Opinion of the European Economic and Social Committee on the Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

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On 23 January 2009 the Council decided to consult the European Economic and Social Committee, under Article 95 of the Treaty establishing the European Community, on the

'Proposal for a regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency'

The Section for the Single Market, Production and Consumption, which was responsible for preparing the Committee's work on the subject, adopted its opinion on 19 May 2009. The rapporteur was Ms GAUCI.

At its 454th plenary session, held on 10 and 11 June 2009 (meeting of 10 June), the European Economic and Social Committee adopted the following opinion by 92 votes in favour and three abstentions.

1. **Summary and recommendations**

1.1 The EESC endorses the Commission's intention to establish a stronger pharmacovigilance system through increased market surveillance by reinforcing monitoring procedures providing for clear roles and responsibilities for the key responsible parties and for a transparent EU decision-making.

1.2 The EESC strongly recommends that the new regulatory framework put the patient at the centre of the EU legislation, providing for sufficient harmonised rules in this area in order to assure to EU citizens, at least on the long run, an equal access to sound information across the EU, and the full availability of safe, innovative and accessible medicines registered in any part of the EEA market at reasonable price.

1.3 Along this line, the EESC is in favour of significant improvements in the present situation, given that the differences emerged between the national legislative, regulatory and administrative provisions on medicinal products have deep repercussions on patients and that these differences could hinder intra-EEA trade and affecting the good functioning of the internal market.

1.4 The Committee, therefore, underlines the importance of involving patients in pharmacovigilance including direct patient interactive reporting of suspected adverse reactions: the responsibility for health care should become increasingly shared with patients taking a more active interest in their own health and care options and in a two-way channel of communication, including a sound use of internet.

1.5 The Committee support clarification and codification of tasks and responsibilities across and between all stakeholders: Member State Competent Authorities, EMEA (including its committees), Commission and Marketing Authorisation Holders, including their Qualified Person for Pharmacovigilance, and patients. The EESC believes that the new elements introduced by the proposals must neither call into question, nor weaken existing structures and procedures at local level, especially those that involve the patient and health professionals, provided that common parameters for comparable data are assured in transparent and rapid procedure.

1.6 The Committee endorses the establishment of a new Pharmacovigilance Committee to replace the existing Pharmacovigilance Working Party within the EMEA and believes that the setting up of such a committee could result in better and faster functioning of the EU system, provided that tasks, procedures and relations with the other existing committees are better clarified.

1.7 The collection and management of pharmacovigilance data in the EudraVigilance database must be fostered with new human and financial resources to become the single interactive point of rapid receipt and fast delivery of pharmacovigilance information for medicinal products together with an effective data management. It is vital for public confidence that there should be a transparent and user-friendly access policy open to all the stakeholders, especially the patients, in an interactive way, respecting data protection and confidentiality.

1.8 The EESC underlines the importance of simplified procedures for small and medium-sized enterprises (SMEs) and asks for the optimisation of the 'SME office', providing financial and administrative assistance to micro, small and medium-sized enterprises.

1.9 As international markets expand and companies operate more and more on an international basis, the EESC recommends to foster the coordination of Member States' and EC actions both at European and international level.

1.10 The EESC requests that within 5 years, the EMEA presents to the EP, the Council and the Committee, an independent external evaluation of its achievements on the basis of its new Regulation and the work programmes together with an evaluation assessment of the working practices and the impact of the new mechanism provided by this proposal, as well of the interactive functioning of the Eudravigilance database.

2. **Preliminary remarks**

2.1 Harmonised Community rules on the pharmacovigilance of medicinal products for human use are provided by Regulation EC/726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMEA), as regards medicinal products authorised by the Commission in accordance with the centralised authorisation procedure of that Regulation, and by the Directive 2001/83/EC.

2.2 Risk assessment during product development should be conducted in a thorough and rigorous manner even if it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterising a product's risk profile and for making informed decisions on risk minimisation.

