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Guidance notes on collection of drug safety information by employees and agents of pharmaceutical companies

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ABPI Pharmacovigilance Expert Network

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1. Overview

It is both a legal and ethical requirement to document and report information about the safety of a pharmaceutical company's medicinal products. This document will explain the processes and background in more detail.

Drug safety or pharmacovigilance (PV) rules are necessary for the protection of public health in order to assess, detect and prevent side-effects (adverse events or adverse reactions), as the full safety profile of medicinal products can only be known after they have been placed on the market.

Any person employed directly by a pharmaceutical company or contracted to work for the company has a responsibility to record and report information about the safety of the company's medicinal products to the company's PV department.

Companies must provide training to all employees and agents on their processes for reporting safety information, so they know what to do if they become aware of a safety concern[1].

See Annex 1 for a summary of this guidance document that may be used for training purposes. See Annex 2 for a list of abbreviations and Annex 3 for an explanation of terms.

Safety information should normally be reported immediately or at least within one business day of awareness by the employee or agent of the company. The awareness date of the information should always be provided.

The minimum information for a report to be sent to the PV department is:

- a company product
- an adverse event or special safety situation.

The following additional information should be collected where possible:

- An identifiable reporter (any one or a combination of: reporter's name, occupation or title, address, telephone number, email address or other contact details).
- A company product (promoted or non-promoted or generic if the brand is not known).
- An adverse event or other special safety situation (eg pregnancy, breast feeding, overdose, interactions, product abuse/misuse, medication error, unapproved/off-label use, occupational exposure or lack of therapeutic effect), see Annex 3.
- An identifiable patient (ie person who experienced the event identified by any one or combination of: gender, age, date of birth, age group, initials).
- Any other information to describe the course and outcome of the event.

All events described as side-effects, adverse events or adverse reactions, whether serious or non-serious, expected or unexpected, should be reported.

[1] European Medicines Agency 2013. Good pharmacovigilance practices Module I, Section I.B.7. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129132.pdf

2. The legal basis of pharmacovigilance

PV regulatory obligations (see section 14 for legislative information) are placed on all companies holding innovative or generic marketing authorisations for medicinal products in the European Union (EU). In order to ensure compliance with this legislation, all companies undergo regular PV inspections by regulatory agencies, including the Medicines and Healthcare products Regulatory Agency (MHRA), the UK's regulatory authority.

PV is the process of:

- Monitoring medicines as they are used in every day practice and in clinical research to identify previously unrecognised adverse effects or changes in the patterns of known adverse effects.
- Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their use.
- Providing information to prescribers and users to optimise effective use of medicines.
- Monitoring the impact of any action taken.

Companies must have an appropriate PV system in place to ensure the appropriate use of their medicines and to take appropriate action when necessary. All companies operating within the EU must employ a qualified person for PV (QPPV) who is responsible for the establishment and maintenance of the PV system, including the processes for the collection, preparation and submission of adverse event (AE) reports, periodic safety update reports (PSURs) and risk management plans (RMPs) to regulatory authorities.

3. Your responsibility as a company employee or agent

Anyone employed directly by the company or on a contractual basis must be vigilant for safety information relating to any of the company's products, even if they do not work in a safety-related function. This includes situations outside of work.

Anyone who communicates with customers of the company in a promotional or non-promotional capacity has a particularly important role to play in the process of collecting safety information, since they will often be the main contact for that customer with the company.

Safety information is frequently identified through medical information enquiries and consideration should be given as to whether safety is the basis of any query.

It must be remembered that safety information may also be found in the medical literature, discussed at scientific meetings or displayed in abstracts and posters at symposia and delegates might talk about safety information to company representatives if the company has a stand at a scientific meeting or symposium. Safety information obtained in this way must also be collected and reported.

Safety information may also be reported via market research projects, patient support programmes, medical educational grant programmes, non-interventional studies, digital media (websites), etc. Your company's PV department should be contacted to discuss how such information will be handled and collected before projects such as these are started, in order to ensure that all legal obligations are met.

