

# ASTHMA IN THE EU

## TOWARDS BETTER MANAGEMENT AND REGULATION OF A PUBLIC HEALTH ISSUE

JØRGEN MORTENSEN & ANDREA RENDA

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### Abstract

Asthma is a common life-long chronic inflammatory disorder of the airways that affects children and adults of all ages and whose prevalence is rising in a number of the most-developed countries. Although the understanding of many aspects of asthma has improved over the past two decades, the fundamental causes of asthma are still not known. Various genes have been associated with an increased risk of developing asthma and increased susceptibility to asthma. Environmental influences also play an important part in the initiation and maintenance of asthma by interacting with the genetic predisposing factors. Despite the repeated expressions of concern by the Council of the European Union, emphasising in particular, the need to focus on children's health, asthma management and care still remains sub-optimal in most EU Member States. In this context note should be taken of the large disparity between EU Member States with respect to asthma prevalence and, thus, the perception of this as a public health problem. With regard to the European Commission's policy on public health issues such as asthma, there seems to be no clear basis for claiming that competence for pharmacovigilance should be moved from the remit of the Directorate General Enterprise and Industry to the Directorate General Health and Consumer Protection (DG SANCO). The current situation mirrors the situation in many Member States inasmuch as the competence for protecting the interest of consumers and for acting as contact point for the industry is concentrated in the same administrative body. The advocacy role of the European Medicines Agency (EMA) should be strengthened and clarified both with regard to pre-authorisation control and to post-authorisation surveillance. The EMA's Guidance Note on Asthma also needs to reflect the current mismatch between the design of clinical trials and endpoints selected and the emerging complexity of asthma pathophysiology. The activities carried out by the EMA should be made more transparent than is currently the case, in line with widely acknowledged principles of better regulation. Finally, the role of patients' (and patients associations') self-reporting should be strengthened within the current system, possibly through the establishment of a forum with healthcare professionals (HCPs), DG SANCO and the EMA.

**Key words:** European Union, public health, asthma, pharmacovigilance, regulatory affairs

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## Executive summary

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In June 2004 the EU Council “noted with concern that childhood asthma is having an increasingly serious health, social and economic impact on the European Community, that childhood respiratory illness as the most common cause of morbidity in children in industrialized countries has serious economic consequences and serious effects on the quality of life of individuals, and that the WHO World Health Report 2000 identified respiratory diseases as one of the five major burdens of disease (in disability-adjusted life years)”.

The Council also pointed out that the joint report of the European Environmental Agency and the WHO regional office for Europe on children’s health and the environment had highlighted a significant increase in childhood asthma in “western affluent” countries over the last few decades, with a trend ranging from a slight up to a three-fold increase. The Council then concluded that a number of pivotal EU programmes, such as those in the fields of public health, environment and research, could have a positive and major impact on reducing the occurrence of childhood asthma.<sup>1</sup>

Notwithstanding this prominent statement by the Council and the various EU activities, asthma management and care remains sub-optimal in most EU Member States.<sup>2</sup>

Understandably, some professionals feel a high degree of impatience with respect to the delay with which the latest results of asthma research are being channelled into the sphere of healthcare policy at the national and EU level. The reasons for this delay in translation are obvious: in the 21<sup>ST</sup> century, Europe faces a broad array of health and environment threats and the fixing of priorities between, for instance, cancer, cardiovascular diseases, respiratory diseases, mental disorders, arthritis and multiple sclerosis is a particular difficult exercise, notably at the level of the 27 Member States.

In addition, on account of the relatively narrow legal basis for the EU to act on health issues, in general it has focused more on public health risk factors, such as indoor and outdoor air pollution, dangerous chemicals and tobacco consumption, and less on specific diseases.

However, despite its relatively narrow legal base for actions in the field of public health, the EU can – and already does – exert substantial influence on health issues via EU policy measures in related fields such as environment, health research, and the European-wide regulation of medicinal products through the EMEA.

There appears to be a real need for strengthening the EU’s activities in the field of asthma especially because it involves all age groups, but especially children. In this context, a critical element of consideration for EU decision makers would be the particular nature of the disease:

- The prevalence is rising in a number of EU countries but is higher the greater the degree of urbanisation and income;

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<sup>1</sup> Finally the Council welcomed the Commission’s Communication on a European Environment and Health Strategy (June 2003). This Strategy emphasized the importance of focusing on children because “investing in children’s health is essential to ensure human and economic development” and in the first phase aims at establishing a good understanding of the link between environment factors and, inter alia, childhood respiratory diseases, asthma and allergies.

<sup>2</sup> In this context note should be taken, however, of the large disparity between EU Member States with respect to prevalence of asthma and, thus, the perception of this as a public health problem.

- There is a need for further and deeper studies of the costs to the economy of asthma, but available estimates suggest that the indirect social and economic costs are very high in proportion to the direct costs for the health care system: asthma does not provoke high costs of surgery or medical treatment;
- There is still a high degree of uncertainty with respect to the causes and the scope for treatment recognising the heterogeneity of the condition and the different impact of interventions according to age. There would seem to be strong arguments in favour of providing adequate resources to further asthma research in future calls for proposals in FP7;
- Specifically, there may be a possibility for treatment through vaccination but research in this field is still in the starting blocks and results can hardly be expected in the short and medium term;
- However, in the short and medium term asthma management is an issue extending beyond the medical profession by interfacing between the individual patient and the socio-economic framework and institutions, including schools and work places.

