EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK - TRANSNATIONAL WORKING GROUPS

ECRIN-TWG

FP6-2005-Life Sciences and Health LSH-2005-3-4

Contract # 037199

DELIVERABLE N° 7

ESTABLISHMENT OF NETWORKS FOR THE DEVELOPMENT OF EU-WIDE POSTMARKETING SURVEILLANCE STUDIES

Date of preparation: 09/09/2008 Draft version n. 1

Working Group 3 **Transnational Working Group on Adverse Events reporting**

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Summary

Abbreviations

AEMPS	Spanish Agency for Medicines and Medical Devices
AIFA	Agenzia Italiana del Farmaco (Italian National Drug Agency)
AMG	Arzneimittelgesetz (German Federal Drug Act)
AFSSAPS	Agence française de Securité Sanitaire des Produits de Santé (french competent authority)
ATU	Temporary Authorisation for Use
CEIC	Clinical Research Ethics Committees
CRC	Clinical Research Centre
CTU	Clinical Trial Unit
CIC	Centre d'Investigation Clinique (French Clinical Investigation Centre)
CNIL	Commission Nationale de l'Informatique et des Libertés
CCTIRS	Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé
CPP	Comite de Protection des Personnes (french research ethics committe)
CTA	Clinical Trial Authorisation
DMA	Danish Medicine Agency
DGS	Direction Générale de la Santé (french General Direction of Heath)
DIMDI	Medical Documentation and Information
DK	Denmark
ECRIN	European Clinical Research Infrastructures Network
ECRIN-PPI	European Clinical Research Infrastructures Network and Biotherapy Facilities: preparation phase for the infrastructure
ECRIN-RKP	European Clinical Research Infrastructure Network – Reciprocal Knowledge
ECRIN-TWG	European Clinical Research Infrastructures Network- Transnational Working Groups
EMEA	European Medicines Agency

EU	European Union
EFCGP	European Forum for Good Clinical Practice
FP	Framework Programme
FR	France
GMP	Good Manufacturing Practice
GTAC	Gene Therapy Advisory Committee
Ger	Germany
GCP	Good Clinical Practice
HU	Hungary
IMP	Investigational Medicinal Product
IR	Ireland
ISS	Instituto Superiore della Sanita
It	Italy
KKS	Koordinierungszentrum für Klinische Studien (German national network)
MPA	Swedish Medical Products Agency
NHS	National Health System
PEI	Paul- Ehrlich-Institute (German competent authority)
PI	Principal Investigator
PIAG	Patient Information Advisory Group
QA	Quality Assurance
QM	Quality Management
REC	Research Ethics committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Sp	Spain
Sw	Sweden

Definitions

CA: Competent authority

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities. *(ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*).

Multicentre CT: Multicenter Clinical trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries. (*Directive 2001/20/EC*)

CTA: Clinical trial authorisation

An authorisation of a clinical trial by the competent authority of a Member State will be a Clinical Trial Authorisation (CTA) and will only be valid for a clinical trial conducted in that EU Member State. This authorisation does not imply approval of the development programme of the tested IMP. *(EU Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial)*

CTAA: Clinical trial authorisation application (often shortened to CTA)

According to Article 9(2) of the Directive the applicant must submit a valid request for authorisation to the competent authority. *(EU Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial)*

EC: Ethics committee

An independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent. (*Directive 2001/20/EC*)

ECRIN: European Clinical Research Infrastructures Network

Based on the interconnection of national networks of academic clinical research infrastructures, the European Clinical Research Infrastructures Network (ECRIN) is designed to bridge the fragmented organisation of European clinical research and to develop an integrated EU-wide clinical research infrastructure.

EudraCT: Clinical trial data base for the Regulatory Authorities in EU

GMO: Genetically modified organism

Means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination; (*Directive on the Deliberate Release into the Environment of Genetically Modified Organisms 2001/18/EG*).

IMP: Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. (*Directive 2001/20/EC*)

However, as the transposition of this definition differs from one country to other, ECRIN SOPs use the term "Medicinal Product". Please see the document "*Deliverable 4: Clinical Research in Europe: national differences in legislative and regulatory framework*" for further information.

ICF: Informed Consent Form

Decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation. (*Directive 2001/20/EC*)

Investigator: a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator. (*Directive 2001/20/EC*)

MS: Member State

Country involved in ECRIN.

SOP: Standard Operating Procedure

Detailed, written instructions to achieve uniformity of the performance of a specific function. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*).

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (*Directive 2001/20/EC*)

Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*).

Subinvestigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*)

Subject: an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control (*Directive 2001/20/EC*)

Within ECRIN framework, the term *participant* seems more adequate because includes both patients (clinical trial subjects) and healthy volunteers

Background

Preliminary consideration

In order to collect data from partner Countries an on-line questionnaire has been designed. Since the deliverables N° 6 & (in part) 7 and 8 required to collect data from the same partners, a unique questionnaire has been designed to avoid duplication and risk of drop-outs.

The survey designed for regulatory requirements for vigilance systems in ECRIN countries is therefore comprehensive of the questions related to:

Deliverable N° 6 & (in part) 7 and 8

- Survey of implementation practice of adverse event reporting in Europe for drugs
- Survey of adverse event reporting practice for non drug intervention

Deliverable 7 - Establishment of networks for the development of EU-wide postmarketing surveillance studies,

Deliverable 8 - A report on the computerization of adverse event reporting

Premises

For an introduction regarding the WP3 activity and more details concerning the survey (that allows collecting data as reporting in the Preliminary Considerations section) please see the ***Deliverable N° 6***.

Considerations on the analysis on results

Introduction

In relation to the specific data required by the deliverable n°7 the sections of the questionnaire selected were:

Section 1 PhV System Organisation

Question 1.01
Is there a Central Reporting Facility for SUSARs?
Question 1.06
Is a standard reporting form imposed?
Question 1.07
Is casuality algorithm imposed

Section 2 PhV Stakeholders

Question 2.01
Subject; Patient; Volunteer; Consumer
Question 2.02
Doctors and Health Professionals (observing physician; observing healthcare professional; observing caregiver; family physician; healthcare institution; investigator).
Question 2.03
Specific Vigilance center.
Question 2.04
Local Health Authorities.
Question 2.05
National/regional Health Authorities (Ministry of Health, Product Agency).
Question 2.06
Supranational Health Authorities (e.g. WHO, EMEA).
Question 2.07
Ethical Committee (local and national/regional). Are Disease Oriented Ethical Committees present?
Question 2.08
Sponsor or Market Authorisation Holders.
Question 2.09
Manufacturer.
Question 2.10
Pharmacist/Distributor.