There are requirements in the ABPI Code of Practice for the Pharmaceutical Industry regarding PV, see section 14.

4. What information should be collected?

Any safety information associated with the company's products (whether the product is promoted, non-promoted or referred to only by its generic name if the brand is not known) should be collected regardless of:

- Whether or not an AE is already listed in the summary of medicinal product characteristics (SmPC), patient information leaflet (PIL) or package leaflet (PL).

- Whether the reporter is a healthcare professional (HCP), eg doctor, nurse, pharmacist, dentist or coroner; or non-HCP, eg patient, carer, friend, relative, lawyer, journalist, etc.
- Seriousness or severity of the event.
- Whether or not a causal relationship to the product has been established.
- Whether or not the reporter has already completed a Yellow Card report to the MHRA (see section 13).

The minimum information for a report to be sent to the PV department is an adverse event or special safety situation and a company product.

In order for the company to fully process safety reports, it is important that the following additional information is obtained where possible:

- **An identifiable reporter**
  - Any one of a combination of: reporter's name, occupation or title, address, telephone number, email address or other contact details.
- **A company product**
  - Promoted or non-promoted or generic if the brand is not known.
  - Including, if possible, dose, duration, indication of use and batch number.
- **An adverse event or special safety situation (see Annex 3 for an explanation of terms)**
  - Including pregnancy, breast feeding, overdose, interactions, product abuse/misuse, medication error, unapproved/off-label use, occupational exposure or lack of therapeutic effect.
- **An identifiable patient**
  - The person who experienced the event identified by any one or combination of: gender, age, date of birth, age group, initials.
- Any other information to describe the course and outcome of the event, eg details of symptoms, severity, duration, treatment and what medical attention (if any) was sought.

For reports received from non-HCPs, companies may be required to confirm the details with a HCP. You must inform all reporters that the information will be passed to your company's PV department who may contact them or their HCP for further information. If they request any information or have any queries, they should be directed to the company's Medical Information department (or equivalent).

If anyone wishes to provide you with safety information, you should collect the information they have provided and ensure any discussions are in line with the ABPI Code of Practice.

5. Data protection[2]

It is important to maintain patient confidentiality and to uphold data privacy rules. If information is received containing personal data, the company's internal procedures must be followed to ensure that such confidential personal data is anonymised and managed appropriately.

You should inform anyone who reports safety information that the report details will be forwarded to your company's PV department, which may contact them for further information and that a rapid reply would be appreciated if they receive such a request.

[2] ABPI 2013. *ABPI Guidance on UK data protection in post-marketing pharmacovigilance, 2013.* Available at: www.abpi.org.uk/our-work/library/guidelines/Pages/data-protection.aspx

6. How to report safety information

Safety information must be sent to the company's PV department. This may be via the Medical Information department or other route. Each company must implement a system (ideally as straightforward as possible) for reporting safety information. This must be adequately documented and all employees and contractual agents must receive training in this process, together with refreshers (usually annually or ad hoc when required).

Safety information must be reported in a timely manner, usually immediately or at least within one business day of awareness. When reporting safety information, it is important to provide the date on which the information was identified.

Any source data that arises from the collection of safety information, such as hand-written notes or the company's adverse event collection form, must also be sent to the PV department.

7. Why collect drug safety information?

There are two main reasons why a company needs to collect this information:

- In order to safeguard patients, the company collects safety information to monitor the benefit-risk profile of a product to identify potential changes at an early stage. When a new product is first marketed, its efficacy has been well defined. However, since a relatively small number of patients who fit particular inclusion and exclusion criteria will have taken part in clinical trials during the development of a new medicine, it is likely that only the more common adverse drug reactions (ADRs) will have been identified. It is only after larger scale use of the product in normal clinical practice that less common ADRs may be detected and an indication of the frequency of the more common ADRs determined.
- As described in section 2, the company has a legal obligation to have an appropriate system of PV in place. Part of this system is to promptly report relevant safety information to the worldwide regulatory authorities.