Taking account of these perspectives there is an increasing need for EU Member States to consider the scope for a common integrated approach to the asthma problem. The report will critically present proposals on how the EU's current activities could be streamlined and improved so as to better complement and support Member States activities on asthma and make a stronger 'European' contribution towards improving the management and regulation of this public health issue across the EU. For example, it would appear attractive to embark into a discussion with Member States as to the benefits of opening an exchange on asthma treatment and management over a wide front within the framework of the Open Method of Coordination (OMC).

The advantages of a common approach to asthma management could be quite important on a condition involving not only ministries of health but also those of education and social affairs in addition to the NGOs by offering services to asthma patients and, naturally, the EMEA and the scientific community.

The work of an OMC activity in the field of asthma could also obtain support from ongoing research and new research projects addressing, on one side the genetic aspects of asthma and on the other side, the correlation of asthma with socio-economic, environmental and other regional factors. There would as suggested above seem to be a good argument for actively exploring, within the framework of FP7, the scope for combating certain categories of asthma through vaccination (an issue already raised in the work programme of the US FDA).

However, progress would require further and deeper research into the socio-economic and environmental aspects of asthma through, notably, longitudinal studies of health profiles. This might best be achieved within regular surveys with a more general thrust, aimed at following the evolution of health over time (not only asthma but also obesity and other basic health features) of children, adolescents and adults according to education, income and other socio-economic characteristics.

The specific issues concerning asthma control must be assessed in the general context of the EU's approach to public health problems and, in particular ex-post control with the market for pharmaceutical products and the reporting on adverse reactions to medicines.

Evidence presented in this report indicates that asthma management is sub-optimal in a high proportion of EU Member States. In addition, we have identified serious disparities between countries with regards to pharmacovigilance, leading to waste of scarce resources and serious aggravation of the risk of insufficient control with the use of medicines and also a lack of

clinical control with adverse long-term effects of the use of certain drugs, notably in children and in older people.

With respect to the assignment of responsibilities within the European Commission our conclusions are as follows:

- There seems to be no firm basis for claiming that competence for pharmacovigilance should be moved to the remit of DG SANCO instead of DG Enterprise. Indeed, the current situation mirrors that in many Member States in as much as the competence for protecting the interest of consumers and for acting as contact point for the industry is concentrated in the same administrative body.
- In contrast, the need to adopt a broader and holistic approach in combating asthma, the leading role played by EMEA in the pharmacovigilance system, and the need to leave *ex ante* risk assessment and *ex post* evaluation in the same hands all call for a strengthening of the current system, without such a major change.
- Nonetheless, the advocacy role of EMEA could be clarified and greatly strengthened both as regards pre-authorisation control and post-authorisation surveillance. The EMEA Guidance Note on Asthma should reflect the current mismatch between clinical trials and the emerging complexity of asthma pathophysiology and response to pharmacological, biological and environmental interventions.
- Overall, the transparency of activities undertaken by EMEA should be improved in order to foster accountability of professionals working for this important advisory body. In particular, assessment reports – both pre-authorisation and post-authorisation – should be made public.
- In addition, within the current system the role of patients' (and patients' associations) self-reporting should be strengthened, possibly through the establishment of a forum with HCPs, DG SANCO and the EMEA.
- Finally, high quality risk assessment guidance has been adopted only recently; in 2006 the Commission adopted a new Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC, and in 2007 the EMEA's Committee for medicinal products for human use (CHMP) set up a working group to review existing models and provide recommendations on ways to improve a) the methodology, and b) the transparency, consistency and communication of the benefit risk assessment by the CHMP.

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### Introduction

In June 2004 the EU Council “noted with concern that childhood asthma is having an increasingly serious health, social and economic impact on the European Community, that childhood respiratory illness as the most common cause of morbidity in children in industrialized countries has serious economic consequences and serious effects on the quality of life of individuals, and that the WHO World Health Report 2000 identified respiratory diseases as one of the five major burdens of disease (in disability-adjusted life years)”.

The Council also pointed out that the joint report of the European Environmental Agency (EEA) and the WHO regional office for Europe on children’s health and the environment had highlighted a significant increase in childhood asthma in “western affluent” countries over the last few decades, with a trend ranging from only slight increase up to a three-fold increase. The Council then concluded that a number of EU programmes, such as those in the fields of public health, environment and research, could have a positive impact on reducing the occurrence of childhood asthma.<sup>3</sup>

The Council Recommendation’s conclusion reveals the firm conviction of EU Health Ministers that the EU can, and should, make a significant contribution towards tackling a public health issue such as asthma. A good deal of the EU’s contribution would need to focus on supporting and complementing existing Member States activities on asthma (including those that have recently joined the EU).