A relevant consideration has to be done as regarding to the Phase IV of clinical trial, since in some country Phase IV is considered, as it should be, under the sector

of pre-marketing area in other Countries in the post-marketing; accordingly to same data may fit in deliverable 6 as well as in deliverable 7.

Data model

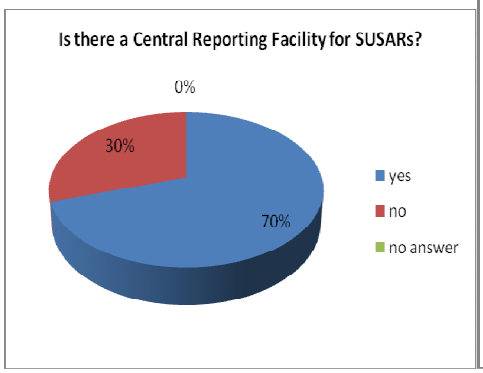
See the same section in Deliverable N° 6 document.

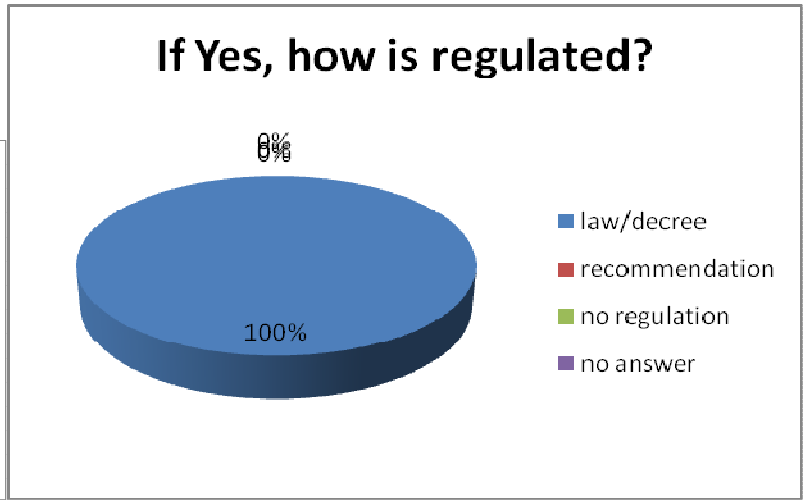
Data representation

In order to achieve WP3 goals related to deliverable N° 7 here we report the data from the sections and the specific items selected. The results were presented below.

Item N°1

Survey Question 1.01
Is there a Central Reporting Facility for SUSARs?



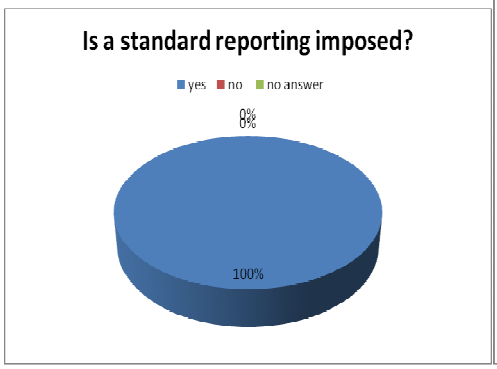


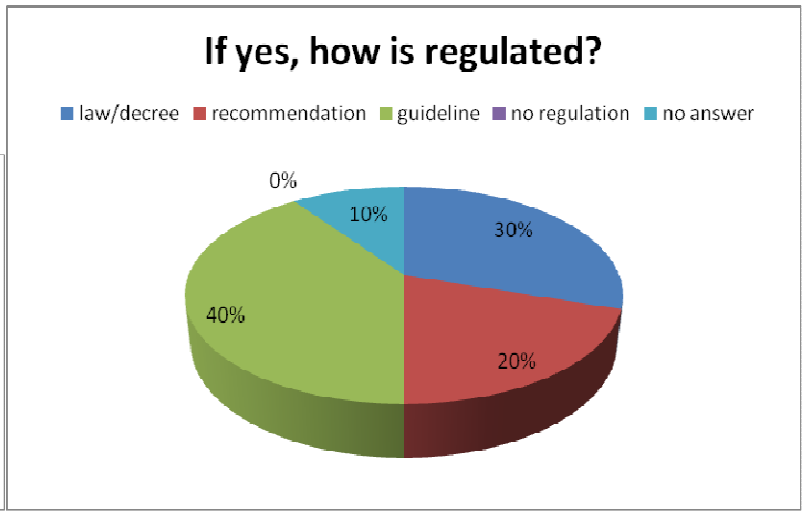
The result of the survey shows a 30% of the countries that seem to have no Central Reporting Facility for SUSARs. With a more deep analysis we could see that 2 countries (Hungary and Sweeden) have anyway a type of reporting (Sweeden has a direct reporting to EudraVigilance). This does it mean that 90% of countries have a reporting system for SUSARs. The important data is that in the 100% of countries (that have a reporting system for SUSARs) the process is regulated by law/decree.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	yes	yes	yes	-
Denmark	**yes**	yes	yes	yes	-
France	**no**	-	-	-	-
Germany	**yes**	yes	yes	yes	-
Hungary	**no**	-	-	-	reporting compulsory to NIP
Ireland	**yes**	yes	yes	yes	-
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**no**	-	-	yes	
UK	**yes**	yes	yes	yes	-

Item N°2

Survey Question 1.06
Is a standard reporting form imposed?