8. What happens if companies do not collect and report safety information?[3]

Under EU law, in order to protect public health, regulatory authorities are obliged to ensure compliance with PV obligations. When non-compliance is detected, the necessary action will be judged on a case-by-case basis. The action will depend on the potential negative public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action.

In the event of non-compliance, possible regulatory actions include: education and facilitation to implement corrective actions; triggered or "for cause" inspections; issuance of Infringement Notices/ warning letters; urgent safety restrictions, variation, suspension or revocation of marketing authorisations; administrative penalties (fixed fines or fines based on company profits) and referral for criminal prosecution with the possibility of imprisonment. Authorities may also consider making public a list of marketing authorisation holders (MAHs) found to be seriously or persistently non-compliant.

[3] European Medicines Agency 2013. Good pharmacovigilance practices Module III, Section III.B.7. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129243.pdf

9. What if someone does not want to report safety information?

If a HCP or consumer does not wish to provide further information on an AE, this is acceptable, provided this is documented and notified to the PV department. The employee or agent must still report the information they have already obtained from the reporter, but inform the PV department that the reporter does not wish to provide any further follow-up.

10. What company action is taken on receipt of safety information?

Safety information is entered into a database and regularly reviewed and assessed by the company's global PV department. It is therefore important that as much detail as possible is obtained when the initial report is received to enable a full assessment of the case. Additional follow-up will generally also be sought in order to obtain any missing information[4].

Pharmaceutical companies are required to report certain safety information within strict timeframes of receipt to the worldwide regulatory authorities.

Safety information must be reviewed on a regular basis to detect potential signals, ie new or potential safety concerns[5].

Periodic reports (eg PSURs) may also be prepared and submitted to regulatory authorities at defined time points in a medicine's lifecycle to summarise and evaluate the benefit-risk profile based on all safety and efficacy information collected on the product up to that time[6].

Overall, the information is used to build up the safety profile of a medicine so that the company, in consultation with the relevant regulatory authority, can advise prescribers and users of any changes, as necessary, or take any other actions such as:

- updates to the product information: SmPC, PIL or PL
- further clinical studies to define an AE
- conducting educational programmes
- issuing special warnings or direct HCP communications
- withdrawal of a medicine from the market in rare circumstances.

11. Risk management plans[7]

It is recognised that at the time of authorisation, information on the safety of a medicinal product is relatively limited. A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk balance is judged to be positive for the target population. However, not all actual or potential risks will have been identified at the time of initial authorisation.

The PV activities necessary to characterise the safety profile of the medicinal product must be planned and therefore risk management plans (RMPs) are produced by the MAH, where required, to detail the ways in which the company intends to minimise and monitor identified and potential risks with their medicines. Where appropriate, training should be provided and tailored with respect to specific activities associated with the RMP.

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[4] European Medicines Agency 2013. Good pharmacovigilance practices Module VI, Section VI.B. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf

[5] European Medicines Agency 2013. Good pharmacovigilance practices Module IX, Section IX.B.3.2. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129138.pdf

[6] European Medicines Agency 2013. Good pharmacovigilance practices Module VII, Section VII.B.2. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129136.pdf

[7] European Medicines Agency 2013. Good pharmacovigilance practices Module V, Section V.B.3. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf

12. Medicinal products requiring additional monitoring

EU legislation requires that recently introduced medicines or other products meeting certain criteria, are listed by the regulatory authorities as requiring additional safety monitoring. These products are identified by the use of an inverted black triangle (▼) on the SmPC and PIL. The following statement must also be printed on the SmPC and PIL: *"This medicinal product is subject to additional monitoring"*, followed by a standard sentence explaining the concept of additional monitoring[8]. These requirements remain in place for a mandatory period of five years, which can be extended.