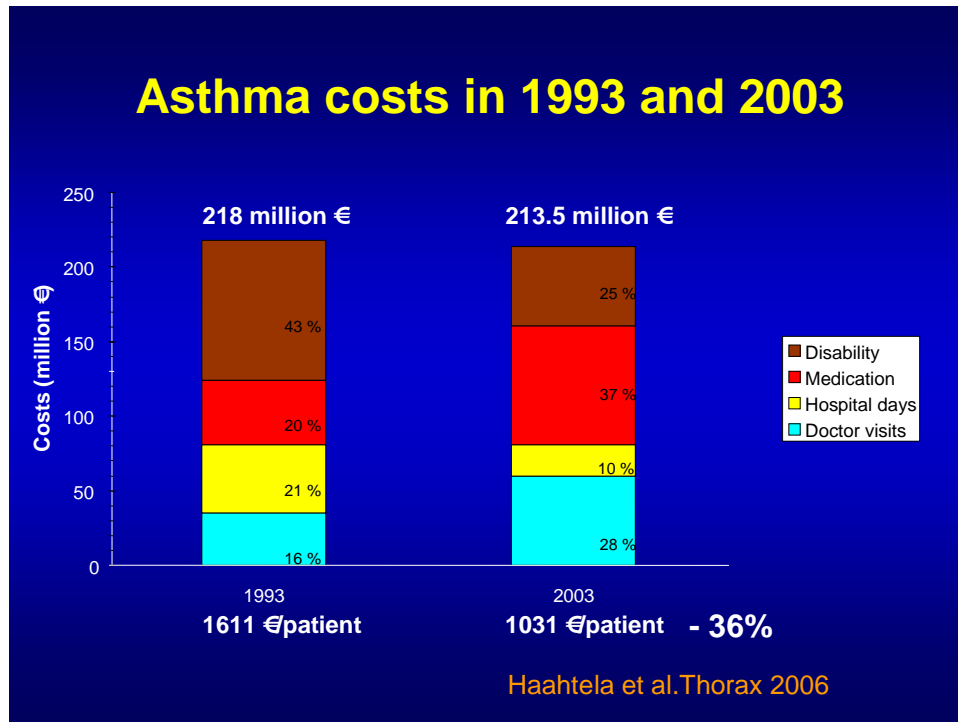
### ***National approaches – Finland and France***

Recent experiences in a number of EU Member States have shown that integrated public health programmes on asthma can result in substantial improvements for patients and dramatically reduce the overall burden of the disease. In particular, the Finnish initiative aimed at improving asthma management at all levels of prevention and care has attracted considerable attention abroad. This programme was implemented from 1994 to 2004 focusing on implementation of new knowledge, especially for primary care. It was deployed within a network of asthma-responsible professionals and development of a post-hoc evaluation strategy. The results were impressive. The programme:

- Helped cutting by half the number of asthma related hospital days;
- Led to a huge reduction in the number of disability pensioners in working age; and
- Resulted in a significant decrease in costs of asthma for social security (see graph below).

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<sup>3</sup> Finally the Council welcomed the Commission’s Communication on a European Environment and Health Strategy (June 2003). This Strategy emphasized the importance of focusing on children because “investing in children’s health is essential to ensure human and economic development” and in the first phase aims at establishing a good understanding of the link between environment factors and, inter alia, childhood respiratory diseases, asthma and allergies.



*Source: EHFG 2006 presentation by Dr. Erkkka Valovirta.*

The success of this programme, presented at a special workshop at the 2006 European Health Forum Gastein, was, to a large extent, due to the broad involvement of all stakeholders. The overall coordination was carried out by a small Steering Group that brought together all relevant actors, civil servants, patients, clinicians and health care professionals, while day-to-day implementation was ensured by a network of asthma-responsible professionals in a series of healthcare centres.

In France, an asthma programme was initiated during 2002-2005 with five objectives:

- 1) Development of information on asthma for asthmatics and for the general public, together with the introduction of advisers regarding the domestic environment;
- 2) Improvement of the quality of asthma care with regard to the treatment of severe acute asthma, follow-up of chronic asthma patients and detection of new cases with management of asthmatic children in the school environment;
- 3) Development of therapeutic education;
- 4) Improvement of the management and detection of occupational asthma; and
- 5) Establishment of a system to collect information on all epidemiological and economic aspects of asthma, and to identify the risk factors.<sup>4</sup>

Apart from a highly detailed and useful report on the results of about one hundred “asthma schools”, the overall outcome of the French “Asthma Plan” has, however, not yet been made publicly available.

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<sup>4</sup> Source: The European Lung White Paper.

## ***Improving asthma management and outcomes across the EU***

Despite comprehensive national programmes such as the ones in Finland and France, specialists still consider asthma management and care in most EU Member States as sub-optimal. Looking at the discrepancies between EU Member States and at ways to improve asthma management and outcomes across Europe a “Summit” of asthma experts, policy makers, regulators and patient groups examined in a meeting sponsored by the European Parliament and the University of Southampton in October 2006 best practice approaches to this disease. Among other things, the Summit called for a number of EU actions on asthma such as:

- A horizontally coherent EU policy approach to asthma;
- An update of the regulatory guidance note on asthma of the EMEA to appropriately reflect the latest clinical evidence and scientific knowledge,
- The encouragement of Member States to adapt best practice solutions in asthma in their own healthcare systems;
- The strengthening of EU pharmacovigilance;
- The promotion of research into asthma, allergies as well as indoor and outdoor air quality under the Seventh Research Framework Programme (FP7).

The participants in this Summit adopted a draft declaration which, in final form, was made public on 9 May 2007. This *Declaration* identifies ten key areas where action is needed and specifies a number of detailed potential measures to be envisaged: (i) by the EU, (ii) by the national authorities and (iii) by other stakeholders (“third parties”). This *Declaration* thus constitutes an important message from the key actors in the field of asthma research, management and patient organisations and is therefore included as an annex to the present report.