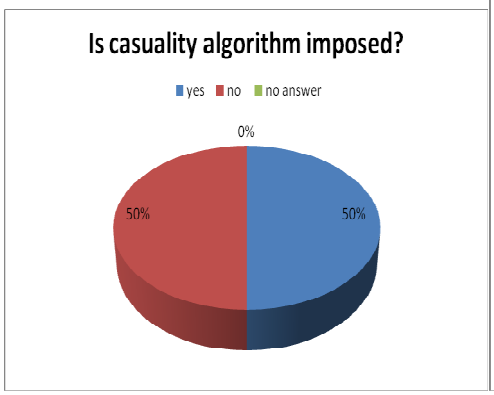


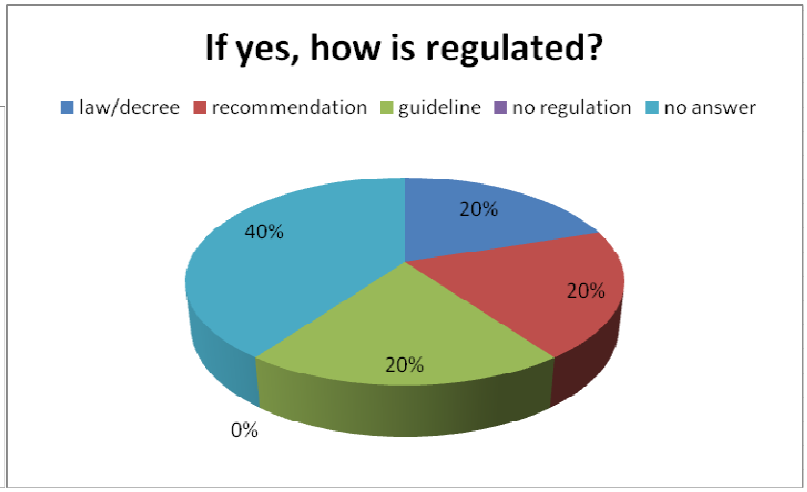
The result of the survey is that in the 100% of countries a standard reporting form is imposed also if with different approaches (law/decree – 20%, recommendation – 40%, guideline – 30%). Only one country (Hungary) didn't give any specification about how the issue is regulated.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	-	yes	yes	Other procedures/guidelines
Denmark	**yes**	-	yes	yes	Other procedures/guidelines
France	**yes**	-	yes	yes	recommendation
Germany	**yes**	-	yes	yes	guideline
Hungary	**yes**	-	-	-	-
Ireland	**yes**	-	yes	unknown	recommendation
Italy	**yes**	yes	yes	unknown	-
Spain	**yes**	yes	yes	yes	-
Sweden	**yes**	yes	yes	yes	-
United K	**yes**	-	-	unknown	guideline

Item N°3

Question 1.07
Is casuality algorithm imposed?



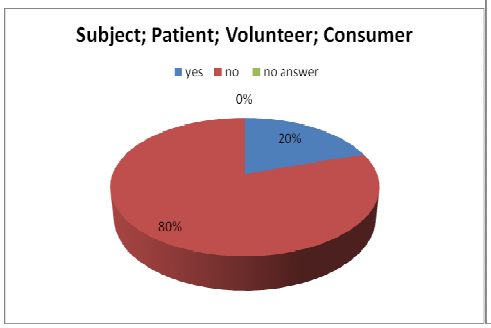


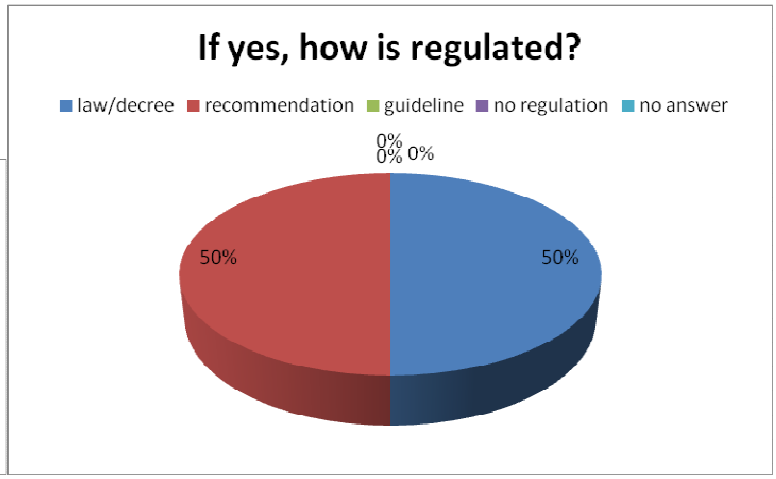
In this case we have a balanced situation (50% yes and 50% no). The further analysis of the yes data shows that we have different approaches: law/decree – 20%, reccomandation – 20%, guideline - 20%. We have also a significant percentage of countries that didn't give any specification about how the issue is regulated.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**no**	-	-	-	-
Denmark	**no**	-	-	-	-
France	**Yes**	-	-	-	Other procedures
Germany	**no**	-	-	-	-
Hungary	**no**	-	-	-	-
Ireland	**yes**	-	-	-	Other procedures
Italy	**yes**	-	-	-	Reccomandation
Spain	**no**	-	-	-	-
Sweden	**yes**	yes	yes	yes	-
United K	**yes**	-	-	unknown	guideline

Item N°4

Survey Question 2.01
Subject; Patient; Volunteer; Consumer.
The question was chosen in relation to the consideration that the adverse event reporting is clearly subjected to whom is presenting and sending the report.



