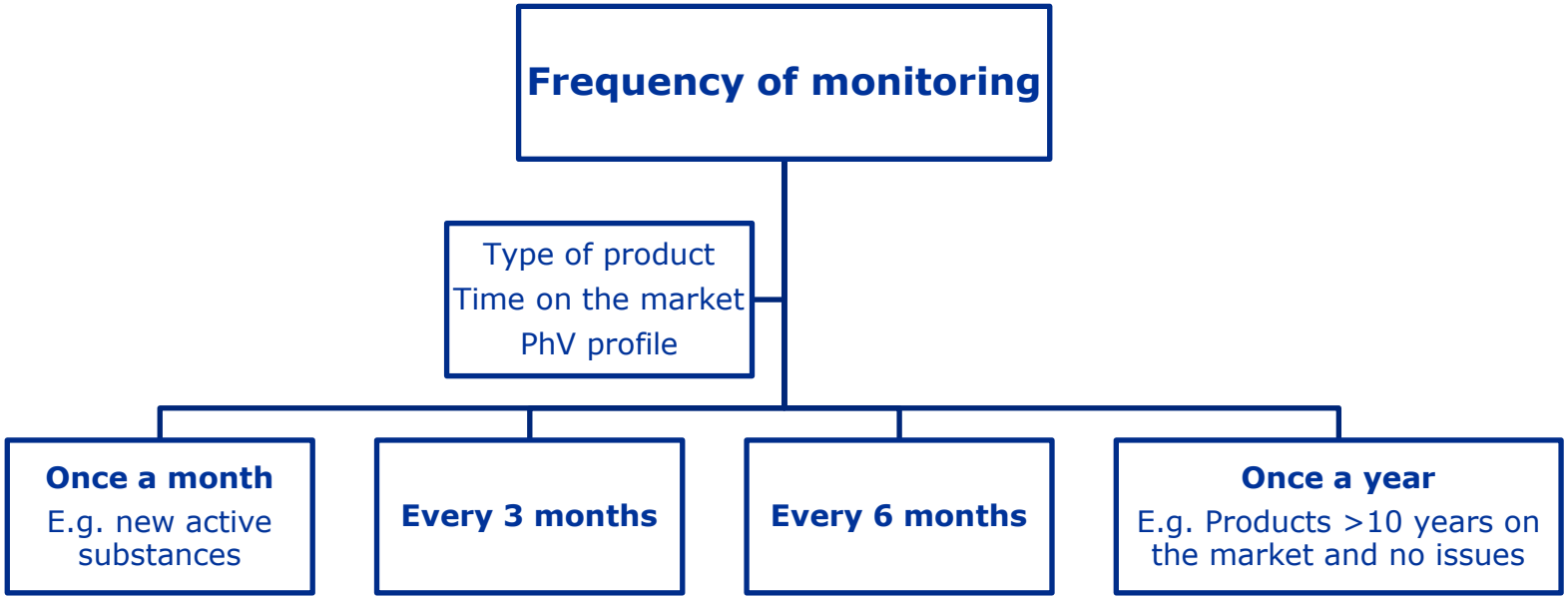
Article 17(3), Commission Implementing Regulation 2021/1281

How to decide on the frequency of monitoring

Appropriate frequency may vary depending on the knowledge of the safety of the product

- **Type of product:**
  - Higher frequency: biologicals (incl. vaccines), antiparasitics
- **Time on the market:**
  - Higher frequency: <10 years on the market
- **Pharmacovigilance profile:**
  - Higher frequency: products with high number of adverse event reports and safety issues

How to decide on the frequency of monitoring



Signal Validation and further Assessment

Signal Validation

- First step in analysing a detected signal to evaluate the initial data as a minimum, MAHs have to check that:
  - Event occurred after exposure to medicinal product (i.e. **temporal association**)
  - Signal is not based on **duplicates**
  - Suspected AE is not already reflected in **SPC**

Questions to ask during signal validation:

- *Does it fulfil the definition of a signal?*
- *Is this new information currently not reflected in the SPC?*
- *Does the event reflect a new aspect of a known risk? (i.e. change in frequency, duration, time to onset, severity, occurrence pattern, outcome) interaction with other VMPS*
- *Has this association previously been addressed?*