Starting from this background, the aim of the present study is to provide a comprehensive analysis of the EU’s approach to tackling public health issues, using asthma as a case example. In so doing, the study will show how the EU can – and already does – exert substantial influence on health issues via EU policy measures in related fields such as environment, health research, and the European-wide regulation of medicinal products through the EMEA, despite its relatively narrow legal base for actions in the field of public health. This report will critically examine these initiatives and present proposals on how the EU’s current activities could be streamlined and improved so as to better complement and support Member States activities on asthma and make a stronger ‘European’ contribution towards improving the management and regulation of this public health issue across the EU.

### **1. What is asthma?**

The public health website of the European Commission defines asthma as an allergic reaction to substances commonly breathed in through the air, such as animal dander, pollen, or dust mite and cockroach waste products. The catch-all name for these substances, allergens, refers to anything that provokes an allergic reaction. Some people have a genetic predisposition to react to certain allergens.

When people breathe in the allergen, the immune system goes into high gear as if fighting off a harmful parasite. The system produces a molecule called immunoglobulin E (IgE), one of a class of defensive molecules termed antibodies. The IgE antibody is central to the allergic reaction. For example, it causes mast cells, a type of specialized defensive cell, to release chemical “weapons” into the airways. The airways then become inflamed and constricted,



leading to coughing, wheezing, and difficulty breathing – an asthma attack (definition provided by the US National Institute of Allergy and Infectious Diseases).

Although, as indicated, the fundamental causes of asthma are still not fully identified, recent research does suggest that lack of childhood exposure to even harmless microbial agents in an increasingly aseptic environment is resulting in a biased development of the immune reaction: possibly resulting in the latter later in life overreacting to the presence of bacteria in the environment.

Most asthma deaths result from acute exacerbations that are generally thought to be avoidable. The observed increases in asthma-associated deaths, especially those persisting over a long period, raise concerns about the potential effects of changes in the medical management of asthma in addition to issues over changes in asthma's underlying prevalence or severity.

### **1.1 European asthma studies and research networks**

The objective of the EU's action in the field of public health (2003-2008) is, among other tasks, to evaluate the impact on asthma prevalence of possible health policy interventions. These interventions should also focus on the reduction of specific asthma risk factors. For this purpose the European Commission supports the IMCA (Indicators for Monitoring COPD and asthma in the EU) Project to develop indicators to monitor asthma in the EU, to describe the prevalence of asthma related symptoms, asthma attacks, physician-diagnosed asthma by age group, gender, socioeconomic status and geographical area and to monitor changes over time of the indicators proposed.

Before the 1990s a large number of epidemiological studies on the prevalence of asthma were carried out. However, no standardized methods were used and their degree of comparability was very low. In the early 1990s two large studies were set up with the aim of standardizing the methods for data collection on asthma. The European Community Respiratory Health Survey (ECRHS) was the first study to assess geographical variations in the prevalence of asthma and allergy in young adults using the same instruments and definitions. The study was set up in 1993 and was carried out in two stages and included individuals from 20 to 44 years of age. In stage I, subjects were sent the ECRHS screening questionnaire asking about symptoms suggestive of asthma, the use of medication for asthma and the presence of hay fever and nasal allergies. In stage II, a smaller random sample of subjects who had completed the screening questionnaire were invited to attend for filling a more detailed interview-led questionnaire, skin prick test (SPT), blood tests for the measurement of total and specific immunoglobulin-E (IgE), spirometry and methacoline challenge.

Another large international study initiated to gain new insights into the aetiology of asthma and allergic disorders in children through standardized comparisons of diverse child populations worldwide was the International Study of Asthma and Allergies in Childhood (ISAAC). In this study participated 463 801 children aged 13-14 years in 155 collaborating centres in 56 countries. In the Phase I of ISAAC the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema in 6-7 and 13-15 years old were assessed and > 20 fold differences in prevalence between centres were found. The information was collected by a self administered questionnaire. Phase II of ISAAC (in a large number of countries) assessed the prevalence of objective markers of atopic diseases and investigates atopic determinants. In this phase children from 9 to 11 were included. In this study bronchial responsiveness was assessed using inhaled hyperosmolar (4.5%) saline.

In contrast with these two studies, more recently, the AIRE (Asthma Insights & Reality in Europe) study has been carried out using different methodologies for data collection (telephone interviews of patients and health professionals) and being nationally representative and

including patients with current asthma and from all age groups. The population prevalence of current asthma can be estimated based on the total number of people reported in each household and the total number of people with current asthma in those households. A total of 213,158 people were reported living in the 73,880 households screened for the survey. The total population prevalence of current asthma was 2.7% for the seven AIRE countries.

Furthermore, the EU's 6th Framework Programme for Research (FP6) is funding a study to examine how genetics and environment influence the development of asthma in Europe. This study (GABRIEL) coordinated by Imperial College, London, and Ludwig-Maximilians-Universität, Munich, groups over 150 scientists from 14 EU countries and Russia aims at using the latest research across a variety of disciplines, to identify key factors in the development of asthma.

Finally, a research network GA<sup>2</sup>LEN (Global Allergy and Asthma European Network) also funded by the European Commission's 6th Framework Programme for Research is working to create a permanent and durable structure to coordinate research capacity in Europe on Allergy and Asthma issues. The objective of this study, which is coordinated by the University of Gent (Belgium), is to establish an internationally competitive network, to enhance the quality and relevance of research, address all aspects of the disease and eventually to decrease the burden of allergy and asthma throughout Europe.

## **1.2 The Global Initiative for Asthma (GINA)**

An important reference in the field of asthma is the Global Initiative for Asthma (GINA), which works with health care professionals and public health officials around the world to reduce asthma prevalence, morbidity and mortality.