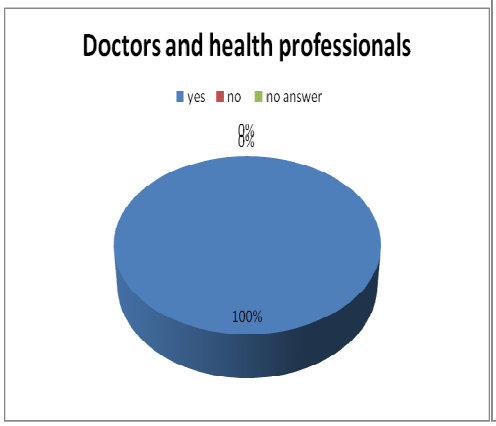


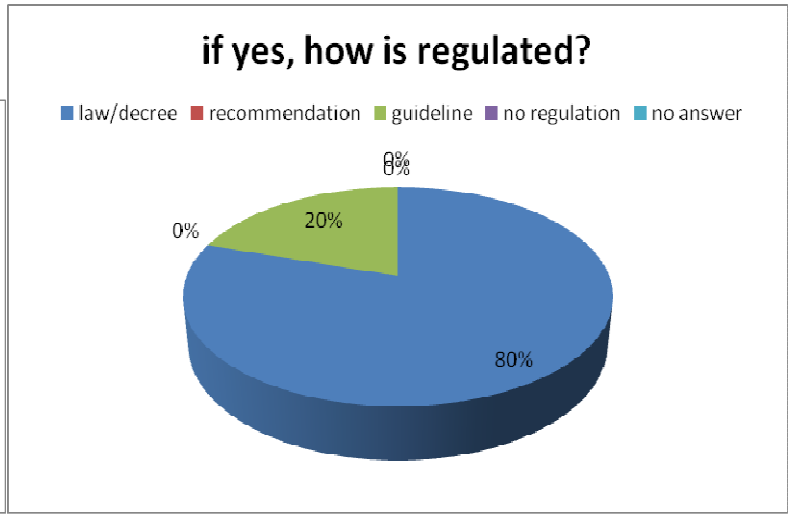
In this case we have a very significant percentage of countries (80%) that answered "no" to the question. The further analysis shows us that the regulation, in the remaining 20% of countries, is balanced beetwen law/decree (50%) and reccomandation (50%). We have also to notice that Denmark answered "yes" to main question also if declared that there is no obligation. In our analysis we considered that Denmark answered "no" to main question in order to have homogeneus data with other countries.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**no**	-	-	-	not mentioned
Denmark	**yes**	-	-	-	no obligation
France	**no**	-	-	-	no obligation
Germany	**no**	-	-	-	no obligation
Hungary	**no**	-	-	-	no obligation
Ireland	**no**	-	-	-	patient to health care professional
Italy	**yes**	yes		yes	patient
Spain	**no**	-	-	-	not mentioned
Sweden	**no**	-	-	-	patient to health care professional
United K	**yes**	-	-	unknown	recommendation

Item N°5

Survey Question 2.02
Doctors and Health Professionals (observing physician; observing healthcare professional; observing caregiver; family physician; healthcare institution;



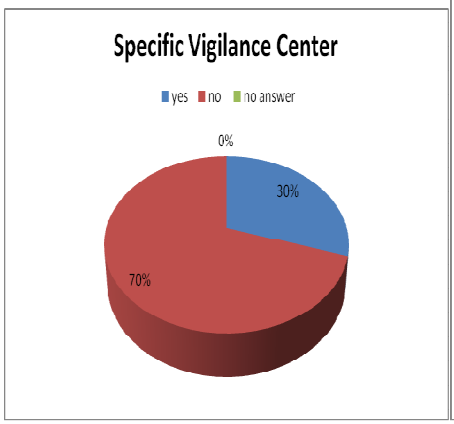


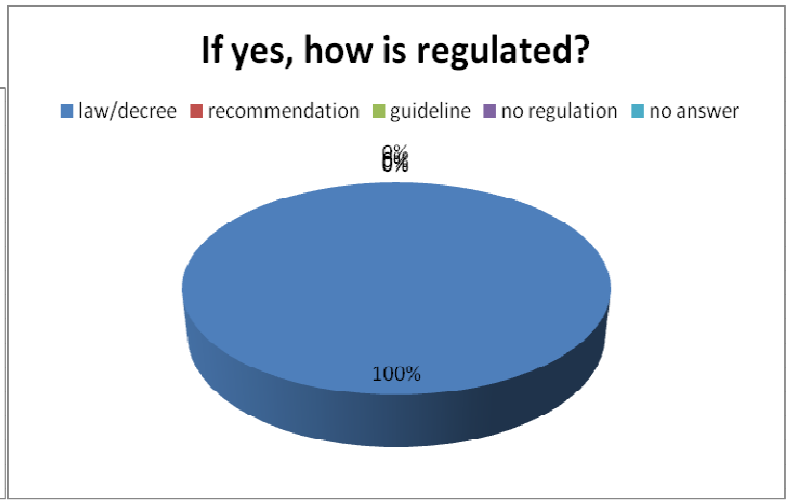
The result of the survey is that the 100% of countries answered "yes" to the main question also if the further analysis shows different approaches (law/decree – 80%, guideline – 20%). The percentage where the issue is regulated by law/decree in very significant (80%).

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	yes	yes	yes	
Denmark	**yes**	-	yes	yes	Other procedures/guidelines
France	**yes**	yes	yes	yes	
Germany	**yes**	-	yes	yes	Other procedures/guidelines
Hungary	**yes**	yes	yes	yes	procedure of the NIP
Ireland	**yes**	yes	yes	yes	-
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**yes**	yes	yes	yes	-
United K	**yes**	yes	yes	yes	-

Item N°6

Survey Question 2.03
Specific Vigilance centre



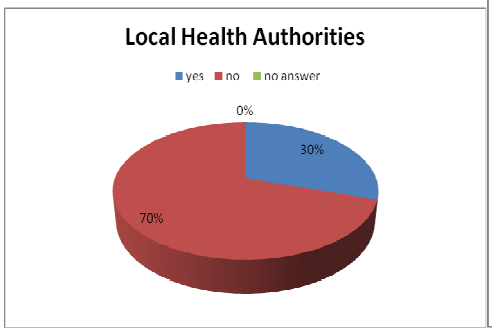


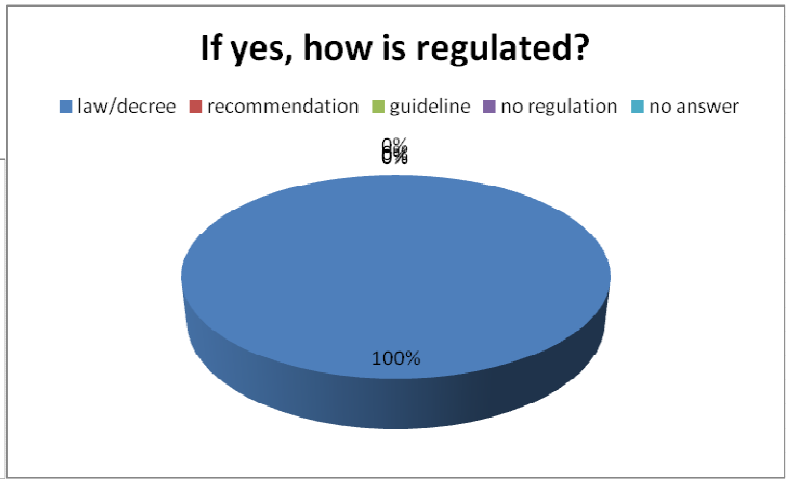
In this case we have a significant percentage of countries (70%) that answered "no" to the question. The further analysis shows us that the regulation, in the remaining 30% of countries, is by law/decree. We have also to notice that 5 countries (Austria, Denmark, Hungary, Sweden and Ireland) answered "no" but they declared that they have a other procedures, i.e the central agency.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**no**	yes	yes	yes	Natl Agency
Denmark	**no**	-	-	-	DMA Agency
France	**yes**	yes	yes	yes	sponsor
Germany	**no**	-	-	-	-
Hungary	**no**	-	-	-	NIP
Ireland	**no**	yes	yes	yes	IMB
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**no**				Swedish MPA-
United K	**no**	-	-	-	-

