



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 8 March 2001
CPMP/PhVWP/2058/99 rev 1

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)
&
EudraVigilance Technical Implementation Group (EV-TIG)**

**JOINT PHARMACOVIGILANCE PLAN
FOR THE IMPLEMENTATION OF THE ICH E2B, M1 AND M2
REQUIREMENTS RELATED TO THE ELECTRONIC TRANSMISSION
OF INDIVIDUAL CASE SAFETY REPORTS IN THE COMMUNITY**

**(FORMER JOINT PILOT PLAN FOR THE IMPLEMENTATION OF THE ELECTRONIC
TRANSMISSION OF INDIVIDUAL CASE SAFETY REPORTS BETWEEN THE EMEA, NATIONAL
COMPETENT AUTHORITIES AND PHARMACEUTICAL INDUSTRY)**

DISCUSSION AT THE PHARMACOVIGILANCE WORKING PARTY (PhVWP)	June 1999
ADOPTION AT THE PHARMACOVIGILANCE WORKING PARTY (PhVWP)	July 1999
APPROVED BY THE CPMP	July 1999
REVISION SUBMITTED FOR DISCUSSION AT THE EUDRAVIGILANCE TELEMATICS IMPLEMENTATION GROUP AND THE JOINT PILOT IMPLEMENTATION GROUP	December 2000
ADOPTED AT THE EUDRAVIGILANCE TELEMATICS IMPLEMENTATION GROUP	March 2001
SUBMISSION FOR ADOPTION AT THE PhVWP	April 2001
SUBMISSION FOR APPROVAL BY THE CPMP	April 2001

Background Information

Taking into account the new developments in the area of electronic data exchange in pharmacovigilance resulting from the ICH activities, the EMEA, National Competent Authorities and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), agreed to streamline the current operations and regulatory procedures and to increase the level of their co-operation. This revised document is a result of the joint effort of all parties involved to define the basis for the testing *and* implementation of the ICH standards i.e. MedDRA (M1), the data elements (E2B) and the message specifications (M2), related to the electronic transmission of Individual Case Safety Reports (ICSRs) in the Community. The results of the first year of the joint pilot activities are presented. The previous pilot testing exercise is extended in a way to ensure the implementation of the ICH standards by all parties involved allowing for the start of the regular electronic submission of ICSRs in pharmacovigilance.

I. INTRODUCTION

As a result of the first Joint Pilot meeting on the Electronic Transmission of Individual Case Reports (ICSRs) held on 14 April 1999 in London, the EMEA, National Competent Authorities and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), committed themselves to exchange pharmacovigilance information electronically.

To achieve this task it was agreed to streamline the operations and regulatory procedures, to increase the level of co-operation between all parties involved and to elaborate a Joint Pilot Plan (JPP) to support these activities.

A pilot group was formed to prepare the content of this JPP (CPMP/PhVWP/2058/99), which was adopted by the Committee for Proprietary Medicinal Products (CPMP) in July 1999. The purpose of the JPP was to support the joint pilot by defining its objectives, the procedure, the structure and the role of the Joint Pilot Group, as well as responsibilities of the EMEA, National Competent Authorities of Member States and pharmaceutical companies.

The pilot, which started in November 1999, was a trial on voluntary basis, interested parties who wished to participate were requested to submit a Declaration of Intent to the EMEA.

The legal obligations related to the reporting of adverse reactions remained unaffected by the pilot i.e. the current way of the regulatory submission of adverse reaction reports continued during the participation in the pilot.

Considering the very promising results achieved within the first year it was proposed by the Joint Pilot Group to revise the scope of the joint pilot and the group's current activities. During the 5th Joint Pilot meeting held in September 2000 at the EMEA, it was agreed to extend the joint pilot's objectives and the group's mandate from the current testing to the final implementation of the ICH E2B (data elements), M1 (MedDRA) and M2 (message specifications) standards in the area of pharmacovigilance.

This revised plan reflects the joint pilot results achieved in 2000, the joint pharmacovigilance activities for 2001 and beyond and the roles and responsibilities of all parties involved. It is an important contribution to ensure the final implementation of the ICH standards related to the electronic transmission of Individual Case Safety Reports between the EMEA, National Competent Authorities and pharmaceutical industry in the area of pharmacovigilance.

II. THE EUDRAVIGILANCE TECHNICAL IMPLEMENTATION GROUP

Based on the decisions of the Telematics Steering Committee (TSC), the management group set up at Community level to define the strategic issues of all IT projects at Community level, the EudraVigilance TIG was established in June 2000. This group is a technical group of IT experts and pharmacovigilance representatives. It deals with the practical and technical implementation of the decisions and strategies as decided by the Telematics Steering Committee (TSC) to ensure the achievement of the EudraVigilance project goals and objectives as described above. The EudraVigilance project includes both EudraVigilance (the development of the Community pharmacovigilance system) and the European Joint Pilot Programme for Individual Case Safety Reports.

The EudraVigilance TIG defines the requirements of the specific projects and further ensures coherence between the different Eudra telematics projects, their compliance with the relevant legislation and the agreed timetables. The EudraVigilance TIG reports back to the Telematics Management Committee (TMC) and regularly updates both, the Human and Veterinary Pharmacovigilance Working Party, on the progress being made.

