OPERATING MANUAL

A basic phamacovigilance system

veterinary medicinal products

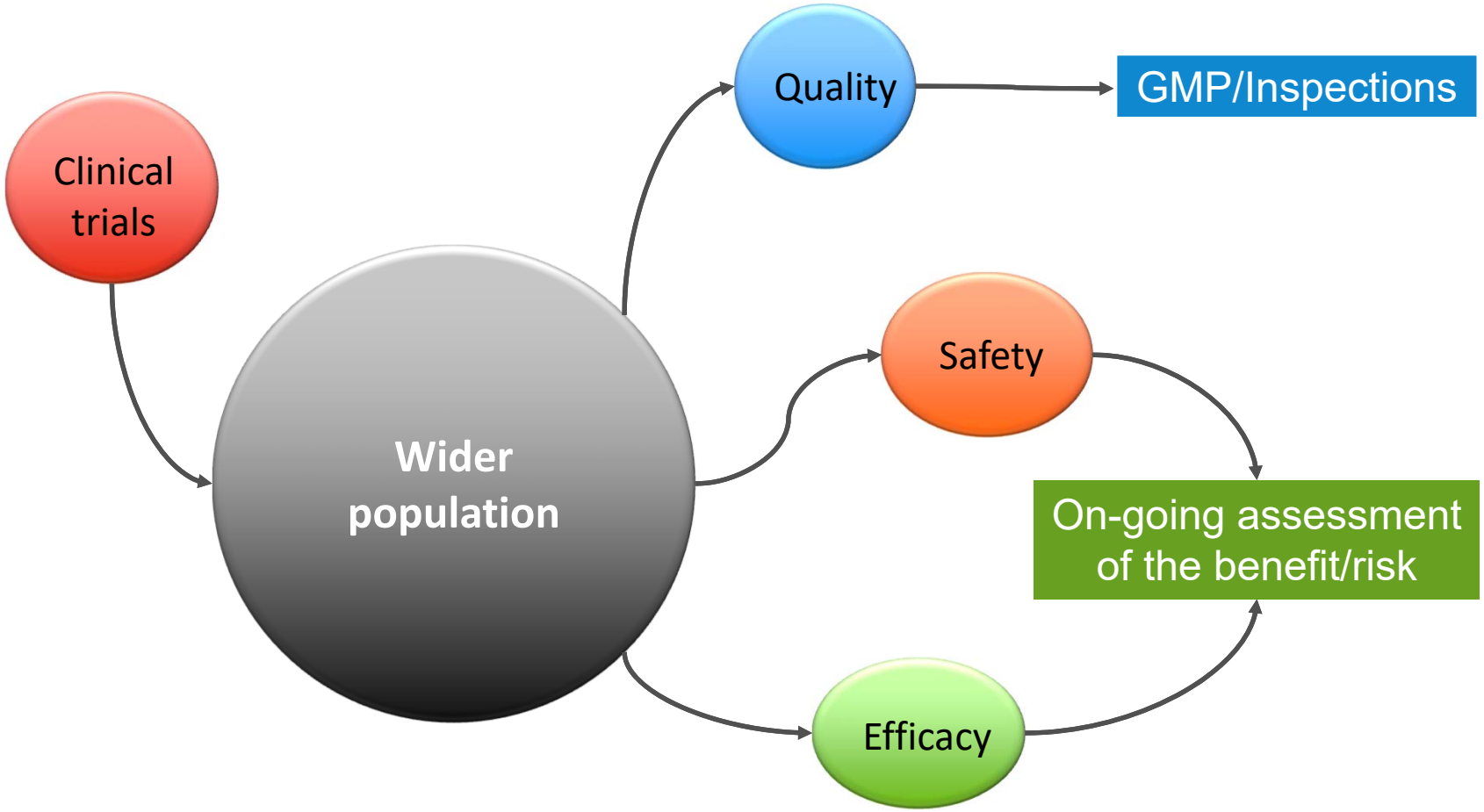
What is Pharmacovigilance

Pharmacovigilance is a process by which information is collected to detect and prevent unexpected or unwanted adverse effects following the use of (veterinary) medicinal products.