Item N°7

Survey Question 2.04
Local Health Authorities



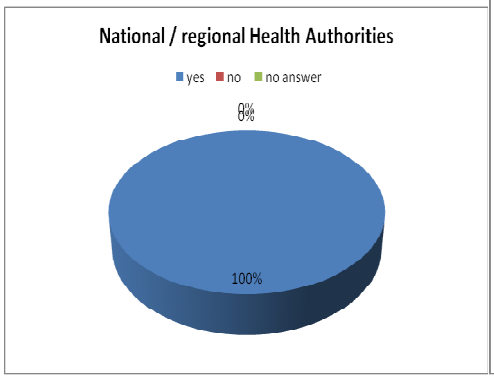


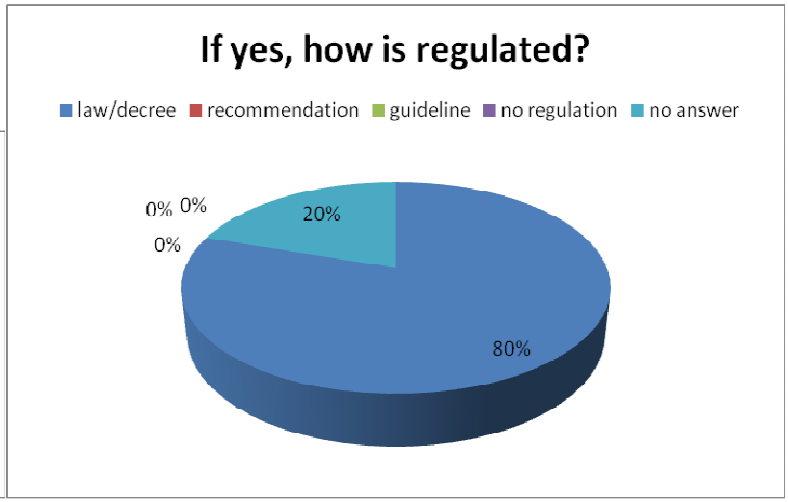
We have a very significant percentage of countries (70%) that answered "no" to the question. The further analysis shows us that the regulation, in the remaining 30% of countries, is always regulated by law/decree. We have also to notice that Denmark answered "no" to main question also if declared that they have a regulation by law/decree. In our analysis we considered that Denmark answered "no" to main question.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**no**	-	-	-	not mentioned
Denmark	**no**	yes	yes	unknown	DMA Agency
France	**no**	-	-	-	ONLY one competent authority the AFSSaPS
Germany	**yes**	yes	yes	yes	-
Hungary	**no**	-	-	-	-
Ireland	**no**	-	-	-	not mentioned
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**no**	-	-	-	-
United K	**no**	-	-	-	-

Item N°8

Survey Question 2.05
National/regional Health Authorities (Ministry of Health, Product Agency).



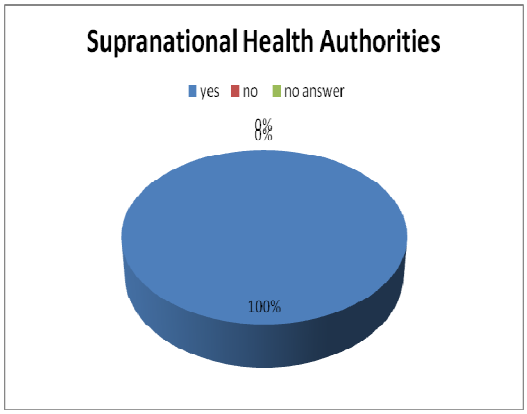


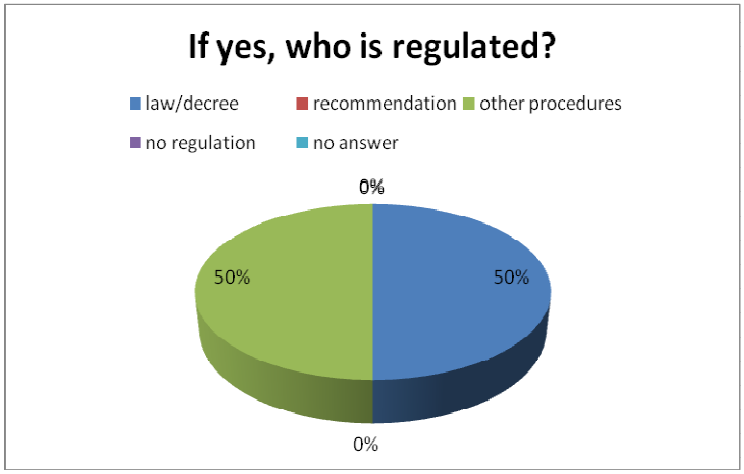
The result of the survey is that the 100% of countries answered "yes" to the main question. The further analysis shows the in the 80% of countries the issue is regulated by law/decree. the remaining 20% of countries didn't give any answer.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	yes	yes	yes	-
Denmark	**yes**	-	yes	unknown	-
France	**yes**	yes	yes	yes	-
Germany	**yes**	yes	yes	yes	-
Hungary	**yes**	yes	yes	yes	-
Ireland	**yes**	-	-	unknown	Other procedures/guidelines
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**yes**	yes	yes	yes	-
United K	**yes**	yes	yes	yes	-

Item N°9

Survey Question 2.06
Supranational Health Authorities (e.g. WHO, EMEA).