Through resources such as evidence-based guidelines for asthma management, and events such as the annual celebration of World Asthma Day, GINA is working to improve the lives of people with asthma in every corner of the globe.

GINA was launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, and the World Health Organization. Its program is determined and its guidelines for asthma care are shaped by committees made up of leading asthma experts from around the world.

The GINA Scientific Committee prepares updates to these guidelines each year, which are made available on the GINA Website as they are completed. The Scientific Committee has developed a sophisticated set of procedures to review the world's literature with regards to asthma management and to update the GINA guidelines to reflect this state-of-the-art information. GINA organizes World Asthma Day, which is held on the first Tuesday in May, in collaboration with health care groups and asthma educators throughout the world and each year chooses a theme and coordinates preparation and distribution of World Asthma Day materials and resources. GINA also maintains the World Asthma Day Internet Headquarters, where materials and resources are posted for downloading and a complete listing of activities around the world is constantly updated.

The first World Asthma Day, in 1998, was celebrated in more than 35 countries in conjunction with the first World Asthma Meeting held in Barcelona, Spain. Participation has increased with each World Asthma Day held since then, and the day has become one of the world's most important asthma awareness and education events.

The GINA Website (<http://www.ginasthma.com/>), which has become one of the most visited health sites on the Internet, provides updates about GINA's activities and information about GINA collaborating groups and contacts throughout the world. It also provides access to the

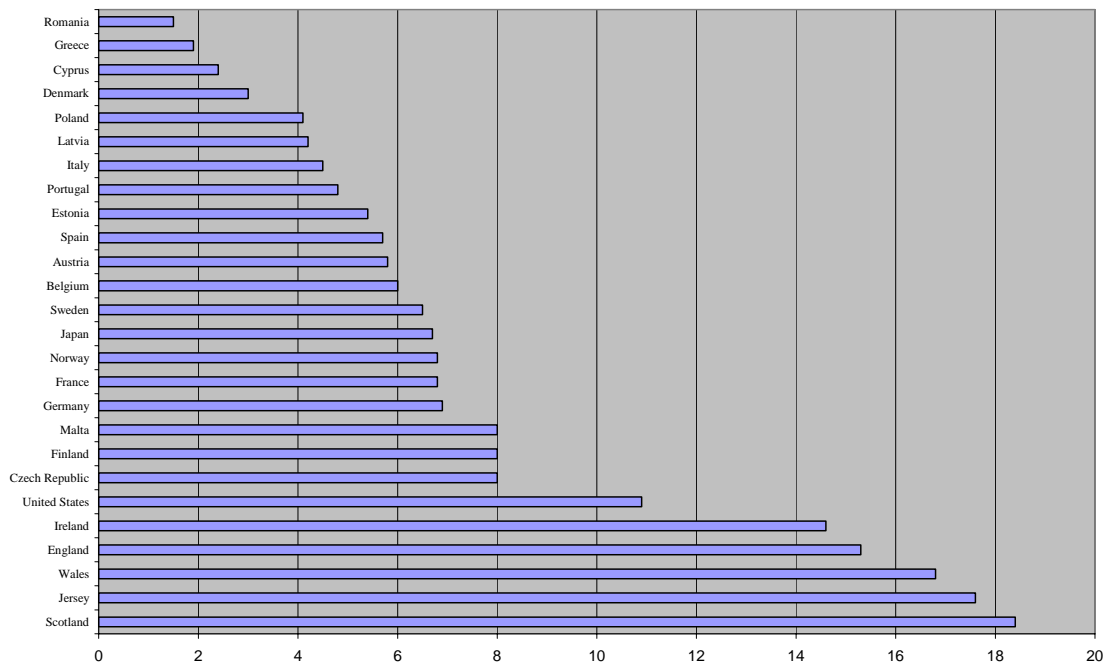
GINA guideline documents and educational materials for patients and the public. The GINA report published in July 2006 constitutes the most recent general presentation and updated discussion of the issues.<sup>5</sup>

## 2. The burden of asthma – prevalence, morbidity and mortality

Despite reinforced worldwide efforts and the development of treatment guidelines based on historical data and practices, asthma still very much constitutes a growing healthcare problem as well as an increasingly heavy cost for society, in terms of medical care and working/living conditions. Worldwide incidence of asthma is thought to have doubled in the past 10 years. Around 300 million individuals are affected globally with up to 250,000 people estimated to now die from asthma annually.<sup>6</sup> The WHO has estimated that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global disease burden.

In the EU, the financial burden of asthma amounts to nearly €17.7bn and productivity lost to poor asthma management is estimated at €0.8bn per annum.<sup>7</sup>

Figure 1. Prevalence of clinical asthma, 2001



Source: GINA, Global Burden of Asthma, 2004.

<sup>5</sup> Global Strategy for Asthma Management and Prevention, Revised 2006: <http://www.ginasthma.com/Guidelineitem.asp?i1=2&i2=1&intId=60>.

<sup>6</sup> WHO Factsheet Nr. 206 (<http://www.who.int/mediacentre/factsheets/fs206/en/>) The global burden of asthma was analysed recently in the GINA July 2006 report which is quoted extensively in this chapter

<sup>7</sup> 2003 White Book of the European Respiratory Society (ERS).

While there are significant differences in the occurrence of asthma across EU Member States there are also inconsistent approaches to asthma management resulting in varying and suboptimal management at a cost to society. Discrepancies are particularly significant between Western and Eastern Europe. In addition to discrepancies such as these, there is a continuing development of data and understandings.