Signal Validation

Checking for previous awareness:

- Important to check with parent product (for generics)
- Previous assessment of the same issue in previous PSURs

Checking for any changes:

- Useful to sort from high to low the number of clinical signs reported and check whether this order has changed compared to the previous period: e.g. emesis (n=987), convulsions (n=856), renal failure (n=345) or if a new clinical sign is reported more often

Checking if AEs already reflected in the SPC:

- Useful to check "Guidance note on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans"
- Allergy, anaphylactic shock, anaphylaxis…

Signal Validation

- Non-validated signals do not require any further assessment and should not be submitted or recorded in the Union pharmacovigilance database

- Once a signal is validated, further assessment should be performed by the MAH

Signal Assessment

- The assessment of a signal should be as comprehensive as possible
- <u>The aim of the assessment is:</u>
  - Reach a **high-quality decision** and signal outcome
  - Decide if the evidence supports a potential **causal association** (i.e. new risk or change in new risk, which might have an impact on the B/R)
  - Decide on the potential **regulatory actions**

What is expected from the MAH?

➢ Cumulative Review

Signal Assessment

Cumulative Review

- In-depth review of **all cumulative cases available** to the MAH
- Number **supportive cases**: positive de-challenge/re-challenge, lack of alternative explanations, temporal association, evaluate potential association (not based on ABON)
- If there are indications from the veterinarian in the case reported, this adds to the strength of evidence
- Possible biological **mechanism**, dose-reaction relationship, plausible pharmacokinetic explanation (e.g. occurrence around Cmax, hepatic metabolism, renal clearance)
- Additional data sources: MAH database, scientific literature, etc.
- **Conclusion** on potential association of adverse event and VMP based on all available evidence

Signal Assessment Outcomes

Signal is refuted

- No need for further evaluation or action is necessary at this point in time other than routine PhV

Need for additional information

- Further follow-up of the signal is necessary/ongoing (i.e. *close monitoring*)

Need for further regulatory action

- Amendment of the product information (SPC)
- To conduct a post-marketing surveillance study
- Additional risk minimisation measures are necessary such as educational materials or dissemination of Direct Animal Healthcare professional communication
- Suspension/withdrawal of the marketing authorisation
- Batch recall
- Any other appropriate actions not listed above

Signal Assessment Outcomes

Signal Refuted

- Potential causal association at present unlikely
- Available information suggests AEs are more likely associated with other factors not related to the exposure of the VMP (e.g. underlying condition of the animal, other medicines, etc.)
- Signal can still be reopened in the future should any new relevant information become available
- Refuted signals from previous annual submissions with no new relevant information available do not need to be resubmitted

Signal Assessment Outcomes

Close Monitoring

- Available information insufficient to conclude on potential causal association but further information expected to provide evidence that could change this conclusion
- MAH to report at each yearly due date the status (updated review if new cases)
- Shorter reporting periods can be set by authorities (e.g. 6 months)
- Signals under close monitoring for extended period (e.g. >2 years) stopping of the close monitoring can be proposed at due date with detailed justification

Signal Assessment

Signal submission

- **Signals where there is a new risk identified or a change to B/R:**
  - Signal should be submitted to the Union pharmacovigilance database
  - 30 day notification requirement
- **Signals assessed throughout the year, where no new risk or changes to B/R identified:**
  - Signals should be submitted to the Union pharmacovigilance database
  - Signal can be submitted at any time throughout the year (due date at the latest)

Signal Assessment

Signals where no new risk or changes to B/R identified

- MAH should submit total number of cases + brief summary of review of cases and the conclusion on the assessment

Example 1

Signal of diarrhoea and "X product" in dogs:

A total of 6 cases reported. 3 cases with too limited information for assessment. 2 cases confounded by the concomitant medication known to cause the event ("Y product" has diarrhoea listed in the product information). 1 case considered related to underlying condition of the dog (…). Conclusion: ***Signal refuted.***