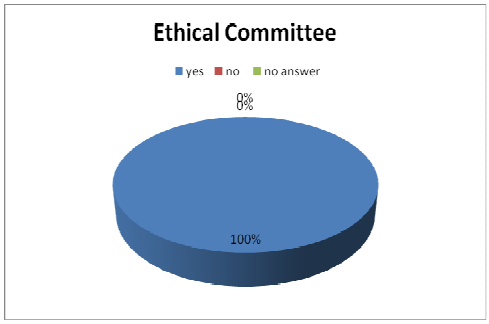


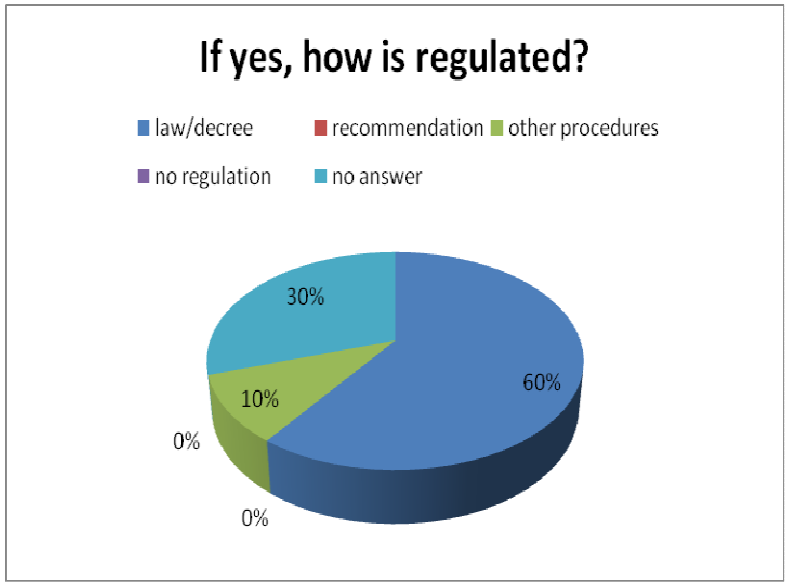
The result of the survey is that 100% of the ECRIN countries answered "yes" to the main question also if with different approaches (law/decree – 50%, other procedures – 50%). We have also to notice that Austria has to be considered as "no" to main question but they have other procedures/guideline, so we considered that Austria answer "yes" to main question.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**no**	-	-	unknown	Other procedures/guidelines
Denmark	**yes**	-	-	yes	Other procedures/guidelines
France	**yes**	yes	yes	yes	-
Germany	**yes**	yes	yes	yes	-
Hungary	**yes**	-	-	yes	Other procedure
Ireland	**yes**	-	-	-	other procedure
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**yes**	-	-	-	other procedure
United K	**yes**	yes	yes	yes	-

Item N°10

Survey Question 2.07
Ethical Committee (local and national/regional). Are Disease Oriented Ethical Committees present?



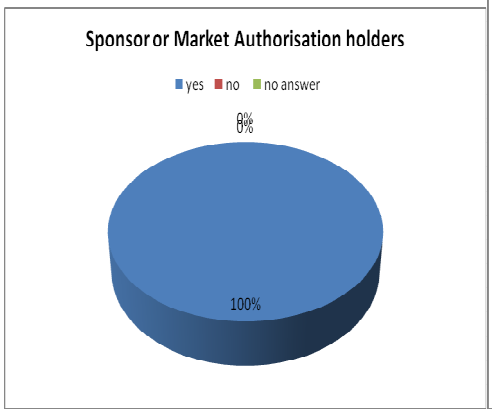


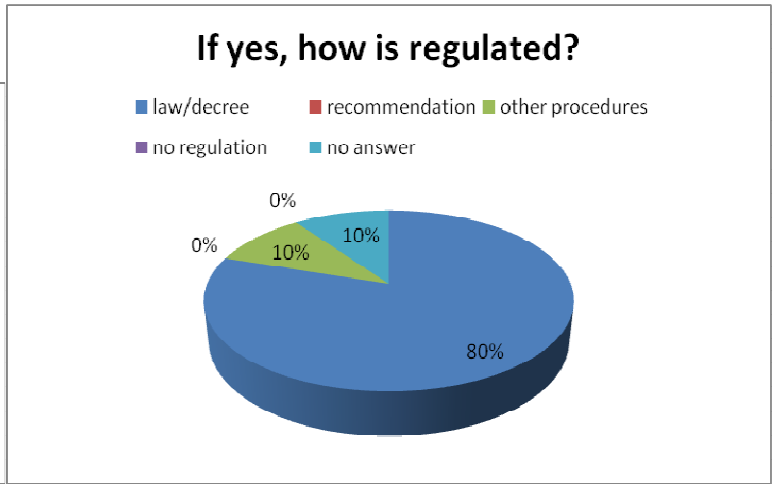
We supposed that the answer is related to the first part of the question. The result of the survey is that the 100% of the countries answered "yes" to the main question also if with different approaches (law/decree – 60%, other procedures – 10%). We have also a 30% of countries that dind't give any more specification (no answer).

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	yes	yes	yes	-
Denmark	**yes**	yes	yes	yes	-
France	**yes**	yes	yes	yes	-
Germany	**yes**	yes	yes	yes	-
Hungary	**yes**	-	yes	yes	Other procedure
Ireland	**yes**				
Italy	**yes**	yes	yes	yes	-
Spain	**yes**				
Sweden	**yes**	yes	yes	yes	-
United K	**yes**	yes	yes	yes	-

Item N°11

Survey Question 2.08
Sponsor or Market Authorisation Holders



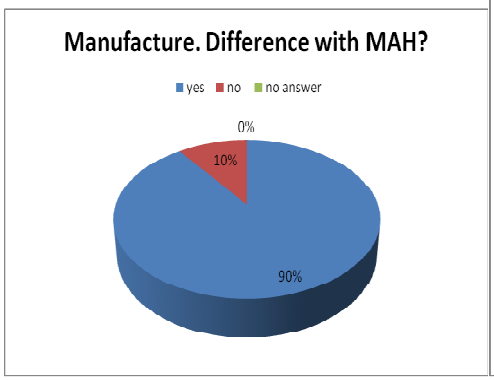


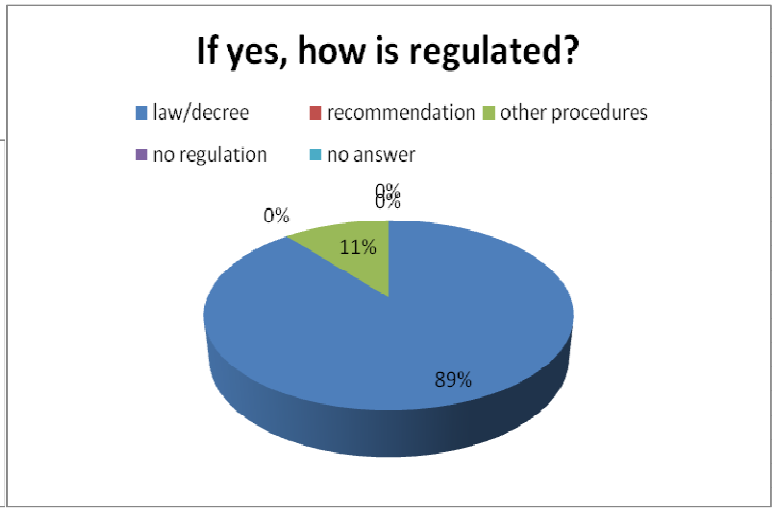
The result of the survey is that the 100% of the countries answered "yes" to the main question also if with different approaches (law/decree – 80%, other procedures – 10%). We have also a 10% of countries that dind't give any more specification (no answer).