## **2.1 The Social and Economic Burden of asthma**

The GINA report stressed that social and economic factors are integral to understanding asthma and its care, whether viewed from the perspective of the individual sufferer, the health care professional, or entities that pay for health care. Absence from school and days lost from work are reported as substantial social and economic consequences of asthma in studies from the Asia-Pacific region, India, Latin America, the United Kingdom, and the United States.

The Report also underlined that the monetary costs of asthma, as estimated in a variety of health care systems including those of the United States and the United Kingdom are substantial. In analyses of the economic burden of asthma, attention needs to be paid to both direct medical costs (hospital admissions and cost of medications) and indirect, non-medical costs (time lost from work, premature death). For example, asthma is a major cause of absence from work in many countries, including Australia, Sweden, the United Kingdom, and the United States.

Comparisons of the cost of asthma in different regions lead, according to GINA, to a clear set of conclusions:

- The costs of asthma depend on the individual patient's level of control and the extent to which exacerbations are avoided.
- Emergency treatment is more expensive than planned treatment.
- Non-medical economic costs of asthma are substantial.
- Guideline-determined asthma care can be cost effective.
- Families can suffer from the financial burden of treating asthma.

Although from the perspective of both the patient and society the cost to control asthma seems high, the cost of not treating asthma correctly is even higher. Proper treatment of the disease poses a challenge for individuals, health care professionals, health care organizations, and governments. According to the GINA Report, as confirmed by the Finnish asthma programme, there is every reason to believe that the substantial global burden of asthma can be dramatically reduced through efforts by individuals, their health care providers, health care organizations, and local and national governments to improve asthma control. The following chapters of this report will analyse the ways in which the European Union is already influencing and supporting efforts by these stakeholders, and will discuss possible next steps that could help to pave the way towards better management and regulation of this public health issue.

## **3. Assessing the impact of EU actions and inaction**

### **3.1 Impact assessment in public policy**

Impact assessment is an old staple of public policy, ranging from scenarios for the (estimated) results of macroeconomic policy measures, such as changes in interest rates or public expenditure through estimates of the effect on the environment of the building of a dam to assessing the effects of regulatory interventions and the elimination of trade barriers. However, with expansion of the technical capacity for storing and examining data and for modelling the

economy and the environment during recent decades, the scope for undertaking comprehensive impact analysis has risen to unprecedented levels.

Over the past decades, the use of Health and Environmental Impact Assessment mechanisms and procedure in the field of regulation has become widespread in OECD countries<sup>8</sup>. The first, complete mechanism for assessing the costs and benefits of a proposed regulation was introduced in 1981 in the US, under the Reagan administration, although other attempts had been made in the US in previous years with the Quality of Life Review and the Inflation Impact Assessment performed by the Council on Wage and Price Stability.

### **3.2 Impact assessment by the European Commission**

The European Commission has applied methods for assessing the impact of its regulations since 1986, when the Business Impact Assessment (BIA) System was launched under the UK presidency. The BIA system, like the UK Compliance Cost Assessment procedure, exhibited a strong focus on the impact of proposed regulations on business enterprises, with no specific emphasis on social welfare as a whole. In 2002, the Commission proposed a comprehensive framework for ‘better lawmaking’ and issued a Communication on Impact Assessment as well as an Action plan aimed at “simplifying and improving the regulatory environment”. The new model introduced in 2002 – which takes into account not only the economic impact, but also the social and environmental impact of the proposals concerned – consists of two main steps: a Preliminary Impact Assessment and, for a selected number of proposals with large expected impact, a more in-depth analysis called Extended Impact Assessment.<sup>9</sup>

The 2004 progress report led to important changes in the Commission’s Impact Assessment system. The Communication on “*Better regulation for Growth and Jobs in the European Union*” (COM(2005)97) of 16 March 2005 stressed the need for a more thorough economic analysis of the potential impacts of proposed new pieces of legislation, improving the existing 2002 Guidelines. For the first time, the new 2005 Guidelines also contain a reference to health, recommending that the impact of new EU legislation on public health and safety be a key concern. In order to enable the adequate consideration of this new aspect, guidance on how to assess and monetize health impacts was annexed to the 2005 Guidelines.

The Commission’s Impact Assessment model was later adopted by the European Parliament and the Council through an Inter-institutional Agreement on Better Lawmaking and the subsequent “Inter-Institutional Common Approach to Impact Assessment”, adopted in 2005. As of April 2007, more than 200 full Impact Assessments have been completed by the European Commission. In addition, the Commission Discussion Document for a Health Strategy, which was open to consultation until 2007, explicitly reported encouraging results in the health assessment of “all policies” and announced the upcoming development of a tool related

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<sup>8</sup> The following paragraphs constitute large, updated, extracts from the work programme of the European Network for Better Regulation (ENBR), a Coordination Action, financed under the 6<sup>th</sup> Framework Programme and coordinated by CEPS.