13. Yellow Card reports

The MHRA's Yellow Card Scheme is the UK's national safety reporting system. Yellow Cards can be completed by HCPs or consumers using either prepaid letter cards or online (www.mhra.gov.uk/yellowcard) or by contacting the Yellow Card information service on 0800 731 6789. Yellow Cards can be downloaded for completion from the MHRA's website or are found, for example, at the back of the British National Formulary.

14. Pharmacovigilance legislation and guidance

The legislation that lays down the obligations of the pharmaceutical industry and regulators regarding PV can be found on the following websites, together with additional information:

Pharmacovigilance in the EU:
The European Medicines Agency is the regulatory authority responsible for PV in the EU.
http://ec.europa.eu/health/human-use/pharmacovigilance/

Good Vigilance Practices:
A series of documents containing measures to facilitate the performance of PV in the EU. Each module covers one major PV process. Location online:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp

Pharmacovigilance in the UK:
The MHRA website contains information on PV in the UK.
www.mhra.gov.uk/Howweregulate/Medicines/Overviewofmedicineslegislationandguidance/Pharmacovigilance/index.htm

ABPI Code of Practice
Relevant sections of the Second 2012 edition of ABPI Code of Practice include Clauses 4.1, 4.10, 15.2, 15.6, 16.2 and 21.1.

[8] European Medicines Agency 2013. Good pharmacovigilance practices Module X. Available at: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129244.pdf

Annex 1: Summary for training purposes

Collection of drug safety information by employees and agents of pharmaceutical companies

It is a legal and ethical requirement to document and report information about the safety of a pharmaceutical company's medicinal products. Drug safety or pharmacovigilance (PV) rules are necessary to protect public health in order to assess, detect and prevent side-effects (adverse drug reactions or adverse events), as the full safety profile of medicinal products can only be known after they have been placed on the market.

Anyone employed directly by the company or contractually, must be vigilant for safety information relating to any of the company's products and must record and report any details to the company's PV department, according to company procedures.

Safety information should normally be reported immediately or at least within one business day of awareness by the employee or agent of the company. The awareness date of the information should always be provided.

The minimum information for a report to be collected is a company product and an adverse event (ie reported side-effect) or special safety situation.

The following information should be collected wherever possible:

- An identifiable reporter (any one or a combination of: reporter's name, occupation or title, address, telephone number, email address or other contact details).
- A company product (promoted or non-promoted or generic if the brand is not known).
- An adverse event or other special safety situation (eg pregnancy, breast feeding, overdose, interactions, product abuse/misuse, medication error, unapproved/off-label use, occupational exposure or lack of therapeutic effect).
- An identifiable patient (ie person who experienced the event identified by any one or combination of: gender, age, date of birth, age group, initials).
- Any other information to describe the course and outcome of the event, eg details of symptoms, severity, duration, treatment and what medical attention (if any) was sought.

Safety information is frequently identified through medical information enquiries and consideration should be given as to whether safety is the basis of any such query. Safety information may also be found in the medical literature, discussed at scientific meetings or displayed in abstracts and posters at symposia. Delegates might also talk about safety information to a company representative if the company has a stand at a scientific meeting or symposium. Safety information obtained in this way must also be collected and reported.

Safety information may also be reported via market research projects, patient support programmes, medical educational grant programmes, non-interventional studies, digital media (websites), etc. Your company's PV department should be contacted to discuss how such information will be handled and collected before such projects are started, in order to ensure that all legal obligations are met.

Safety information associated with the company's products should be collected regardless of:

- Whether or not an adverse event is listed in the summary of medicinal product characteristics (SmPC), patient information leaflet (PIL) or package leaflet (PL).
- Whether the reporter is a healthcare professional (HCP), eg doctor, nurse, pharmacist, dentist or coroner; or non-HCP, eg patient, carer, friend, relative, lawyer, journalist, etc.
- Seriousness or severity of the event.
- Whether or not a causal relationship to the product has been established.
- Whether or not the reporter has already completed a Yellow Card report to the MHRA.