2.3 The present opinion is dealing with the Commission's proposals on amendments to the present Regulation only, whilst another opinion of the Committee is dealing with the amendments to the Directive 2001/83/EC [1].

2.4 The EESC is strongly in favour of significant improvements in the existing Community legal framework, given that the differences are emerged between the national legislative, regulatory and administrative provisions on medicinal products and that these differences could hinder intra-Community trade and affecting the good functioning of the internal market.

2.5 A lack of coordination would deny the Member States access to the best scientific and medicinal expertise for the evaluation of the safety of medicines and for risk minimisation.

2.6 The Committee has already pointed out that 'a strong pharmacovigilence system is vital and believes that existing systems must be strengthened. All health professionals involved in the prescribing or dispensing processes, as well as patients, should participate in an effective post-marketing surveillance system applied to all medicines' [2].

2.7 The EESC endorses the Commission's intention to establish an increased market surveillance by reinforcing monitoring procedures providing for clear roles and responsibilities for the key responsible parties and for a transparent EU decision-making on drug safety issues in order to deliver measures that are equally and fully implemented for all relevant products in EU.

2.8 The responsibility for health care is becoming increasingly shared with patients taking a more active interest in their own health and care options. The importance of involving patients in pharmacovigilance including direct patient reporting of suspected adverse reactions is recognised and the EESC welcomes the emphasis on creating and supporting ways of ensuring patient involvement at all levels.

2.9 The EESC recognises the benefit to EU citizens and patients of the new provisions for pharmacovigilance which will result in an improved access to health and medicines information and a proactive collection of high quality data on the safety of medicines. This collection and management of pharmacovigilance data in the EudraVigilance database must be fostered with new human and financial resources to become an interactive single point of receipt and delivery of pharmacovigilance information for medicinal products for human use.

2.10 The EESC is dealing with all the different aspects of the Pharmaceuticals Package of Proposals that are treated in various opinions [3] on specific subjects. To this effect an important and fruitful public hearing was held in Brussels under the chairmanship of President Bryan Cassidy with the participation of representatives of firms and of national and European organisations.

3. **The Commission proposals for amended regulation**

3.1 The objective of the proposals is to improve the protection of public health in the Community while enhancing the single market in medicinal products, by strengthening and rationalising EU pharmacovigilance and removing disparities between national provisions in order to ensure the proper functioning of the internal market for such products.

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[1] See opinion CESE 1024/2009 (opinion not yet published in the Official Journal).

[2] OJ C 241/7, 28.9.2004.

[3] EESC works on opinions CESE 1022/2009, Rapporteur Heinisch, CESE 1023/2009, Rapporteur Gauci, CESE 1024/2009 (INT/471) Rapporteur Cedrone, CESE 1191/2009 (INT/472), Rapporteur Morgan, CESE 1025/2009, Rapporteur Cedrone and R/CESE 925/2009 (INT/478), Rapporteur van Iersel (opinion not yet published in the Official Journal).

3.2 The proposals aim to contribute to the strategic goals of the Community framework for the authorisation, supervision and surveillance of medicinal products through:

— improving the protection of public health across the Community in relation to the safety of medicinal products;

— supporting the achievement of the internal market in the pharmaceutical sector.

3.3 The specific objectives of the proposals are:

— establishing clear roles, responsibilities and clear standards against which they perform their roles, with regular reporting by the European Commission, pharmacovigilance inspections and EMEA audit;

— rationalising EU decision-making, the timing of the establishment of the new EMEA committee structure and the number of pharmacovigilance referrals to the EMEA;

— establishing medicines safety websites by each Member State and launching of the EU safety web-portal by the EMEA in order to foster transparency and communication on medicines safety and to increase the understanding and trust of patients and health professionals on these questions;

— strengthening companies' pharmacovigilance systems, while reducing their administrative burdens;

— fostering the EudraVigilance database on the safety of medicines through risk management, structured data collection and periodic reporting of suspected adverse reactions;

— strengthening the coordination of Member States' and EC actions aimed at reinforcing strategic S&T cooperation to stimulate innovation in the pharmaceutical sector, through the FP7 programme and the Innovative Medicines Initiative;

— involving stakeholders in pharmacovigilance;

— simplifying the current Community pharmacovigilance procedures.