<sup>9</sup> The selection of proposals for extended impact assessment forms part of the Commission programming and planning cycle. On the basis of a preliminary impact assessment statement, the Commission decides in the Annual Policy Strategy or (at the latest) in its annual Legislative and Work Programme which proposals should undergo an extended impact assessment. In deciding, it takes into account whether the proposal will result in substantial economic, environmental and/or social impacts on a specific sector or several sectors; whether the proposal will have a significant impact on major interested parties; whether the proposal represents a major policy reform in one or several sectors.

specifically to Health Systems Impact Assessment, a relatively new concept which looks at health infrastructure rather than directly at population health status”.<sup>10</sup> An evaluation of the current system is being undertaken by external consultants to the Commission, and the results will be published in late April 2007

While a main priority of the EU’s impact assessment initiatives has been to improve the regulatory environment for business and the efficiency of the economy, much in line with the Commission’s emphasis on “growth and jobs”, health, environment and the quality of life have thus subsequently been incorporated into these procedures, ensuring that health impact is being taken into account quite literally in “all EU policies” and thus fulfilling the explicit commitment of the EU under Article 152 of the Treaty of Amsterdam (EC, 1999) to ensure that human health is protected in the definition and implementation of all Community policies and activities.

### **3.3 The health impact assessment study by IMPACT**

Further clarification on the issue of health impact assessment (HIA) was provided in the study undertaken for DG SANCO by IMPACT (The International Health Impact Assessment Consortium) with the aim of developing and testing an HIA methodology for use by the European Community and its institutions in EU policy development.

As presented in the Report a search strategy was developed and used to locate secondary data on HIA methodologies and methods used in selected EU Member States and other countries. It defined the scope of the search, the data sources and locations, methods, search terms and inclusion and exclusion criteria. This provided a framework to ensure a consistent approach between the partners. The search yielded over 114 contacts in 19 countries with more than 160 HIA articles, reports and case studies retrieved for content analysis.

The collected HIA case studies, methodologies and methods were critically reviewed in order to select appropriate methods to adapt for use. A classification framework defining typology and quality criteria was developed to aid in this selection.

An overview of EU policy types, levels and activities was undertaken, as well as a mapping of the decision-making process in the EU. An EU policy was then chosen to test the draft European policy health impact assessment (EPHIA) methodology. The partners agreed on a set of selection criteria, the most important of which were timing (i.e. a policy that would enable a prospective HIA) and the availability of evidence to demonstrate the links between the policy area and health outcomes. The selection criteria were applied to EU policies in the 2002 and 2003 work programmes. From a short-list of 10 policies identified and submitted to DG SANCO the project partners selected the European Employment Strategy. Furthermore, to test the draft methodology, the partners conducted pilot HIAs in their own countries and an EU-wide HIA. Some aspects of these pilots were similar including national policy analysis, a review of the employment and health evidence-base and community profiling.

A core health and employment related indicator set common to all partners was identified and corresponding data collected for population profiles. Supplementary Member State data was also collected.

Following piloting, evaluation and refinement, a methodology has been produced for DG SANCO, with the aim of assisting policy makers in undertaking or commissioning HIAs. This EPHIA methodology is applicable for conducting HIAs relatively quickly and also for

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<sup>10</sup> See *infra*, note 5.

undertaking detailed assessments. The project has also produced a completed HIA of a major EU policy and a detailed description of how the methodology was applied. This provides a practical demonstration of what the EPHIA methodology can achieve when assessing complex EU policies and an example for EPHIA practitioners in DG SANCO to consult in the future. It also provides material for wider dissemination to raise awareness and interest in EPHIA in Member State countries and internationally.

Finally, good-quality risk assessment guidance has been adopted only recently; in 2006 the Commission adopted a new Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC, and in 2007 the EMEA set up a CHMP working group to review existing models and provide recommendations on ways to improve a) the methodology, and b) the transparency, consistency and communication of the benefit risk assessment by the CHMP.

Nevertheless, the state of health of any population is only known with a certain degree of approximation. Up to recently indicators of the global health status were mainly based on qualitative indicators and even for specific diseases estimates of prevalence and incidence are difficult to obtain, not to speak of estimates of the effect on health of “other policies”. Health impact assessment is therefore a complex exercise involving considerable risks of policy failures. It would therefore be advisable not to expect health impact assessments to lead to a full “objectivisation” of the impact on health of, say, pollution or the Common Agricultural Policy but only to provide additional elements and arguments for the weighing of pros and cons in policy decisions.

### **3.4 Health in other policies**

Many Community policies and actions have an impact on health and health systems across Europe. They are often developed within a specific policy logic and decision makers are often not well aware of potential health effects. Important health determinants cannot be influenced by health policy on its own; there is a need for co-ordinated actions involving other policy areas such as environmental, social or economic policies.

The Lisbon agenda is the key EU policy on economic growth and productivity, and mainstreaming health into the Lisbon Agenda is one of the most important achievements of mainstreaming health into other policies. The link between health and economic prosperity is more and more widely recognised, in particular in relation to the ageing population. The Healthy Life Years indicator, a measure of years lived in good health, is one of the European Structural Indicators of the Lisbon Agenda.

Joint strategies and initiatives with other health-related policy areas are important tools to ensure that health concerns are being properly addressed from the beginning. Such joint approaches have been developed e.g. on health and the environment, health and social policy, health telematics, research on life sciences and on health policy or health and pharmaceuticals policy. To improve coordination and integration of health protection within the Commission services, a health Inter-Service Group involving representatives from most Commission Directorates General is chaired by DG SANCO, and meets every 6 months. This group allows different Commission services to present work in their areas of responsibility which could have a health impact, and also allows SANCO to share its own work with other Commission departments. The public health programme also contains provisions to support joint work in these areas, and the health strategy will also support Health in all Policies aims.