Signal Assessment

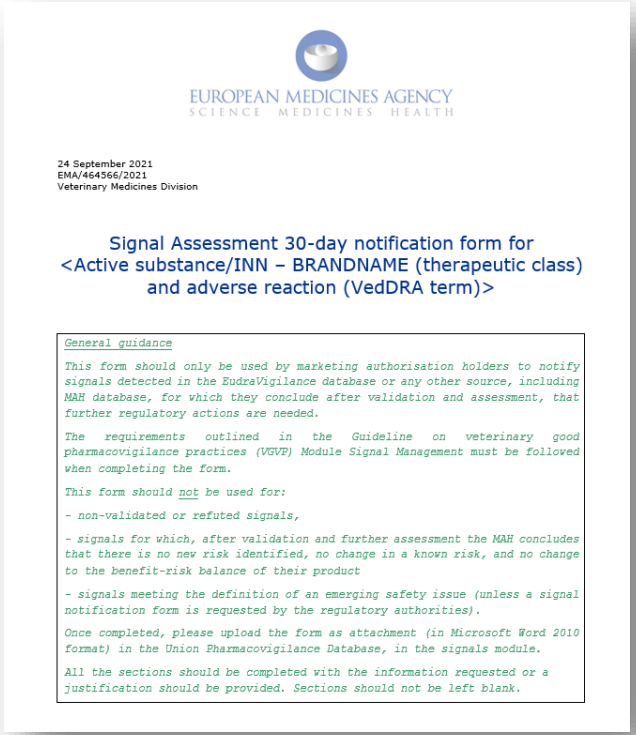
Example 2

Signal of blindness and "XXX product" in cats:

A total of 4 cases reported. 2 cases with too limited information for assessment. 1 case confounded by underlying condition (diabetes) and old age of the cat. 1 case where the event occurred 3 months after the product was administered.
Conclusion: ***Close monitoring.***

Signal Assessment Notification form (30 day notification)

- Form to be used by MAHs for notification of signals requiring 30 day notification
- Form to be included as attachment with the signal entry in the signal module of the Union pharmacovigilance database (EVV)
- Not to be used for non-validated signals or signals with no proposals for further regulatory actions



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24 September 2021
EMA/464566/2021
Veterinary Medicines Division

Signal Assessment 30-day notification form for
<Active substance/INN – BRANDNAME (therapeutic class)
and adverse reaction (VedDRA term)>

General guidance

This form should only be used by marketing authorisation holders to notify signals detected in the EudraVigilance database or any other source, including MAH database, for which they conclude after validation and assessment, that further regulatory actions are needed.

The requirements outlined in the Guideline on veterinary good pharmacovigilance practices (VGVP) Module Signal Management must be followed when completing the form.

This form should not be used for:

- non-validated or refuted signals,

- signals for which, after validation and further assessment the MAH concludes that there is no new risk identified, no change in a known risk, and no change to the benefit-risk balance of their product

- signals meeting the definition of an emerging safety issue (unless a signal notification form is requested by the regulatory authorities).

Once completed, please upload the form as attachment (in Microsoft Word 2010 format) in the Union Pharmacovigilance Database, in the signals module.

All the sections should be completed with the information requested or a justification should be provided. Sections should not be left blank.

Signal Assessment Notification form (30 day notification)

1. ADMINISTRATIVE INFORMATION

Date of this notification	DD month YYYY
Active substance(s) (invented name(s)) of the medicinal product for veterinary use	<Text>

- Administrative part to include the date of the report and the active substance and the veterinary medicinal product
- All other administrative information to be included already in the signal entry of the Union pharmacovigilance database

Signal Assessment Notification form (30 day notification)

2. SIGNAL DESCRIPTION

2.1. Highlights

Clinical relevance: <Text>

<Please briefly summarise if seriousness criteria were met in the cases, e.g. fatal, life-threatening, hospitalisation etc. specifying if the event concerns a medically important (MI) term or if the event concerns an adverse reaction in human. Please briefly explain the potential public health, animal health and environmental protection implications. See VGVP Module Signal Management>

Relevant statistical measures: <Text>

<Please provide the relevant ROR values (in particular the lower bound of the 95% confidence interval) from EudraVigilance, as well as any other relevant statistical measures if applicable.>