The EudraVigilance TIG is a technical group composed of pharmacovigilance and IT experts. The 26 National Agencies have nominated one expert (1 Expert by Agency either IT or a pharmacovigilance representative) who is co-ordinating all project related issues at national level (please refer to Annex A).

The Joint Pilot Group is a subgroup of the EudraVigilance TIG.

III. JOINT PILOT RESULTS: NOVEMBER 1999 - NOVEMBER 2000

II.1. Joint Pilot Group

Following the joint meeting between the EMEA CPMP PhVWP and the EFPIA ad hoc PhVWP in April 1999, 5 joint pilot meetings were organised at the premises of the EMEA in London until the end of 2000. The meetings were chaired by a representative of the European Commission, Directorate General, Pharmaceuticals and Cosmetics Unit.

Transparency was a major issue since the start of the pilot. The Joint Pilot meetings were open to all pharmaceutical companies having a medicinal product authorised within the Community and to all National Competent Authorities. As a result, the membership of the original Joint Pilot Group (4 representatives from EFPIA and National Competent Authorities, 2 representatives from the European Commission and from the EMEA) increased substantially.

Since the actual start of the joint pilot in November 1999, representatives from seven Member State Authorities and 17 pharmaceutical companies (table 1) have committed themselves to participate in the joint pilot, including one representative of the MedDRA Maintenance and Support Service Organisation (MSSO), who was following the activities.

Although many participants were not yet ready to actively test the electronic transmission of ICH E2B and M2 messages, the approach permitted all parties to follow the experience with others who were ready for testing with the EMEA, to streamline the pharmacovigilance procedures related to the electronic adverse reaction reporting and to provide, at an early stage, for technical adjustments within the locally established pharmacovigilance systems where necessary.

Table 1: Participating National Competent Authorities and Pharmaceutical Companies:
Joint Pilot November 1999- November 2000

Pilot Participants: National Competent Authorities
Agence Française de Sécurité Sanitaire des Produits de Santé (ASSAPS), France
Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Germany
Denmark Lægemiddelstyrelsen, Denmark
Instituto Nacional da Farmácia e do Medicamento (INFARMED), Portugal
Medicines Control Agency, United Kingdom
Ministerio della Sanità, Italy
College Ter Beoordeling van Geneesmiddelen, The Netherlands

Pilot Participants: Pharmaceutical Industry
Abbott France Laboratories, France
AstraZeneca, United Kingdom
Aventis, France
Bayer Vital GmbH & Co., Germany
Bristol-Meyers Squibb, Belgium
Eli Lilly and Company Limited, United Kingdom
GlaxoWellcome, United Kingdom
Lundbeck A/S, Denmark
Merck Sharp & Dohme (MSD), United Kingdom and United States
Novartis, United Kingdom
N.V. Organon, The Netherlands
Pasteur Merieux MSD, France
Pfizer, France

Pilot Participants: Pharmaceutical Industry
Procter & Gamble Pharmaceuticals, United Kingdom
Roche Products Ltd., United Kingdom and United States
Schering Plough Europe, United Kingdom
Yamanouchi Europe, The Netherlands

In the frame of these meetings, the EMEA in collaboration with the European Commission, three pharmaceutical companies (Bayer Vital, Bristol Meyers Squibb, Lundbeck) and one Member State authority (INFARMED, PT) presented and demonstrated the pharmacovigilance system used to support the joint pilot activities. In addition, the EMEA together with the European Commission, Joint Research Centre (JRC), held three technical meetings with pharmaceutical companies to discuss specific technical matters related to the pilot. A web site was created by the JRC in collaboration with the EMEA that provides supportive information in relation to the joint pilot activities (<http://icsr.eudra.org/>).

II.2. Procedures and Results

This chapter summarises the overall results of the first 12 months of the pilot activities between the EMEA, five pharmaceutical companies and two Member State authorities (table 2) taking into account the pilot objectives as described in the Joint Pilot Plan (CPMP/PhVWP/2058/99). Main focus was put on the testing of the safety message transmission and the subsequent data validation and processing. Technical details are reflected in the joint pilot technical note (JPP/tn/000523), which can be accessed from the joint pilot web site. The activities of Member State authorities at national level are not presented.

II.2.1. Safety Message Transmission

The EMEA in co-operation with the JRC, set up a testing environment for a common regulatory reporting point within the EU, thereby complying with the ICH ESTRI Gateway concepts. This testing environment provided two options:

- (i) The use of EudraSafe, a secure document delivery system accessible through the Internet using Secure Socket Layer (SSL) technologies over the HyperText Transfer Protocol (http). Confidentiality of data was ensured by the secure communication link and by server encryption. This option has been tested between the EMEA, Lundbeck A/S, Merck Sharp & Dohme, and Roche.
- (ii) The use of EudraSafe/Automated Data Exchange (EudraSafe/ADE), a logical infrastructure that offers a common interface for connecting together legacy systems i.e. a service or a set of services within the organisation that is supposed to exchange information with another service/set of services. This option has been tested between the EMEA and Bayer Vital.

In addition, EudraNet, provides secure electronic transmission of information between administrators working in the various departments of the National Competent Authorities. Data exchange between the EMEA and the MCA and IMB was based on the use of EudraNet.