The **scope** of veterinary pharmacovigilance is mainly the safety and efficacy in animals and safety in people.

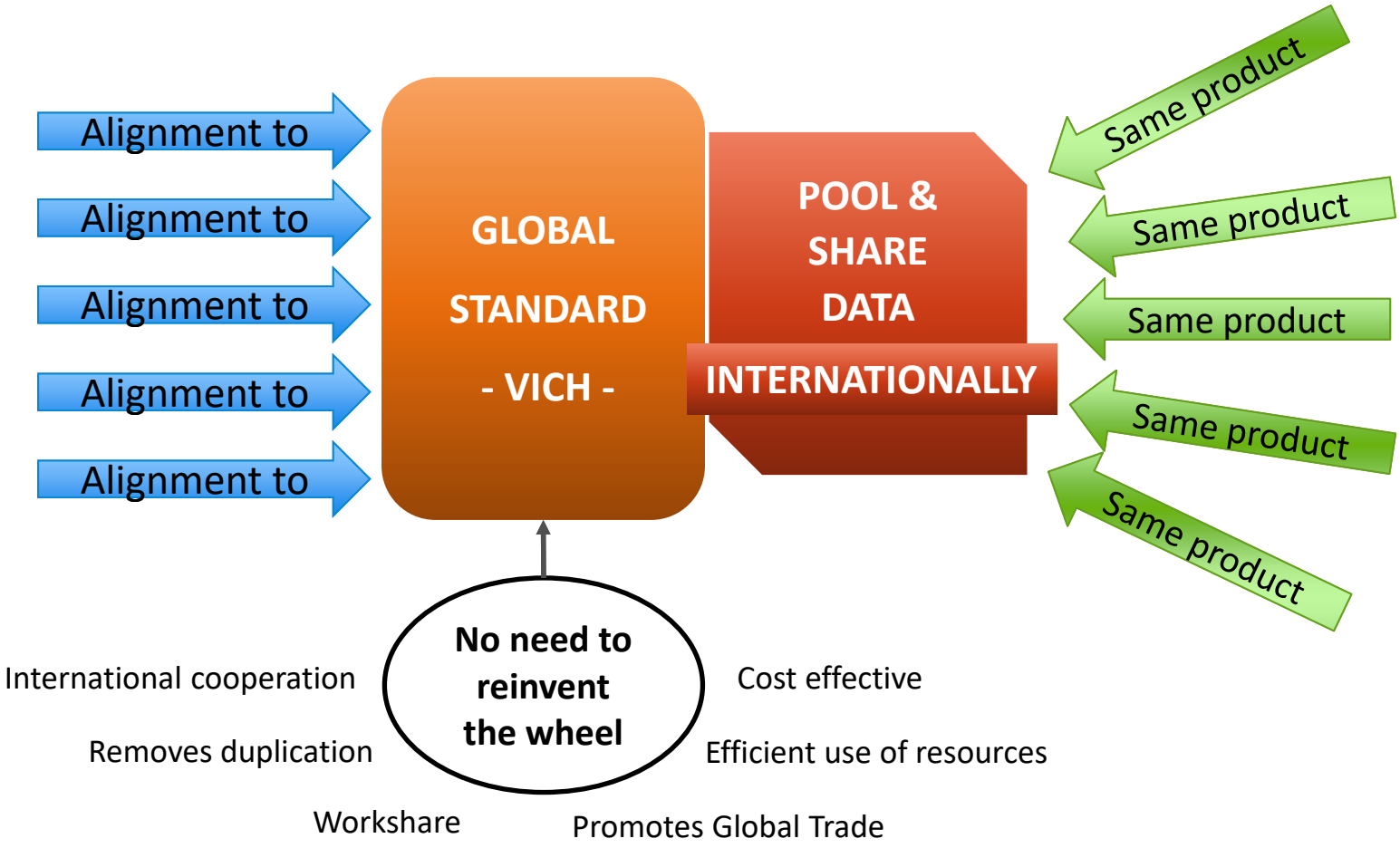
A basic pharmacovigilance system

Why is Pharmacovigilance important?