3.4 The proposals underline the need for adequate funding of activities related to pharmacovigilance by the Agency through the collection of fees charged to marketing authorisation holders, the resources for the EMEA Telematics Master Plan and the overall impact on the EMEA budget.

4. **The Committee's comments**

4.1 **Basic endorsement**: The Committee endorses the basic objectives of the proposals of the achievement of the internal market in the pharmaceutical sector, improving the protection of public health as stated above.

4.1.1 In the context of the renewed Lisbon Strategy, the Committee reiterates the concern expressed about the importance of simplification of the regulatory framework to benefit citizen, patients, firms and society, and underlines the need of 'an integrated approach in order to build advantage for the industry and patients as well as to stimulate its continued development as a major contributor to a dynamic knowledge-based, competitive economy in Europe' ([4]).

4.2 **Clear roles and responsibilities**. The Committee underlines the importance that 'all health professionals involved in the prescribing or dispensing processes, as well as patients, should participate in an effective post-marketing surveillance system applied to all medicines. This spontaneous reporting system should be particularly stringent for newly marketed medicines' ([5]).

4.2.1 The Committee is convinced that the norms as they are now can be improved with the participation of all stakeholders since one of the shortcomings is the fact that there is a lack of knowledge or information regarding the different characteristics and risks which marketed medicines have.

4.2.2 The EESC strongly support clarification and codification of tasks and responsibilities across and between all stakeholders: Member State Competent Authorities, EMEA (including its committees), Commission and Marketing Authorisation Holders, including their Qualified Person for Pharmacovigilance. Another EESC opinion is dealing with the new proposals on codification.

4.3 **Rationalising EU decision-making**. The Committee endorses the establishment of a new committee to replace the existing Pharmacovigilance Working Party within the EMEA and believes that the setting up of such a committee, to specifically deal with pharmacovigilance issues across the EU, is a step in the right direction in order to harmonise safety signals across the EU.

4.3.1 The Committee would wish greater clarity and further refinement of some of the proposals, in particular: around the interface between CHMP and the new Pharmacovigilance Committee, patient and public involvement including patient reports of suspected adverse reactions, the role of an intensive monitoring list and the definitions for non-interventional studies.

([4]) See footnote 2.
([5]) See footnote 2.

The EESC would like to refer to the recently established Committee for Advanced Therapies (CAT) which specifically deals with licensing and post-marketing issues including pharmacovigilance and follow-up of efficacy and of advanced therapy medicinal products as defined under Regulation (EC) 1394/2007. This regulation was based on the need to have the required expertise to assess such complex and specialised products.

4.3.2 Therefore, the EESC questions whether a general pharmacovigilance committee will have the relevant expertise to regulate pharmacovigilance issues for specialised products, such as advanced therapy medicinal products. It is thus suggested that for these products, the CHMP through the CAT is consulted during the risk/benefit assessment.

4.3.3 The contribution of the future new Committee on Pharmacovigilance for safety analysis should be reconsidered within the more general framework of risk-benefit ratio analysis which is and should continue to be the responsibility of the CHMP.

4.4 **Patient first**. The patient must be at the centre of the proposed new regulatory framework. Today EU legislation does not provide for sufficient harmonised rules in this area and as a consequence EU citizens have unequal access to information across the EU. Patients must be encouraged to report adverse reactions directly to the national authority for all medicines instead of to the marketing authorisation holder. The Committee is in favour of direct reporting as an essential tool to empower patients and to improve their involvement in the management of their own health.