II.2.2. Safety Message Validation and Processing

The European Reporting System, called EudraVigilance, was used by the EMEA to support the pilot activities. The system allowed to send and receive ICH conform safety messages based on the ICH M2 DTD version 2.0, to create new safety reports interactively, integrity and consistency checking, automatic classification of reports and generation of acknowledgements related to the outcome of the transaction. It also provided the necessary tools to support the scientific and administrative data evaluation.

The validation process of the received data was as follows:

II.2.2.a. Well-formed parsing

The aim of this checking was to evaluate if the received safety message is a correct Standard Generalized Markup Language (SGML) message i.e. a checking on the safety message instance according to the SGML syntax. The EMEA used for the pilot the Extensible Markup Language (XML), a subset of SGML that is completely compatible with SGML. The EMEA recommended to insert in all safety messages the XML version (to support the XML standard) and the encoding ISO-8859-1 (Latin-1), which is a precondition in handling data in the multilingual environment of the Community. Errors encountered during the parsing process were reported back to the sender.

II.2.2.b. DTD Validation

The Document Type Definition (DTD) validation allowed the EMEA the checking of the message instance according to the ICH ICSR DTD version 2.0, which defines each element of the ICSR being transmitted and reflects how the various data elements are related to each other. For test purposes the EMEA corrected identified errors where possible, a feedback was provided to each sender to reflect corrected errors. The safety messages were then further processed within EudraVigilance.

II.2.2.c. Integrity Rules and Report Classification

In a next step the safety message instances were checked in accordance with the integrity and consistency rules, inside and outside the ICH M2 specification and automatically classified in accordance with the rules as defined in the comments on the XML Document Type Definition version 2.0. (document can be accessed via the pilot web site) and finally loaded within EudraVigilance.

II.2.2.d. Acknowledgement

The ICSR Acknowledgement Messages, as defined in ICH M2 DTD version 2.0, were automatically generated through EudraVigilance in order to communicate to the sender the results of the outcome of the validation of the transmitted data set.

Until the end of November 2000, the EMEA received overall test data from 5 pharmaceutical companies and 2 National Competent Authorities, for which an overview is presented in table 2. Please note that according to the ICH M2 specifications, one safety message may have one or several safety reports attached.

Table 2: Overview of test data submitted to and processed at the EMEA

Sender	Transmission	Safety Message	Safety Reports
Astra Zeneca, UK	Floppy Disk	2	82
Bayer Vital, DE	EudraSafe/ADE	525	525
IMB ¹ , IE	EudraNet	1	105
Lundbeck, DK	EudraSafe	4	584
MCA, UK	EudraNet	3	14
MSD, UK & US	EudraSafe	13	36
Roche, UK & US	EudraSafe	112	112

¹ Irish Medicines Board, Ireland
CPMP/PhVWP/2058/99 rev 1

IV. JOINT PHARMACOVIGILANCE ACTIVITIES IN 2001 AND BEYOND

On the basis of the results achieved during the joint pilot in 2000, the Joint Pilot Group agreed to revise the scope of the joint pilot and the group's current activities. During the 5th Joint Pilot meeting held in September 2000 at the EMEA, it was agreed to extend the joint pilot's objectives and the group's mandate. Testing will be continued, however the main goals with regard to these pharmacovigilance activities will be to

- (i) Finalise the implementation of the ICH E2B, M1 and M2 specifications by all parties involved and
- (ii) Start the regular electronic exchange of safety reports in the Community.

III.1. Joint Pharmacovigilance Objectives

To achieve this twofold goal, the following principles, agreed at the first joint meeting in April 1999, the ICH E2B, M1 and M2 standards will be implemented by all parties as follows:

1. **Paper reporting of Adverse Drug Reactions (ADRs) will be replaced by electronic safety reporting independently of the authorisation procedure of the medicinal products** involved. The mandatory dates (deadlines) for the implementation of electronic safety reporting in pharmacovigilance based on the ICH E2B, M1 and M2 requirements will be discussed at the EudraVigilance TIG and, following agreement, published in Volume 9 of the Rules governing medicinal products in the European Union.
2. **ICH Gateway Recommendation for the Electronic Transfer of Regulatory Information (ESTRI Gateway):** a gateway that permits companies to report to a common regulatory point across the European Union (EU) using secure communication as defined in the ICH gateway recommendations (e.g. SMTP/SMIME). Pharmaceutical companies will send Case Safety Reports to the established EUDRA mailboxes (formal addresses) of National Regulatory Authorities and EMEA, using EudraSafe or other existing electronic facilities. Acknowledgement messages will be sent to the sender via the same established route. This approach will ensure compatibility of information and communication tools and security of communication over the Internet.
3. **The ICH E2B and M2 data element and message definitions for the electronic transfer of Case Safety Reports:**
 - Data Elements for the Electronic Transmission of Individual Case Safety Reports. Revised step 4 document, version 4.4, November 9, 2000.
 - Electronic Transmission of Individual Case Safety Reports Message Specifications, DTD Version 2.0 (Document Version 2.24 March 8, 1999, CPMP/ICH/285/95): this version will be used until the 1st June 2001,
 - Electronic Transmission of Individual Case Safety Reports Message Specifications, DTD Version 2.1 (Document Version 2.3 November 9, 2000, CPMP/ICH/285/95): this version will be mandatory from 2nd June 2001.
4. **MedDRA Lowest Level Terms (LLTs)** will be used as described in the Note for Guidance on Electronic Exchange of Pharmacovigilance Information for Human and Veterinary Medicinal Products in the European Union (EMEA/CXMP/2056/99) considering the recommendations on versioning control as published by the MedDRA Maintenance and Support Service Organisation. The mandatory dates for implementation will be published in Volume 9 of the Rules governing medicinal products in the European Union.