Incidence: <Text>

Previous awareness: <Text>

<Please provide information on any regulatory actions or previous assessments, performed at national, EU or non-EU level in relation to the signal. Please ensure, wherever possible, that the signal is not already addressed in other EU SPCs for the active substance, or considered by EMA.>

Additional sources other than EudraVigilance:

- ☐ Literature
- ☐ MAH database
- ☐ Clinical trials
- ☐ Other *[please specify below]*

Signal Assessment Notification form (30 day notification)

2.2. Background

<Text here.>

<This section should include a concise summary of the relevant information on the product(s)/ active substance (including therapeutic indication(s), target species, etc), and on the adverse reaction(s) (e.g. morbidity, epidemiology, case definition, etc.)>

Signal Assessment Notification form (30 day notification)

2.3. Signal validation and further assessment

2.3.1. Evidence from EudraVigilance

Date of the query: <DD month YYYY> Monitoring periodicity: <Text here.>

<Text here.>

<This section should include a summary of evidence from EudraVigilance, highlighting the strength of evidence, clinical relevance and a summary of the supportive cases. This includes the VedDRA terms used, the total number of cases, and from those, the number of supportive cases, positive de-challenge or re-challenge, seriousness, dose-reaction relationship, lack of potential alternative causes, possible mechanism based on the biological and pharmacological plausibility, temporal plausibility, causality assessment, clinical context (e.g. potential drug-drug interactions, specific species affected, risk factors) and quality of documentation should be provided. See VGVP module signal management.>

2.3.2. Evidence from other sources

<Text here.>

<This section should include a summary of all additional evidence if available from other sources, e.g. from the MAH database, scientific literature (i.e. findings regarding similar cases in the scientific literature, including information on substances of the same class of medicinal products), data from experimental, non-clinical or clinical-trials, information from other databases with larger datasets, information from other regulatory authorities worldwide>

Signal Assessment Notification form (30 day notification)

3. Conclusion and proposal for action by the marketing authorisation holder

<Text here.>

<This section should include the most relevant evidence in support of the signal and a brief statement highlighting whether the available evidence reviewed supports a potential causal association between the veterinary medicinal product or active substance concerned and the suspected adverse event.

The proposed regulatory actions to address the signal should be provided, e.g.:

- *Update the product information to add the event as a potential adverse drug reaction, include a new warning, add a new contra-indication, add a new interaction, information on risk minimisation measures, etc.*
- *Propose a post-marketing surveillance study to confirm and/or quantify the risk or identify potential risks factors, etc.>*
- *Withdrawal of the marketing authorisation of the product*
- *[…]*

Signal Assessment Notification form (30 day notification)