A basic pharmacovigilance system

Why are international harmonisation and standard reporting formats important?



Roles and responsibilities

1. The role of the National Competent Authority (NCA)

- Responsibility for developing and implementing appropriate national legislation and additional guidance
- Collaborate with other regional NCAs and global bodies
- Share best practice
- Work with academics and other bodies to ensure appropriate pharmacovigilance training modules for veterinarians and other stakeholders

Roles and responsibilities

2. The role of the Marketing Authorisation Holder (MAH)

- Legal responsibility to comply with local pharmacovigilance legislation
- Ensure cases are reported in a timely manner
- Have a process for recognising and capturing pharmacovigilance cases

Roles and responsibilities

3. The role of the Veterinarian

- Have an ethical responsibility to recognise potential pharmacovigilance issues
- Report them to the MAH and/or NCA

4. The role of the Animal Owners

- Have an ethical responsibility to report an adverse event to either their veterinarian or the MAH or the NCA
- Support the on-going monitoring of authorised VMPs in the market-place

Scope of Pharmacovigilance

Ambitions and scope ⟺ **available resources**

- Form of IT/People
- Budget (funding)
- Number of anticipated adverse event reports
- Number of products on the market
- Local culture of reporting

What products will be in scope:

- Medicinal products
- Other types of products

→ Separate systems and AER forms

What adverse events will be in scope

- Treated animal
- The user
- Residues
- Environmental

→ Can it be traced to an individual product ?

Timing for adverse event reporting

- Expedited case reports-where action may be needed
- Periodic summary reports-for periodic review of B:R
- Enter into Database – within 30 days

Format

- Globally aligned formats

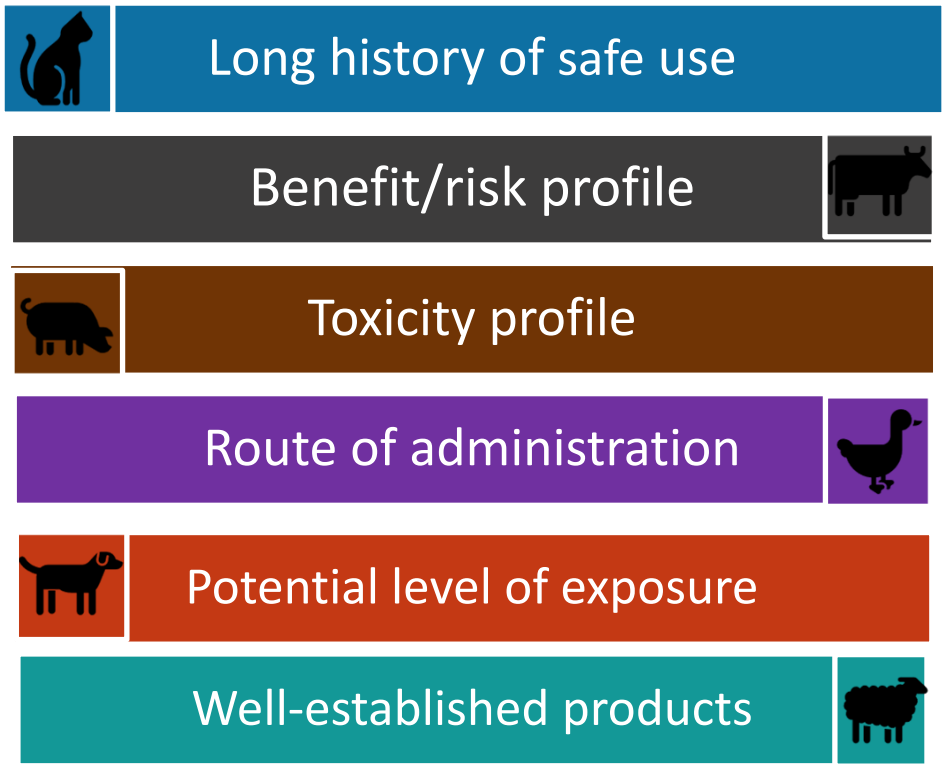
Should third country reports be included?