4.4.1 It is important that clear and transparent safety information, namely a pictogram ([6]) to help consumer distinguish immediately intensively monitored drugs, the conclusions and recommendations of the Periodic Safety Update Reports (PSURs) and medicines consumption data are made public, respecting confidentiality on data protection and commercial interest. Eudravigilance has to be regularly updated and easily and fully accessible by patients.

4.4.2 The Committee believes that the patient information leaflets need to be designed to convey potential adverse reactions more clearly with the introduction of safety information on the package leaflet and the warning for medicines under intensive surveillance. In any case, information dumping must be avoided and information must be tuned on the different audience needs and supported by an appropriate use of internet: on this question the EESC is providing a specific opinion ([7]).

4.4.3 The final aim for the Committee must be the completion of a effective single European market in pharmaceuticals built on the needs and interests of European patients and citizens, in terms of availability of safe, innovative and accessible medicines needed by patients under a unified EU approach that reduce the dependence of the market on the decision-making processes in the 30 different national governments.

4.5 **Transparency and communication**. In supporting the current proposals to enhance communication with healthcare professionals and patients via product information, the Committee strongly suggests that this opportunity is taken to make both PILs and SPCs ([8]) more useful, user friendly and coherent.

4.5.1 Pharmacovigilance information for medicinal products for human use needs an interactive European database network. The EESC is strongly in favour of strengthening the Eudravigilance database as the single point of receipt of information on adverse reactions in human beings arising from use of the product within the terms of the marketing authorisation 'as well as from any other use, including overdose, misuse, abuse, medication errors, and those occurring in the course of studies with the medicinal product or after occupational exposure'.

4.5.2 Transparency should be favoured in acts and decisions at all levels of the agencies and of the EMEA. An important aspect of that is the accurate and timely communication of emerging data on risk as an essential part of pharmacovigilance. Risk communication is an important step in risk management as well as a risk minimisation activity. Patients and healthcare professionals need accurate and well communicated information about the risks associated with both the medicinal product, and the condition for which it is being used. ([9])

4.5.3 The EESC feels that the key message is to bring the ever-growing importance of a transparent policy concerning the public access to the data and that such requests must be provided within the delay prescribed by the legislation. It is vital for public confidence that a transparent access policy is agreed by all Member States. The Committee would like to have a clearer justified reason on the denied public access to the transparent and non-promotional post-marketing studies or to the results of these studies while launching the EU safety web-portal by the EMEA. The EESC underlines its strong support for

([6]) Like the black triangle scheme used in the UK.

([7]) See CESE 1024/2009, Rapporteur Cedrone (opinion not yet published in the Official Journal).

([8]) PIL & SPC = Patient Information Leaflets (PILs) and Summaries of Product Characteristics (SPCs).

([9]) See also: proposed Recommendation on 'Pharmacovigilance Urgent Measures' procedure under Art. 107 of Directive 2001/83/EC; and Directive 65/65/EEC as amended, Council Regulation 2309/93 on Rapid Alert System (RAS) in Pharmacovigilance.

guiding principles and oversight of a subset of Post-authorisation safety studies -PASS ([10]), in line with Articles 24, 26 and Article 57 (1)(d) of Regulation (EC) No 726/2004 ([11]).

4.5.4 The Committee supports the proposal for the EMEA to carry out all literature monitoring, since this would provide a significant reduction in duplication of work. The Agency shall monitor selected medical literature, in cooperation with the Marketing Authorisation holders, for reports of all suspected adverse reactions to medicinal products for human use containing certain active substances to be entered into the Eudravigilance database and in a published list of active substances being monitored.

4.6 **Simplification of procedures**. The EESC welcomes the proposed initiative to reduce administrative burden with respect to ADR reporting and to decrease the current duplicate reporting system that exists across the EU for Individual Case Summary Reports via both paper and electronic copies across different Member States. The Committee believes that it would be useful to introduce a specific legal obligation to follow the requirements of the International Conference on Harmonisation — ICH ([12]) for electronic submission.