For reports received from non-HCPs, companies may be required to confirm the details with a HCP. You must inform all reporters that the information will be passed to your company's PV department who may contact them or their HCP for further information. If they request any information or have any queries, they should be directed to the company's Medical Information department (or equivalent). If anyone wishes to provide you with safety information, you should collect the information they have provided and ensure any discussions are in line with the ABPI Code of Practice.

It is important to maintain patient confidentiality and to uphold data privacy rules; if information is received containing personal data, the company's internal procedures must be followed to ensure that such confidential personal data is anonymised and managed appropriately.

Overall, the information is used to build up the safety profile of a medicine so that the company can advise prescribers and users of any changes, as necessary, or take any other actions such as:

- updates to the product information: SmPC, PIL or PL
- further clinical studies to define an adverse event
- conducting educational programmes
- issuing special warnings or direct HCP communications
- withdrawal of a medicine from the market in rare circumstances.

Failure to meet these requirements could result in regulatory actions ranging from education and facilitation to implement corrective actions; triggered or "for cause" inspections; issuance of Infringement Notices/ warning letters; urgent safety restrictions, variation, suspension or revocation of marketing authorisations; administrative penalties (fixed fines or fines based on company profits) and referral for criminal prosecution with the possibility of imprisonment. Authorities may also consider making public a list of marketing authorisation holders (MAHs) found to be seriously or persistently non-compliant.

If there is any doubt whether or not any information you receive regarding your company's medicinal products is a report of safety information, you should contact the relevant department immediately to discuss the situation.

Annex 2: Abbreviations

Abbreviation	
ABPI	The Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reaction
AE	Adverse Event
EMA	European Medicines Agency
EU	European Union
HCP	Healthcare Professional
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
PIL	Patient Information Leaflet
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics

Annex 3: Explanation of terms

Adverse Event (AE) – synonym: side-effect

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR)

An ADR is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Special safety situations

All of the following situations associated with the use of a company product should be reported, whether or not there is an associated AE:

- Use during pregnancy, ie drug exposure to a foetus in utero (whether the foetus is exposed via the mother taking the product or transmission via semen following paternal exposure)
- Exposure to a drug during breast-feeding/lactation
- Overdose (whether intentional, accidental or prescribed)
- Drug abuse or misuse
- Medication errors or near misses (including dispensing errors, accidental exposure, maladministration, etc)
- Unapproved or off-label use (ie intentional medical use of a product not in accordance with the authorised product information) including off-label use in children or the elderly.
- Reports of lack of therapeutic effect or other product complaints associated with an adverse event, including suspected use of counterfeit medicine

The following other safety situations should also be reported:

- Drug-drug or drug-food interactions
- Suspected transmission of an infectious agent
- Occupational exposure (as a result of one's professional or non-professional occupation)

Safety information

Any information collected about the safety or efficacy of a pharmaceutical company's medicines.

Expected/Listed and Unexpected/Unlisted Adverse Events/Reactions

ADRs that are known about and documented within the labelling, eg Summary of Product Characteristics (SmPC) for the medicinal product are considered to be expected or listed. Events that are not consistent with the nature, severity or outcome of the events documented within the product's labelling are considered unexpected or unlisted.

Serious and Non-Serious Adverse Events/Reactions

AEs or ADRs may be defined as serious or non-serious according to well-established international criteria. This assessment will be made by the company's PV department.

Pharmacovigilance (PV)

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The underlying objectives of PV are:

- Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure
- Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

PV is therefore an activity contributing to the protection of patients and public health.

Annex 4: Revision history

- Title change from *Collection of adverse event reports – The role of the company representative to Collection of drug safety information by employees and agents of pharmaceutical companies,* to reflect the expanded scope of the guideline.
- Updates throughout the guideline to reflect the changes introduced by EU Regulation No 1235/2010 and Directive 2010/84/EU, adopted by the European Parliament and European Council in December 2010.
- Addition of an 'Overview' as section 1 to give a brief synopsis of pharmacovigilance reporting requirements.
- Addition of a short summary of the guideline for training purposes (Annex 1).
- General reorganisation and restructure of the guideline.

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