- Including 3rd countries will lead to the submission of many 1000s of cases
- Will divert attention from local pharmacovigilance cases

Timing for adverse event reporting

Frequency of PUR's

- Tailored to level of risk and a product's risk profile



Legislation and Guidance

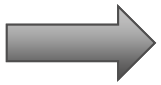
Need a legal basis to impose requirements and rules

- Establish structures and systems
- Obtain government funding
- Enforce regulatory measures
- Provide legal clarity on responsibilities of each actor

Legal requirement to report→ carrot or stick ?

Unadvisable to put operational details in legislation

- Keep legislation high level
- Put details in guidance
- Consult all stakeholders



More flexible
System can evolve and grow
Can adapt with experience
Easier to update

Guidelines

Provide operational details in guidelines

- Reference the legal basis
- Guidelines for NCA operational details
- Management of adverse event cases - process timelines, receipt and filing procedures, storage and archiving
- Evaluation of cases-how are cases going to be assessed
- Communication with the MAH-timeline, methods, expectations
- Investigation of identified issues and subsequent risk management measures

Guidelines

Guidelines for compliance of MAH

- Details on requirements
- Details on expectations for the MAH staff training and frequency of retraining
- Details on reporting adverse event cases

Consult all stakeholders

- System must work for everybody = smooth running
- Raising awareness
- Builds “buy-in”- facilitate smooth inplementation

Setting up a Pharmacovigilance System

Define, scope, obtain funding, draft legal and guidance

- Plan implementation of the system within the NCA
- Estimate scale & volume of AER's-how many products & volume of sales
- Responsibilities-Who does what-adequate staff
- Documentation-report form, filing system
- Process, SOP's, Language
- Paper, spreadsheet or database system
- Define responsabilities and obligations of companies

Standard formats

- VICH GL24 + 30 for standard AE forms and definitions
- VEDDRA standardised terminology for report data entry
- Set up a spreadsheet with VEDDRA term and local term

Responsibilities and obligations of the national competent authority (NCA)

- To establish a pharmacovigilance system:
  - collect information
  - scientific evaluation and product group analysis
  - collate with data on sales or use, and local epidemiology
    - ✓ For local context and incidence rate
  - monitor compliance of companies
  - do risk-based inspections and perform controls
  - take corrective actions where necessary
- Initiate further investigation and assessment of identified safety concerns
- Implement conditions and restrictions on products
- Encourage reporting
- Make companies and veterinarians aware of their obligations

Responsibility of Marketing Autorisation Holder

Responsible for ensuring an appropriate system of pharmacovigilance surveillance
Risk Management
Ensure action can be taken, when necessary

Responsibilities and obligations of MAHs should be defined, covering information collection format
Language, timelines, rules, communication

Are responsible for collecting, storing and analysing the pharmacovigilance data on their products
Further communication
Adverse event information

Documentation

Aim: Transparent-Consistent-Smooth Implementation

> *SOP's – guidelines – standard forms*

> *International standards – consult stakeholders – MAH & vets*

- Reporting form for adverse events
- System for reception of spontaneous adverse event reports
- Assignment of case numbers and filing
- Acknowledgment of receipt
- Procedure for causality assessment
- Data input management, follow-up for missing essential data
- Tools for data analysis; aggregation of data, signal detection; trends
- Analyse across substances, products and species
- Procedures for decisions on regulatory action

Documentation

Plan training of internal staff

- Training materials
- Training and refresher
- Staff back-up

Promoting and Communicating the System

Make companies and veterinarians aware of their obligations

- Communication plan
- Deadline for implementing new system-go live
- Distribution-availability of reporting forms & submission papers
- Where to access the standard reporting forms
- Promote collaboration-efficient, effective system
- Education-vet schools, conferences, continued professional development