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	yes	yes	yes	-
Denmark	**yes**	yes	yes	yes	-
France	**yes**	yes	yes	yes	-
Germany	**yes**	yes	yes	yes	-
Hungary	**yes**	-	-	-	other procedure
Ireland	**yes**	-	yes	yes	-
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**yes**	yes	yes	yes	-
United K	**yes**	yes	yes	yes	-

Item N°12

Survey Question 2.09
Manufacturer.Difference with MAH?



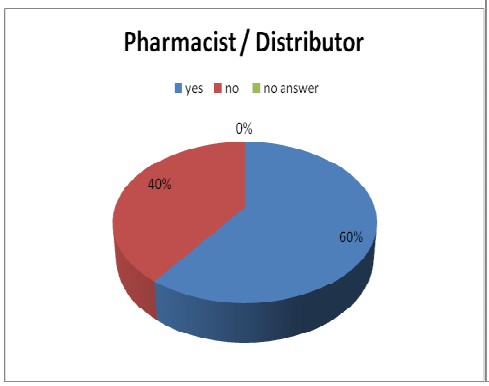


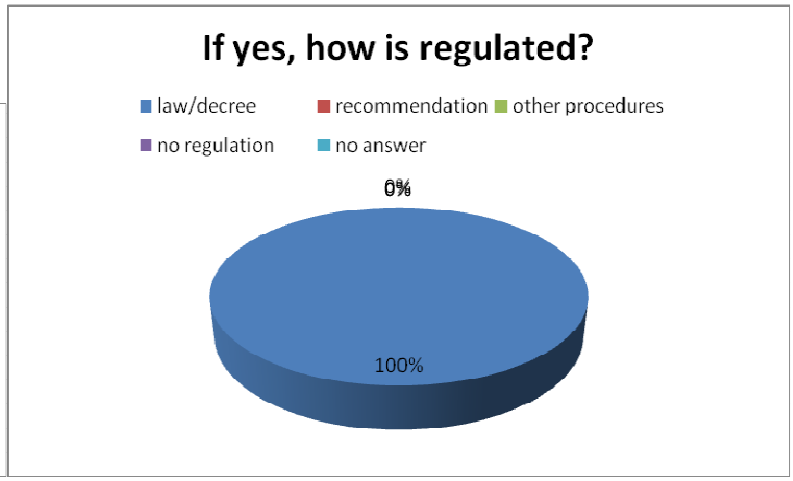
The result of the survey is that the 90% of the countries answered "yes" to the main question also if with different approaches (law/decree – 89%, other procedures – 11%).

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	yes	yes	yes	-
Denmark	**yes**	-	yes	unknown	other procedure
France	**yes**	yes	yes	yes	-
Germany	**no**	-	-	-	-
Hungary	**yes**	yes	-	yes	the same procedure to NIP
Ireland	**yes**	yes	yes	yes	-
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**yes**	yes	yes	-	-
United K	**yes**	yes	yes	yes	-

Item N°13

Survey Question 2.10
Pharmacist/Distributor





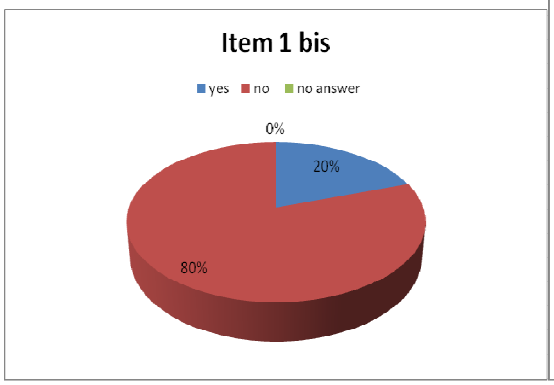
We have an important percentage of countries (40%) that answered "no" to the question. The further analysis shows us that the regulation, in the remaining 60% of countries, is always regulated by law/decree.

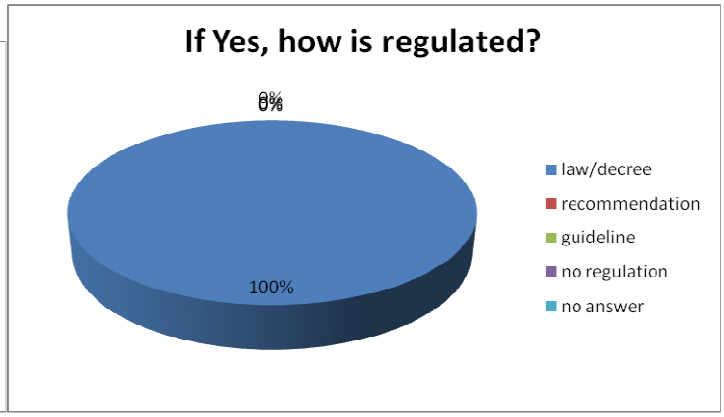
		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**yes**	yes	yes	yes	-
Denmark	**yes**	yes	yes	yes	-
France	**yes**	yes	yes	yes	-
Germany	**no**	-	-	-	-
Hungary	**yes**	yes	-	unknown	-
Ireland	**no**	-	-	-	-
Italy	**yes**	yes	yes	yes	-
Spain	**yes**	yes	yes	yes	-
Sweden	**no**	-	-	-	-
United K	**no**	-	-	-	-

Item 13 bis

A specific consideration has to be made about the distinction in term of notification of adverse reaction according to the fact that the signalling occurs during Phase IV or as general post-marketing.