5. **The description of medicinal products and active substances as well as the coding of pharmaceutical forms** should be performed in accordance with the Note for Guidance on Electronic Exchange of Pharmacovigilance Information for Human and Veterinary Medicinal Products in the European Union (EMA/CXMP/2056/99). For non-centrally authorised medicinal products, the use of the medicinal product name or the active substance name as stated in the WHO Drug Dictionary (WHO-DD) is highly recommended wherever feasible. The current limitations of the WHO DD (e.g., Company Drug codes in clinical trials, delay in updates) are discussed within the JPhIG, which will elaborate a proposal to overcome these difficulties.
6. **The official languages in the narrative fields (uncoded information)** will be used as described in the Note for Guidance on Electronic Exchange of Pharmacovigilance Information for Human and Veterinary Medicinal Products in the European Union (EMA/CXMP/2056/99) permitting and supporting the usability of pharmacovigilance information across the EU.
7. Each party will provide for the necessary **business practices** for the management of pharmacovigilance information including:
 - identification and classification of Case Safety Reports and cases,
 - identification and management of duplicates and follow-ups,
 - nullification of cases,
 - identification of errors and
 - acknowledgement of case safety reports.

National Competent Authorities, the EMA and pharmaceutical companies in the Community are expected to implement the necessary information and communication infrastructure to comply with the aforementioned principles within the deadlines published in Volume 9 of the Rules governing medicinal products in the European Union.

III.2. Joint Planning, Testing and Implementation Procedure

As it has been demonstrated in the Joint Pilot (please refer to chapter II) intensive planning, preparation and testing between all parties is required before electronic safety reporting can replace the current reporting mechanisms, which were mainly based on paper.

This chapter describes a three phased approach that needs to be followed by all parties involved to ensure a successful implementation of the regular electronic data exchange in pharmacovigilance:

III.2.1. Phase I: Planing

III.2.1.A. Declaration of Intent

The purpose is to notify the EMA/National Competent Authorities on the intention and the envisaged date to start the regular electronic exchange of ICSRs. It allows the EMA/National Competent Authorities to plan the necessary resources for the testing and the regular electronic exchange of safety reports with the pharmaceutical industry partners accordingly.

Who has to submit a Declaration of Intent?

- Pharmaceutical Companies having a medicinal product authorised within the Community;
- National Regulatory Authorities reporting to the EMA;

To whom needs the Declaration of Intent to be sent?

- Pharmaceutical Companies send the declaration to the EMEA and all National Regulatory Authorities where according to the authorisation procedure of the medicinal product reporting obligations as defined in the Community legislation exist;
- National Competent Authorities having reporting obligations as defined in the Community legislation towards the EMEA;

What is the scope of the Declaration of Intent?

The declaration defines the specific partnership as indicated below:

- National Competent Authority reporting to the EMEA or
- Pharmaceutical industry reporting to National Competent Authority(ies) or
- Pharmaceutical industry reporting to the EMEA;

A list of contact points at the level of the EMEA and National Competent Authorities is attached in Annex A.

III.2.1.B. Preparation of Implementation Plan

The Implementation Plan should provide for the necessary transparency of the business processes related to the locally established pharmacovigilance systems and should present

- Exact timeframes for testing and start of the regular electronic transmission of ICSRs,
- Methods of communication with other parties,
- Mapping of data items,
- Approach to upload/download of Case Safety Reports; generation of messages,
- Approach to identify and classify Case Safety Reports and cases,
- Management of follow-ups and duplicates,
- Use of a product dictionary: product names, forms, substances,
- Use of MedDRA: implementation, term level, codification,
- Correspondents directory and identification,
- Use of official languages.

Who needs to prepare an Implementation Plan?

Every party (i.e. pharmaceutical companies, National Competent Authorities, EMEA) has to prepare an implementation plan.

III.2.1.C. Obtain certification (for Internet communication)

All parties should obtain a digital certificate that allows for the secure communication over the Internet. The procedure to be followed is:

- Request certificate to Registration Authority (EMEA)
- Obtain certificate from the Certification Authority (JRC)

III.2.2. Phase II: Testing of Electronic Exchange of Case Safety Reports

Intensive testing is essentially required before the regular exchange of ICSRs can be performed electronically on a routine basis. In order to streamline the testing procedures between pharmaceutical companies and the EMEA/National Competent Authorities and considering the results of the joint pilot activities in 2000 as well as the pharmacovigilance objectives outlined in chapter III.1, all parties should put the main emphasis on:

- Testing the secure communication of safety and acknowledgement messages;
- Message parsing: syntax, lengths, required info, controlled fields;
- Implementation and use of MedDRA and other standard terminology;
- Exchange test messages with EMEA/National Authorities;
- Checking of integrity rules and report classification;
- Checking of uploaded case safety reports;
- Testing of the management of cases;
- Checking of acknowledgements.

What needs to be considered?

The legal obligations related to the reporting of adverse reactions remained unaffected during testing i.e. the established way of the regulatory submission of adverse reaction reports will be continued during phase II.