4.6.1 Furthermore, it is important to point out that, at present, a lot of precious resources for pharmacovigilance at a National Competent Authority — NCA level are used up acknowledging and dealing with Individual Case Safety Reports — ICSRs — sent by companies with an unuseful duplication of activities. These resources could be better utilised by encouraging a stronger collaboration between the authorities, maximising the expertise available, work-sharing and simplifying the administrative aspects of the activities related to the submission and administration of all the safety reports.

4.6.2 The EESC underlines the importance of simplified procedures for small and medium-sized enterprises (SMEs) and asks for the optimisation of the 'SME office', providing financial and administrative assistance to micro, small and medium-sized enterprises (SMEs) pursuant to Commission Regulation (EC) No 2049/2005.

4.7 **Coordination of Member States' and EC actions**. As international markets expand and companies operate more and more on an international basis, the task of regulatory authorities to assess compliance with legislation and monitor the safety of medicines becomes increasingly important and resource-intensive as 'the EU pharmaceutical industry operates in a global economy' ([13]). In response to this overall situation and to address the challenges of the internal and international market, which can pose potential risks to public health, there is the need of intensified global cooperation on two different levels:

— at Community level, to enhance dynamic coordination between Community institutions and national authorities, including national agencies whose natural mission consists in animation, expertise and decision-making;

— at European and international level, to ensure a stronger voice within the Council of Europe, World Health Organisation-IMPACT, the International Conference on Harmonisation ICH and ICH Global Cooperation Group, EU-US Framework for Advancing Transatlantic Economic Integration on Administrative Simplification in Medicines Regulation ([14]), EU-Russia Common Economic Space & Regulatory Dialogue on Industrial Products, EC Agreements with Switzerland, Australia, New Zealand, Canada, Japan, the EU-China Consultation and Cooperation Mechanism on pharmaceuticals and medical devices.

4.7.1 As the Commission Vice-President Günter Verheugen ([15]) said: 'The pharmaceutical sector makes an important contribution to European and global well-being through the availability of medicines, economic growth and sustainable employment'.

4.7.2 The increasing internationalisation of the sector and the 'shortcomings in the EU pharmaceutical market which affect patients' access to medicines and to relevant information is hampering the competitiveness of the industry' ([16]). On this line, the Committee strongly recommends:

— to foster initiatives finalised to EU pharmaceutical research and international research cooperation;

— to intensify cooperation with major partners (US, Japan, Canada) to improve medicines' safety worldwide;

— to strengthen cooperation with emerging partners (Russia, India, China).

([10]) PASS: The proposed definition is: 'a pharmaco-epidemiological study or a clinical trial with an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product'.

([11]) The draft proposal of the EudraVigilance Access Policy is published for public consultation on the EMEA website (http://www.emea.europa.eu/htms/human/raguidelines/pharmacovigilance.htm).

([12]) International Conference on Harmonisation, an international organisation that attempts to standardises globally the regulatory and scientific aspects of clinical research, drug development, and pharmaceutical product registration.

([13]) See COM(2008) 666 final of 10.12.2008 and CESE 1456/2009, (INT/478) Rapporteur van Iersel (opinion not yet published in the Official Journal).

([14]) See also the agreement on mutual recognition between the European Community and the United States of America.

([15]) See Commission Vice-President Günter Verheugen, IP/08/1924, Brussels, 10.12.2008.

([16]) See EC Press Release IP/08/1924, 10.12.2008.

4.8 **Independent external evaluation of EMEA achievements**. The EESC requests that, in its report for 2015, the EMEA presents an independent external evaluation of its achievements on the basis of its founding Regulation and the work programmes together with an evaluation assessment of the working practices and the impact of the new mechanism provided for the CHMP, the CAT and the new Pharmacovigilance Committee, taking into account the views of the stakeholders, at both Community and national level.

Brussels, 10 June 2009.

The President
of the European Economic and Social Committee
Mario SEPI