Promoting and Communicating the System

Publicity….feedback - essential for continued motivation for reporting

1. Descriptive statistics
2. Success stories
3. Summaries of actions taken
4. Emphasise value & importance of reporting

Make it easy to report: Availability of reporting forms, via
- sales reps - websites - professional bodies
- Apps - accessable contact - tel nº - 24hr cover

Workshops
NCA & MAH's-how to improve the system
NCA & vets
Animal producer groups

Reception & Processing of Spontaneous AER's

Starting point: reports must use standard definitions & terminology

- VEDDRA GL 30 – definitions of VMP, AE, Serious AE

Standard content:

- An identifiable reporter, including name and contact details
- An affected animal (defined by species at minimum) or human being
- An identifiable veterinary medicinal product
- One or more adverse signs or description of the event

Reception & Processing of Spontaneous AER's

Standard terminology:

- Drop-down pick-lists online
- Guidance for filling the form
- Language

More details highly desirable to enable correct case analysis

(see chapter10 box2)

Language:

- Worldwide reporting - English
- Converting VEDDRA terms to local language-d-b ? Excel ?

Data process for spontaneous AE's

Reception of the AER:

- Assign case number
- Confirmation of receipt
- Follow up to obtain missing info or for personal response

Handling and storage:

- Paper format-must be archived-paper or electronic format (scan)
- Electronic format-must be archived
- Security of storage-controlled access, fire/water/theft, longevity of storage media

Data process for spontaneous AE's

Data entry and records:

- Data entry to computer system-aids storage and analysis
- Verification of data entry
- Data fields (International standards-VICH GL30142)

Coding and assessment:

- Medical review-evaluation of the data
- Causality assessment

Submission of Individual AER's

Timeline:

- Too short=incomplete reports-no timle to obtain missing data
- Several follow up submissions=more work

Timeline examples:

- Expedited/serious 15 days
- Other 30 days

Or

- All reports 30 days
- NCA to be alerted to serious cases ASAP

Coding the data

Adequate resources needed to ensure timely

data entry -> coding -> review -> evaluation

Data entry VEDDRA

- Free text description-must closely reflect the wording of the reporter
- Standard terms in data fields-use VEDDRA based pick-lists "clinical dictionary"
  - Allows analysis via structured data query
- VEDDRA clinical dictionary
  - established by VICH GL 30
  - maintained/updated by an international group within VICH

Causality Assessement

Each AER must have a causality coding after assessement:

- Associative connection with the treatment,
  - in time or in anatomical sites
- Pharmacological and/or immunological explanation
  - blood levels, dose-effect relationship.
- Any characteristic product-related clinical or pathological phenomena.
- Previous knowledge of similar reports.
- Exclusion of other causes.
- Completeness and reliability of the data in the case reports.
- De-challenge and re-challenge information if available.

Causality Assessement

Examples of causality scoring algorithms

1. The clinical sign level
   - e.g. modified-Kramer system (used by FDA – see reference)
2. The case level
   - e.g. ABON system (used by EU – see reference)

     whereby causality is classified as
     - A - Probable
     - B - Possible
     - O1 - Inconclusive
     - O - Unclassifiable/Unassessable
     - N - Unlikely

More on data storage/archiving

- Depends on the chosen system-paper-based, electronic
- Adverse event reports using electronic data storage
  a. facilitates analysis
  b. is access-controlled and prevents unauthorised access
  c. is protected against fire, water, data loss and theft

- A simple (vet-specific) pharmacovigilance database compatible with international standard format is preferable
  a. Facilitates easier reporting
  b. Facilitates exchange of data

- Prepare operating procedures for storage and archiving

Archiving

Archive periods

- **For the MAH:**
  should be retained for a period of 2 years after the *expiration date of a product*

- ***For the NCA:***
  for at least 3 years after *the marketing authorisation* has expired