How will the testing be organised?

In accordance with the Community legislation it is expected that the information flow in the EU will respond to a three layer structure independent of the authorisation procedure of a medicinal product, with:

- Pharmaceutical companies reporting to the EMEA,
- Pharmaceutical companies reporting to National Competent Authorities and vice versa,
- National Competent Authorities reporting to the EMEA and vice versa;

The flow of safety² and acknowledgement messages during phase II is outlined in table 3a and 3b:

² It is recommended that safety messages are submitted to all parties involved even though some may still be in the process of implementing the ICH requirements. It will allow these parties to process the data for test purposes at a later time.

Table 3a: Centrally authorised medicinal products: Flow of safety and acknowledgement messages in the Community during phase II

Medicinal products authorised through the centralised procedure Council Regulation (EEC) No. 2309/93 as amended			
Type of ICSR	Message Type	Sender	Receiver
Suspected serious adverse reactions occurring within the Community (EU cases)			
Article 22, paragraph 1: The person responsible for placing the medicinal product on the market shall ensure that all suspected serious adverse reactions occurring within the Community to a medicinal product authorised in accordance with the provisions of this Regulation which are brought to his attention by a health care professional, are recorded and reported immediately to the Member States in whose territory the incident occurred, and in no case later than 15 days following the receipt of the information.	Safety message including one or several ICSRs	Pharmaceutical company (person responsible for placing the medicinal product on the market)	Competent Authority (Member State) on which territory the adverse reaction occurred <u>plus</u> EMA ³ during phase II for test purposes
Article 22, paragraph 1 continued	Acknowledgement message	Competent Authority (Member State) on which territory the adverse reaction occurred	Pharmaceutical Company (person responsible for placing the medicinal product on the market)
Article 23: Each Member State shall ensure that all suspected serious adverse reactions occurring within their territory to a medicinal product authorised in accordance with the provision of this Regulation which are brought to their attention are recorded and reported immediately to the Agency and the person responsible for placing the medicinal product on the market, and in no case later than 15 days following the receipt of the information.	Safety message including one or several ICSRs	Competent Authority (Member State) on which territory the adverse reaction occurred	EMA (Agency)
Article 23 continued	Acknowledgement message	EMA (Agency)	Competent Authority (Member State) on which territory the adverse reaction occurred

³ In order to test the electronic transmission with a sufficient number of ICSRs and in order to ensure compatibility of the requested standards between all EU agencies it is recommended that the EMA is also part of this information flow during phase II.

**Medicinal products authorised through the centralised procedure
Council Regulation (EEC) No. 2309/93 as amended**

Type of ICSR	Message Type	Sender	Receiver
Article 23 continued	Safety message including one or several ICSRs	Competent Authority (Member State) on which territory the adverse reaction occurred	Pharmaceutical company (Person responsible for placing the medicinal product on the market)
Article 23 continued	Acknowledgement message	Pharmaceutical company (Person responsible for placing the medicinal product on the market)	Competent Authority (Member State) on which territory the adverse reaction occurred
Article 23 continued The Agency shall inform the national pharmacovigilance systems.	The EMEA (Agency) will make the data available through EudraVigilance.		
Suspected serious unexpected adverse reactions occurring in the territory of a third country (non-EU cases)			
Article 22 paragraph 1: The person responsible for placing the medicinal product on the market shall ensure that all suspected serious unexpected adverse reactions occurring in the territory of a third country are reported immediately to Member States and the Agency and in no case later than 15 days following the receipt of the information.	Safety message including one or several ICSRs	Pharmaceutical company (person responsible for placing the medicinal product on the market)	All Competent Authorities (Member States) <u>and</u> EMEA (Agency)
Article 22 paragraph 1 continued	Acknowledgement message	All Competent Authorities (Member States)	Pharmaceutical company (person responsible for placing the medicinal product on the market)
Article 22 paragraph 1 continued	Acknowledgement message	EMEA (Agency)	Pharmaceutical company (person responsible for placing the medicinal product on the market)

Table 3b: Nationally authorised medicinal products including those authorised through the mutual recognition procedure: Flow of safety and acknowledgement messages in the Community

Medicinal products authorised nationally including those authorised through the mutual recognition procedure Commission Directive 2000/38/EC of 5 June 2000			
Type of ICSR	Message Type	Sender	Receiver
Suspected serious adverse reactions occurring within the Community (EU cases)			
<p>Article 29, paragraph 2-3: The marketing authorisation holder shall be required to record and report all suspected serious adverse reactions which are brought to his attention by a health care professional immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information. The marketing authorisation holder shall be required to record and report all other suspected serious adverse reactions which meet the reporting criteria in accordance with the guidance referred to in Article 29 g of which he can reasonably be expected to have knowledge immediately to the competent authority of the Member State in whose territory the incident occurred, and in no case later than 15 calendar days following the receipt of the information.</p>	Safety message including one or several ICSRs	Pharmaceutical company (marketing authorisation holder)	Competent Authority (Member State) on which territory the adverse reaction occurred
Article 29, paragraph 2-3 continued	Acknowledgement message	Competent Authority (Member State) on which territory the adverse reaction occurred	Pharmaceutical Company (marketing authorisation holder)

**Medicinal products authorised nationally including those authorised through the mutual recognition procedure
Commission Directive 2000/38/EC of 5 June 2000**