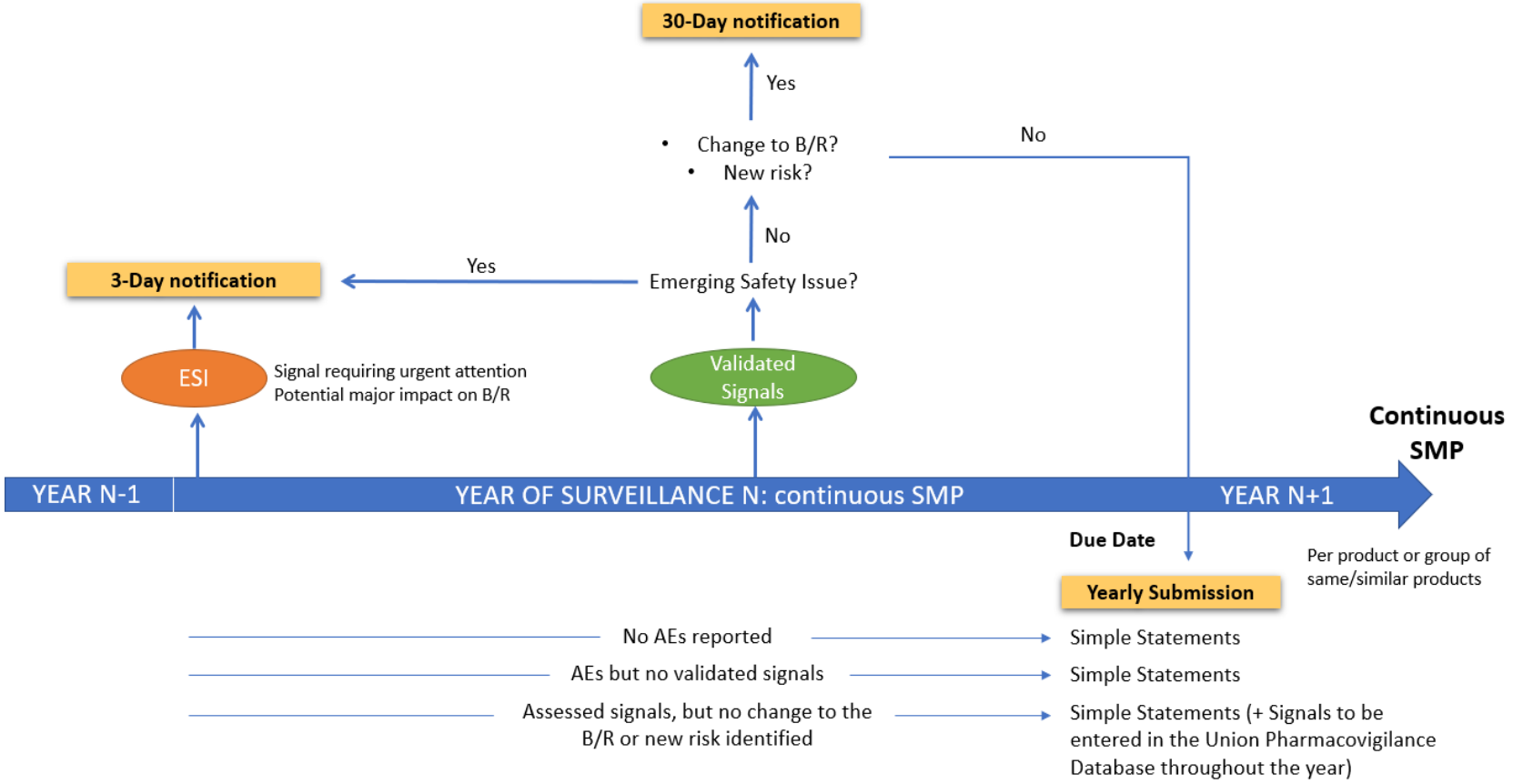
4. ANNEXES

<Text here.>

<List of literature references, if applicable>

<List of attachments, if applicable>

Due dates for Signal Management



Due dates for Signal Management

Legal Requirement:

- Art 81(2) Regulation 2019/06 and Art 19(1) of EU Implementing Regulation establishes that MAHs have to submit at least once a year:
  - Statement with a conclusion on the B/R balance
  - Statement confirming that signal management process has been conducted
- To facilitate and coordinate evaluation of data during 1st year of implementation, **due dates** are proposed based on ATCvet code and system organ class
- Current list includes due dates spread throughout the year for all products
- After 2022, other grouping criteria will be used based on gained experience

Due dates for Signal Management

Category		target spp	CAP	Rapporteur
QI02AB Inactivated bacterial vaccines (including mycoplasma, toxoid and chlamydia	31-May	cattle	Startvac	DE
			Coxevac	FR
			Ubac	DE
QI02AC Inactivated bacterial vaccines and antisera	31-May	cattle		
QI02AE Live bacterial vaccines	31-May	cattle		
QI02AF Live bacterial and viral vaccines	31-May	cattle		
QI02AG Live and inactivated bacterial vaccines	31-May	cattle		
QI04AB Inactivated bacterial vaccines (including mycoplasma, toxoid and chlamydia	31-May	sheep		
QI04AC Inactivated bacterial vaccines and antisera	31-May	sheep		
QI04AE Live bacterial vaccines	31-May	sheep		
QI04AF Live bacterial and viral vaccines	31-May	sheep		
QI04AG Live and inactivated bacterial vaccines	31-May	sheep		
QI03AB Inactivated bacterial vaccines (including mycoplasma, toxoid and chlamydia	31-May	goat		
QI03AC Inactivated bacterial vaccines and antisera	31-May	goat		
QI03AE Live bacterial vaccines	31-May	goat		
QI03AF Live bacterial and viral	31-May	goat		
QI03AG Live and inactivated bacterial vaccines	31-May	goat		
QI07AI Live viral and inactivated bacterial vaccines	31-May	dog	Versican Plus Pi/L4	DE
QI07BI Live viral and inactivated bacterial vaccines	31-May	fox		
QI07XI Live viral and inactivated bacterial vaccines	31-May	other canidae		