Periodic Summary Reports

Purpose - to provide an update at defined time points

International Birthdate IBD

- Each VMP has an International Birth Date (IBD).
- Harmonizing MAH periodic reporting dates, and the Data Lock Point (DLP) for PSRs

PSR Frequency

- Risk based-new/unknown vs well established/known safety profile
- More frequent in early years – less frequent
  e.g. typical frequency is 0,5 1 1,5 2 3 (4 5) 6 9 12 years
- New country - do not restart-PSR cycle
  - use IBD and global PSR schedule for International products

PSR Language

- Global reports-English
- Translation needed - only the PSR conclusions

PSR Contents

- All AERs since the last PSR from anywhere in the world
- Product names and MA numbers of all products covered by the PSR
- The period covered by the PSR and the IBD
- Summary of any regulatory actions taken anywhere in the world
- A line listing of any AERs received but not yet submitted to the NCA
- Estimated exposure and incidence rates
- Bibliography following a bibliographic search
- Critical analysis and review of the benefit-risk assessment

Calculating the Incidence Rate

- Sales data-use data, based on recommended use (label)
- All reasoning for the calculation assumptions should be explained/justified
- Animal standard weights-see GL p.19 or local stds
- Multiple species on label ? Provide estimation, explain/justify
- Standardise the calculations-allows comparisons between products. Consistent approach for estimating exposure to a VMP
- Overall incidence of all AER's)easy but crude 5ABON°
- Causality coded incidences

Analysis of Aggregated Data

Analysis at meaningful intervals
- By product
- By group of similar products e.g. same active substance
- By species
- By AE type

Periodicity of analysis
- Risk-based approach - see PSR frequency

Method
- Depends on number of AER's involved
- Line listing review for few cases
- Spreadsheet analysis for large number of cases
- Database with statistical tools and software
- Detect trends and potential signals (threshold trigger)

Put data into context
- Incidence rate-increase in sales
- Reporting rate

Signal Management

1. A signal is defined as the detection of a new AE or a change in the rate of a known AE.
2. Signals should be prioritised based on their potential severity. All detected potential signals need to be validated, evaluated
3. A confirmed signal is considered a risk
   a) either a potential risk
   b) or as identified risk
4. The risk level is defined based on its severity
   a) low risk - no risk mitigation measures are considered to be necessary
   b) important risk - risk mitigation measures are considered necessary.
5. The time frame for implementing the measures should reflect the level of risk

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Risk Management and follow Up

Follow up regulatory measures for risk management

- Should be risk based

  i.e. depending on level of risk, potential or direct causality established

Further investigation may be warranted

- low risk – may be sufficient to just follow PHV closely

Risk-mitigation measures may be needed

- Re-education of users
- Warning statements EU labels/pack leaflets/websites
- Letter to vets
- Other label changes
- Additional clinical studies
- Suspension/revocation of MA

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Risk Management and follow Up

Timeframe-depends on severity of risk

- Immediate/recall
- ASAP
- Next planned label change (stock depletion)

Good communication important

NCA <-> MAH

Similar products

- apply same regulatory measures

Communicating Pharmacovigilance Outcomes

- An important part of pharmacovigilance activities
  - Develop guidance for industry
- Publish
  - The outcomes of the analysis, not the raw data itself
  - Information about the safe and effective use of VMPs
  - Important changes to the product information
- Communicating
  - Bring significant new information to the attention of veterinarians before the general public
  - Agree all communication between the NCA and MAH
  - Determine which pharmacovigilance outcomes to communicate
  - Use international classification of frequency of adverse events (CIOMS)
  - Examples of communication:
    - Safety Bulletin, Dear Healthcare Professional letters, Training program

Inspections and Compliance

- Pharmacovigilance inspections - responsibility of the NCA
- Adequate resources needed
- Use a risk-based approach to inspection frequency and scope
- To reduce duplicative activities and use resources efficiently, consider
  - Combining pharmacovigilance with other routine inspections
  - International/regional collaboration

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Types of inspections