Type of ICSR	Message Type	Sender	Receiver
<p>Article 29, paragraph 5: In case of medicinal products which have been considered within the scope of Directive 87/22/EEC, or which have benefited from the procedures of mutual recognition foreseen in Article 7 and 7a of Directive 65/65/EEC, Article 9(4) of this Directive, and medicinal products for which there has been a referral to the procedures foreseen by Article 13 and 14 of this Directive, the marketing authorisation holder shall additionally ensure that all suspected serious adverse reactions occurring in the Community are reported in the format and at intervals to be agreed with the reference Member State, or a competent authority acting as the reference Member State, in such a way as to be accessible to the reference Member State.</p>	Safety message including one or several ICSRs	Pharmaceutical company (marketing authorisation holder)	Competent Authority (Member State) on which territory the adverse reaction occurred and reference Member State, or a competent authority acting as the reference Member State <u>plus</u> EMEA during phase II for test purposes
<p>Article 29, paragraph 5 continued</p>	Acknowledgement message	Competent Authority (Member State) on which territory the adverse reaction occurred	Pharmaceutical Company (marketing authorisation holder)
<p>Article 29, paragraph 5 continued</p>	Acknowledgement message	reference Member State, or a competent authority acting as the reference Member State	Pharmaceutical Company (marketing authorisation holder)
<p>Article 29, paragraph 5 continued</p>	Acknowledgement message	EMEA during phase II for test purposes	Pharmaceutical Company (marketing authorisation holder)
<p>Article 29f, paragraph 2: Making use of the network foreseen in the first paragraph, Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the Agency and the other Member States, and in any case within 15 calendar days of their notification, at the latest.</p>	Safety message including one or several ICSRs	Competent Authority (Member State) on which territory the adverse reaction occurred	EMEA (Agency) and the other Member States
<p>Article 29f, paragraph 2 continued</p>	Acknowledgement message	EMEA (Agency)	Competent Authority (Member State) on which territory the adverse reaction occurred

Medicinal products authorised nationally including those authorised through the mutual recognition procedure
Commission Directive 2000/38/EC of 5 June 2000

Type of ICSR	Message Type	Sender	Receiver
<p>Article 29f, paragraph 3: The Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are immediately made available to the marketing authorisation holder, and in any case within 15 calendar days of their notification at the latest.</p>	<p>Safety message including one or several ICSRs</p>	<p>Competent Authority (Member State) on which territory the adverse reaction occurred</p>	<p>Pharmaceutical company (marketing authorisation holder)</p>
<p>Article 29f, paragraph 3 continued</p>	<p>Acknowledgement message</p>	<p>Pharmaceutical company (marketing authorisation holder)</p>	<p>Competent Authority (Member State) on which territory the adverse reaction occurred</p>
<p>Article 29 f, paragraph 1: The Agency, in collaboration with the Member States and the Commission shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the Community intended to allow all competent authorities to share the information at the same time.</p>	<p>The EMEA (Agency) will make the data available through EudraVigilance.</p>		
<p>Suspected serious unexpected adverse reactions occurring in the territory of a third country (non-EU cases)</p>			
<p>Article 29 paragraph 4: The marketing authorisation holder shall ensure that all suspected serious unexpected adverse reactions occurring in the territory of a third country and brought to his attention by a health care professional are reported immediately in accordance with the guidance referred to in Article 29g, so that they are available to the Agency and to the competent authorities of the Member States where the medicinal product is authorised, and in no case later than 15 days following the receipt of the information.</p>	<p>Safety message including one or several ICSRs</p>	<p>Pharmaceutical company (marketing authorisation holder)</p>	<p>EMEA (Agency) and All Competent Authorities (Member States)</p>
<p>Article 29 paragraph 4 continued</p>	<p>Acknowledgement message</p>	<p>EMEA (Agency)</p>	<p>Pharmaceutical company (marketing authorisation holder)</p>
<p>Article 29 paragraph 4 continued</p>	<p>Acknowledgement message</p>	<p>All Competent Authorities (Member States)</p>	<p>Pharmaceutical company (person responsible for placing the medicinal product on the market)</p>

At the last Joint Pilot meeting on 29 September 2000 the joint pilot group recommended to extend the testing to all three ICH regions. It was suggested that pharmaceutical companies, where applicable, would send the same data to the FDA, MHW and the EMEA/National Competent Authorities to test compatibility and conformity of the exchanged data at international level. This recommendation will be followed as of 1 January 2001 where possible.

III.2.3. Phase III: Implementation

III.2.3.A. Adoption of Interchange Agreements between correspondents

The Interchange Agreement defines the roles and responsibilities in relation to the regular exchange of ICSRs between two parties.

III.2.3.B. Start of the operational phase

Following the successful completion of phase I-III, the regular electronic exchange of ICSRs will be initiated.

During the first 6 months of regular electronic submission the sender will distribute to the receiver(s) a paper copy of each submitted ICSR in parallel to the electronic version. This will allow all parties to perform a final integrity check of all submitted data.

III.3. Joint Pharmacovigilance Implementation Group and Meetings

Taking into account the recommendations of the Joint Pilot Group as put forward at its meeting on 29 September 2000, it was agreed to reform the Joint Pilot Group to a Joint Pharmacovigilance Implementation Group (JPhIG) for the Electronic Transmission of Individual Case Safety Reports and MedDRA in pharmacovigilance. The composition of the former Joint Pilot Group will remain unchanged.