Pre- e post marketing differences





The analysis showed that only France and Germany make a distinction between pre- and post-marketing and this choice is supported by distinct governmental laws.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*
Austria	**no**	-	-	-	-
Denmark	**no**	-	-	-	-
France	**yes**	yes	yes	-	-
Germany	**yes**	yes	yes	-	-
Hungary	**no**	-	-	-	-
Ireland	**no**	-	-	-	-
Italy	**no**	-	-	-	-
Spain	**no**	-	-	-	-
Sweden	**no**	-	-	-	-
United K	**no**	-	-	-	-

Conclusions

Deliverable 7: Guidelines

- Establishment of networks for the development of EU-wide postmarketing surveillance studies, that involve collaboration between clinicians, regulatory bodies, and pharmaceutical companies.

According to the results of the survey, we observe that vigilance systems in all countries rely on the notification of adverse events both by the marketing authorization holder (MAH), that must declare at the Governmental Agency the adverse effects or directly to EudraVigilance the information obtained by themselves or from the health professionals and/or investigators.

The procedures are relatively similar for MAH in all countries (see diagrams in deliverable 6), because they are obliged also to report to EudraVigilance., However, divergences exist from country to country and require implementation for harmonisation.

One point concern norms: although a standard for reporting is used in all EU MSs the standard itself is not identical and in some cases not even similar. In order to harmonize the system, MSs should firstly be encouraged to use a similar standard and, not secondly, to used algorithms to define causality of adverse event.

A second point relates to some specifications:

- Definition of Seriousness criteria on 'Important Medical Events' is not included in the list of seriousness criteria defined in Directive 2001/20/EC and not addressed as such in Detailed Guidance ENTR/CT 3 but is required to assist the seriousness assessment in clinical trials of reactions which fall outside the 5 seriousness criteria defined in Directive 2001/20/EC

- Definition of Unexpected Adverse Drug Reactions (ADRs); depending on sponsor procedures, an ADR may be included in IB and considered expected after it has been reported only once or after assessment of several reports

- In relation to Adverse Drug Reactions causality assessment is required either the need of the determination of a causality assessment between an Adverse Event (AE) and an IMP or clearly define the rule as to which causality assessment should be taken into account when there is disagreement between investigator and sponsor

A third point is on the organizational nature. In order to have correct statistics, also related to EudraVigilance system, it is necessary that the stakeholders that can report adverse events are the same in all MSs. It is necessary therefore to foster the similar reporting capacity of different parties who ,at present, are reporting only in some MSs, in particular nurses, pharmacists and patients. With regard to this last group, it has to be defined also

whether patients can report by themselves or whether they have to go to their own doctor to report together the adverse event.

Last, but not least, between doctors and competent national authority, there exists in some MSs Centres that mediate reporting. Although this may be useful for translating the report from paper to electronic systems, it may represent a mediator that can modify the original report and might be one of the causes of reduced NCA reporting to EudraVigilance. Further guidance for vigilance centres is required in order to harmonize reporting to EudraVigilance.

The implementation needed to overcome the disharmony requires specific intervention from the Commission; it is hoped that the new Directive in course of consultation might include some of the issues highlighted in the present survey.

The software program, that allows to manage the survey and the questionnaire, was built up as an open system in order to manage in the future other and new ECRIN countries data and information or as well other different surveys and investigations.

Appendix

Notes

The documents are available on the questionnaire online at the address of the European Correspondent (and expert) of the single Country and on the address:
http://www.cirm.net/wp3/login.php
Username: fsavarese
Password: admin
The questionnaire allows to consultation data for each Country, the answers for single question and the data for the partners for each Country.

Questionnarie Sections

We report below the 4 sections forecasted by the survey.

Section 1 PhV System Organisation

Question 1.01
Is there a Central Reporting Facility for SUSARs?
Question 1.02
Is Electronic Reporting available? How is it regulated? Is the purchase of MedDRA publicly restricted? How MedDRA training in delivered (free/other fees)? Other coding system are used?
Question 1.03
Is coding with MedDRA required/recommended? Is the purchase of MedDRA publicly subsidised? How MedDRA training is delivered (free/other fees)? Other coding system are used?
Question 1.04
Is EudraVigilance Reporting mandatory? Who must report?
Question 1.05
Is Education and Training in Vigilance required/recommended? For whom? How much? Is certificate required for certain stakeholders?
Question 1.05.1
Are the EMEA London Eudravigilance coursers mentioned? Is attendance subsidised by the public sector?
Question 1.05.2
Are there national courses about Vigilance reporting? Please specify (academic, private, government, with website or reference).
Question 1.06

Is a standard reporting form imposed?
Question 1.07
Is casuality algorithm imposed

Section 2 PhV Stakeholders

Question 2.01
Subject; Patient; Volunteer; Consumer
Question 2.02
Doctors and Health Professionals (observing physician; observing healthcare professional; observing caregiver; family physician; healthcare institution; investigator).
Question 2.03
Specific Vigilance center.
Question 2.04
Local Health Authorities.
Question 2.05
National/regional Health Authorities (Ministry of Health, Product Agency).
Question 2.06
Supranational Health Authorities (e.g. WHO, EMEA).
Question 2.07
Ethical Committee (local and national/regional). Are Disease Oriented Ethical Committees present?
Question 2.08
Sponsor or Market Authorisation Holders.
Question 2.09
Manufacturer.
Question 2.10
Pharmacist/Distributor.

Section 3A Adverse Event Reporting Regulation - By medical research type

Question 3.A.01
Clinical Trials on Medicinal Products.
Question 3.A.01.1
Phase I, II, III, IV.
Question 3.A.01.2
Specific Interventions.
Question 3.A.02
Clinical Research on Medical Devices.

Question 3.A.03
Other Therapeutic Trials.
Question 3.A.04
Diagnostic studies.
Question 3.A.05
Clinical Research on Nutrition.
Question 3.A.06
Other CLinical Research.
Question 3.A.07
Epidemiology/observational studies

Section 3B Adverse Event Reporting Regulation - By product category

Question 3.B.01
Biovigilance.
Question 3.B.02
Cosmetovigilance.
Question 3.B.03
Haemovigilance.
Question 3.B.04
Pharmacovigilance.
Question 3.B.05
Medical Devices Vigilance.
Question 3.B.06
Toxicovigilance (add specification about subject: drug abuse or therapeutical use).