ATCvet Codes	category	Product (CAP)	NCA Country
QJ01M QUINOLONE AND QUINOXALINE ANTIBACTERIALS	systemic use	**Veraflox**	DE (BVL)
QJ04 ANTIMYCOBACTERIALS	systemic use	n/a	n/a
QJ54 ANTIMYCOBACTERIALS FOR INTRAMAMMARY USE	intramammary	n/a	n/a
QP53AC08 cypermethrin	pyrethrins/pyrethroids	n/a	n/a
QP53AC10 fluvalinate	pyrethrins/pyrethroids	n/a	n/a
QP53AC11 deltamethrin	pyrethrins/pyrethroids	n/a	n/a
QP53AC12 cyfluthrin	pyrethrins/pyrethroids	n/a	n/a
QP53AC13 tetramethrin	pyrethrins/pyrethroids	n/a	n/a
QP53AC14 fenvalerate	pyrethrins/pyrethroids	n/a	n/a
QP53AC15 acrinathrin	pyrethrins/pyrethroids	n/a	n/a
QP53AC30 combinations of pyrethrines	pyrethrins/pyrethroids	n/a	n/a
QP53AC51 pyrethrum, combinations	pyrethrins/pyrethroids	n/a	n/a
QD DERMATOLOGICALS	organ class	**Apoquel**	IE
QD DERMATOLOGICALS	organ class	**Cytopoint**	IE
QD DERMATOLOGICALS	organ class	**Cortavance**	DK
QD DERMATOLOGICALS	organ class	**Hydrocortisone aceponate Ecuphar**	FR

Annual submission statements

	Benefit-risk balance
X	I confirm that the benefit-risk balance remains unchanged
	A procedure is ongoing concerning the benefit-risk assessment

	Adherence to VGVP guidelines
X	I confirm that the signal management process has been conducted in compliance with the pharmacovigilance guidelines published by the Agency (VGVP) and all assessed signals have been submitted

Due dates for Signal Management

What else is expected from MAHs by the due date?

- Signals assessed throughout the year, where no change to the B/R, new risk, or change to a known risk is identified *(signals can also be submitted at any time, but by the due date at the latest).*
- Other additional information:
  - **Scientific literature findings** on suspected AEs from group of humans who cannot be identified individually
  - Risks or relevant issues from **off-label** use cases **with no suspected AEs**
  - Risks or relevant issues from "**special situation cases**" (misuse, medication error, accidental exposure) **with no suspected AEs**

Due dates for Signal Management

What else is expected from MAHs by the due date?

- All MAHs shall conduct at least one signal detection analysis per year for each of their active substances or products in the Union pharmacovigilance database (EVV)
- Signal detection analysis on EVV should be performed **within 2 months before due date**
- Status and updates from signals under close monitoring (submitted >6 months ago)
- Signals under close monitoring for extended period of time (e.g. more than 2 years), stopping of close monitoring can be proposed with justification (changes to refuted signal)

➢ **Incidence/sales data** – to be developed and agreed (legal deadline 2024)

Targeted Signal Management

Targeted Signal Management

- Article 81(3) from Regulation (EU) 2019/6 gives NCAs and Agency the option to perform a targeted signal management process for a given veterinary medicinal product or group of veterinary medicinal products.
- Regulators can start a signal management procedure at any time throughout the year.
- MAHs should collaborate with the Agency and NCAs and provide any requested information in a timely manner.

Any questions?

Further information

vetchange.programme@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

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