The JPhIG will become a subgroup of the EudraVigilance Telematics Implementation Group, which co-ordinates, under supervision of the Telematics Management Group and the Telematics Steering Group, all EudraVigilance project related issues on Community level.

The Joint Pharmacovigilance Implementation Group meetings, will, as previously for the Joint Pilot Group meetings, be organised at the premises of the EMEA in London, and will be open to all pharmaceutical companies having a medicinal product authorised within the Community and to all National Competent Authorities.

Roles and Responsibilities

IV.1. EMEA

As of 1st January 2001 the EMEA will perform 1st with all parties having provided a Declaration of Intent the necessary testing as described in chapter III.2.2.

The EMEA will implement the joint pharmacovigilance objectives as described in chapter III.1 within the mandatory dates published in Volume 9 of the Rules governing medicinal products in the European Union.

The EMEA will start the regular electronic exchange of case safety reports with each party immediately after successful completion of phase II as described in chapter III.2.2.

In a first step the EMEA will put main emphasis on implementing the regular electronic exchange of ICSRs related to centrally authorised medicinal products. The next step will cover the implementation of the electronic submission of ICSRs related to medicinal products authorised nationally including those authorised through the mutual recognition procedure.

The EMEA will provide scientific assistance and support for the generation and checking of Case Safety Reports according to the ICH specifications. If necessary meetings with

pharmaceutical companies or Competent Authorities can be arranged to outline the specific requirements and to clarify open questions related to the electronic exchange of data.

To guarantee and maintain public confidence in the way sensitive patient information is handled and to ensure authentication of the exchanged data the EMEA in co-operation with the European Commission, JRC, will provide a secure communication infrastructure over the Internet and the necessary guidelines to use it.

The EMEA, as part of its coordination role in pharmacovigilance, will make the information received available through a pharmacovigilance database, as defined in Article 51, paragraph c, of Council Regulation (EEC) No. 2309/93.

The EMEA has published its Implementation Plan in September 2000.

The EMEA contact persons for all issues related to the Joint ICH Pharmacovigilance Implementation of MedDRA and the Electronic Transmission for Individual Case Safety Reports between the EMEA, National Competent Authorities and pharmaceutical industry are:

Sabine Brosch
EMEA Unit for the Evaluation of Medicinal Products for Human Use
Sector Pharmacovigilance and Regulatory Affairs
Ph: +44.171.418 8569 Fax: +44.171.418 8668
E-mail: sabine.brosch@emea.eudra.org

Francois Maignen
EMEA Unit for the Evaluation of Medicinal Products for Human Use
Sector Pharmacovigilance and Regulatory Affairs
Ph: +44.171.418 8619 Fax: +44.171.418 8668
E-mail: francois.maignen@emea.eudra.org

IV.2. National Competent Authorities

National Competent Authorities will take all necessary measures at national level to ensure for the complete implementation of the Joint Pharmacovigilance objectives as outlined in chapter III.1 within the deadlines that will be published in Volume 9 of the Rules governing medicinal products in the European Union.

National Competent Authorities will announce to all parties involved the date when they will be ready to actively participate at the test phase as described in chapter III.2.2 taking into account the agreed deadlines.

National Competent Authorities will start the regular electronic exchange of case safety reports with the EMEA/ National Competent Authorities immediately after successful completion of phase II as described in chapter III.2.2.

National Competent Authorities will communicate with the EMEA and pharmaceutical companies using the established EudraNet/EudraSafe secure communication infrastructure.

National Competent Authorities are invited to participate actively at the Joint Pharmacovigilance Implementation Group meetings and to provide feedback on a regular basis of the developments at national level.

IV.3. Pharmaceutical Companies

Pharmaceutical companies will take all necessary measures to ensure for the complete implementation of the Joint Pharmacovigilance objectives as outlined in chapter III.1 within the deadlines that will be published in Volume 9 of the Rules governing medicinal products in the European Union.

Pharmaceutical companies will notify the EMEA and National Competent Authorities as soon as possible on the date when they will be ready to actively participate at the test phase as described in chapter III.2.2 considering the agreed deadlines published in Volume 9.

Pharmaceutical companies will communicate with the EMEA and National Competent Authorities using the provided secure communication infrastructure over the Internet.

Pharmaceutical companies will start the regular electronic exchange of case safety reports with the EMEA/ National Competent Authorities immediately after successful completion of phase II as described in chapter III.2.2.

Pharmaceutical companies are invited to participate actively at the Joint Pharmacovigilance Implementation Group meetings and to provide feedback on a regular basis of the developments at company level.

Annex A

List of contact points for the co-ordination of the Implementation of the Electronic Transmission of Individual Case Safety Reports and MedDRA in pharmacovigilance at the level of the EMEA and National Competent Authorities

EMEA	Co-ordinator	Address	Tel No	Fax No	E-mail address
EMEA	Sabine BROSCHE	7 Westferry Circus, Canary Wharf London E14 4HB	+44 207 4189592	+44 207 4188668	sabine.brosch@emea.europa.eu
EMEA	Francois MAIGNEN	7 Westferry Circus, Canary Wharf London E14 4HB	+44.171.418 8619	+ 44.171.418 8668	francois.maignen@emea.europa.eu

Member State	Co-ordinator	Address	Tel No	Fax No	E-mail address
Austria	Mr. Robert SCHARINGER	BM f. Soziale Sicherheit und Generationen Präsidialabteilung B/8 - IT Gesundheit Radetzkystr. 2 A-1030 WIEN, Austria	43 1 71100/4183	43 1 7189470/1023	robert.scharinger@bmg.gv.at robert.scharinger@at.europa.eu
Belgium	Mr. Wa Mbuna KOTO NGBABO	Ministry of Health, Social Affairs and Environment Pharmaceutical Inspectorate Boulevard Bischoffsheim 33 B-1000 Brussels	32 2 227 5648	32 2 227 5641	wambuna.koto@afisp.fgov.be
Denmark	Pia BUCH	Danish Medicines Agency Frederikssundsvej 378 DK-2700 Brønshøj	45 44 88 92 63	45 4 491 73 73	JRE@DKMA.DK
Finland	Dr. Riitta TOKOLA	Läkelaitos Mannerheimintie 166 FIN-00300 Helsinki		358 9 47 33 42 97	Riitta.tokola@nam.fi
France	Mr. Pascal AURICHE	AFSSAPS 143-147 Bd. Anatole France F-93285 Saint-Denis Cedex	33 1 5587 3544	33.1.5587.3532	Pascal.auriche@afssaps.sante.fr

Germany	Dr. Karlheinz ZINNHOBLER	Bundesinstitut für Arzneimittel und Medizinprodukte Friedrich-Ebert-Strasse D-53113 Bonn	49 228 207 5918	49 228 207 5903	k.zinnhobler@bfarm.de
Germany	Dr. Brigitte KELLER- STANISLAWSKI	Paul-Ehrlich-Institut Paul-Ehrlich Straße 51-59 D – 63225 Langen	49 6103 77 10 10	49 6103 77 12 63	kelbr@pei.de
Greece	Mr. Marto ARJAN & Dr. Gregoria Athanasίου	C/o Pharmetrica SA 15, Adrianou Str. 11525 Athens	30 1 671 3974	30 1 671 7282	Arjan Marto [arjan@pharm2.pharmetrica.gr]
Iceland	Mrs Rannveig GUNNARSDÓTTIR	Icelandic State Committee on Pharmaceuticals Eidistorg 13-15 IS – 172 Seltjarnarnes	354 520 21 00	354 561 21 70	rannveig.gunnarsdottir@lyfjanefnd.is
Ireland	Ms. Suzanne McDONALD	IMB - Irish Medicines Board (Bord Leigheasra na hÉireann) The Earlsfort Centre Earlsfort Terrace IRL- Dublin 2	353 1 676 49 71	353 1 676 78 36	-
Italy	Dr. Valeria PROIETTI	Ministero della Sanita Dipartimenta per la Valutazione dei Medicinali e la Farmacovigilanza Viale della Civiltà Romana, 7 00144-Roma Italy	39 06 5994 38 49	39 06 5994 31 43	v.proietti@sanita.it
Luxembourg	Mrs. Jacqueline GENOUX-HAMES	Ministère de la Santé Division de la Pharmacie et des Médicaments Villa Louvigny Allée Marconi L-2120 Luxembourg	352 478 55 93	352 26 20 01 40	jacqueline.genoux-hames@ms.etat.lu

Netherlands	Dr. Arthur P. MEINERS	Medicines Evaluation Board Kalvermarkt 53 P.O. Box 16229 NL-2500 BE Den Haag	31 70 356 7492	31 70 356 7515	ap.meiners@cbg-meb.nl
Norway	Mr. Harald LISLEVAND	The Norwegian Medicines Control Authority Sven Oftedals Vei 6 NO-0950 Oslo	47 22 89 75 68	47 22 89 77 99	Harald.lislevand@slk.no
Norway	Mr. Jan SVENDSEN	The Norwegian Medicines Control Authority Sven Oftedals Vei 6 NO-0950 Oslo	47 22 89 7720	47 22 89 77 99	Ian.svendsen@slk.no
Portugal	Mr. Luis PINHEIRO	INFARMED Parque de Saúde de Lisboa Av. do Brasil 53 P-1749-004 Lisboa	351 21 798 7100	351.21.798.7124/ 20	Regina.carmona@infarmed.pt
Spain	Dr. Mariano MADURGA SANZ	Agencia española del medicamento Pl. del Prado 18-20 E-28071 Madrid	34 91 596 7810	34 91 596 7891	mmadurga@agedmed.es
Sweden	Ms. Åsa KLING	MPA Box 26 S-75103 Uppsala	46 18 17 47 52	46 18 54 85 66	Asa.kling@mpa.se
UK	Ms. Shelley K. BHASIN	M.C.A. Post Licensing Division Market Towers 1 Nine Elms Lane London SW8 5NQ	0207 273 0209	0207 273 0675	Shelley.bhasin@mca.gov.uk
UK	Mr. Shaun FIDDES	M.C.A. Post Licensing Division Market Towers 1 Nine Elms Lane London SW8 5NQ	44-171-273 0708	44-171-273 0675	E-mail: Shaun.Fiddes@mca.gov.uk E-mail: UK- H.PHARMACOVIGILANCE@UK- H.EUDRA.ORG