The Finnish Ministry of Health and Social Affairs took up the theme of Health in All Policies as part of its 2006 Presidency of the European Union. With co-funding from the Community public health programme the Presidency co-ordinated a project entitled “Europe for health and

wealth”, which consists of influencing determinants of health in other national and Community policies and gathering the best available knowledge on good practices to engage other sectors in improving health and reducing health inequalities. As part of the project the Presidency organised a High Level Ministerial conference in September 2006 on the theme and produced a publication: *Health in All Policies: Prospects and Potentials (HiAP)* in collaboration with the participating countries and the WHO European Observatory.

The Report stressed (page 275) that as a result of the increasingly multidimensional nature of policy-making there is, in general, an increasing need for consultation so as to increase policy coherence both between the various sectors and the various levels of policymaking. At European level, there has already been positive development in the European Council as several presidencies have increasingly brought issues from other policy areas with health implications to the Council Working Party on Public Health. Also, as regards the European Parliament, in the spring of 2006, it finalized its first reading of the future Public Health Programme, clearly moving from a disease-based perspective towards that of health determinants and broad action for health across sectors.

Formulating stands for the EU-level policies at national level in intersectoral and political arenas is extremely important as the policy mandates and perspectives may differ between the various sectors at Community level on the one hand and at national level on the other. As regards HiAP, it is not least at national level that the health perspectives need to be integrated in terms of the national stands on the various policy proposals. In Finland, health impact assessment (HIA) has been used as an instrument for not only assessing health implications but also for helping in the process of making health implications visible and taken into serious consideration in the policy-making processes. In this country HIA has its bases not only in other impact assessments, but also in healthy public policy and policy science. The scope of HIA varies from a small desk assessment of the directions of likely health impacts of the policy options to assessments aiming at good estimates of the size of impact. The investment in HIA should be proportional to the importance of the policy decision. According to a survey on the use of HIA in a variety of European countries the extent of the use of HIA varies by country but is strongest in the United Kingdom.

The role of the health care sector in the vigilance of HiAP varies from country to country. Without clear responsibilities, health sector professionals may tend to consider their role to be mainly in the curative services, or at best in disease prevention and health promotion activities within the premises of the health services.

As an additional measure, on 30 November 2006 the Health and Social Affairs Council adopted Council Conclusions on Health in All Policies which aim to raise the visibility and value of health in the development of Community legislation and policies.

However, as shown in the following chapter, as in many EU policy areas the scope for following up the resolutions of the European Council with concrete policy measures is determined by legal and budgetary margins of manoeuvre. In this field there cannot be doubt that hopes for designing and implementing a “high profile” health strategy at the level of the EU were severely dampened as a result of the 2006 compromise on the budget for 2007-2013.

## **4. The health strategy of the EU**

### **4.1 The legal limits of EU action in the field of health**

Legally speaking, the public health programme, as implemented by DG SANCO, is based on Article 152 (4) of the Treaty establishing the European Community. The programme is an



‘incentive measure designed to protect and improve human health’, ‘excluding any harmonisation of the laws and regulations of the Member States’.

It constitutes one of the Community actions foreseen by Article 152 in the field of public health, together with the promotion of co-operation and co-ordination between Member States and other legislative measures. All these actions shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.

The Commission implements the public health programme assisted by a Committee composed of representatives nominated by the EU Member States. This Committee has to give its opinion on the implementation measures defined and decided by the Commission. These measures include the annual work plan, selection criteria and financing of actions and methods for evaluating the programme.

Thus, most of the competence for action in the field of health is held by Member States who have the exclusive say on ‘core’ health issues such as treatment-related questions as well as pricing and reimbursement of medicinal products. The EU’s competence, as set out in the Treaty, is limited to undertaking certain actions which complement the work done by Member States, for example in relation to cross border health threats, patient mobility, and reducing health inequalities.

## **4.2 The current EU health strategy**

In 2000 the Commission adopted a first health strategy which gave rise to the public Health Programme (2003-2008), setting out a framework for action on health determinants, health threats, information and monitoring. In late 2004, the Commission consulted stakeholders on what future action the EU should take in the field of health through the initiative ‘Enabling Good Health for All – A Reflection Process for a new EU Health Strategy’. The reflection process generated a broad debate amongst stakeholders, attracting around 200 responses from national and regional authorities, NGOs, universities, individual citizens and the private sector<sup>11</sup>.

This process generated a major debate in the EU and beyond with close to 200 contributions mainly from national authorities, NGOs, universities, citizens and companies. The Ministries of Health of the UK, France, Ireland, Sweden, Finland, Poland, Latvia and Norway participated in the reflection process. The largest proportion of participants represents European or national NGOs active in the field of health.

Approximately 1/4 of all respondents including Ireland, Sweden, the Netherlands, Germany, the UK, Lithuania Malta and Poland urged the EU to pro-actively promote health and prevent illness.

Measures proposed include the need to focus on children and teenagers, to implement a nutrition/obesity strategy, to tackle smoking and alcohol, to address a wide range of issues affecting health and to act on important diseases including cancer, respiratory and cardiovascular diseases.

Approximately 1/5 of all respondents including France, Germany, Ireland, the Netherlands, Sweden, Finland and Lithuania asked the EU to mainstream health. Respondents urged the Commission to implement a comprehensive and coherent EU approach to health, encompassing policies as diverse as Education, Trade, Internal Market, Social, Environment, Agriculture,

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<sup>11</sup> Extended Impact Assessment: Commission Staff Working Paper: Annex to the Health and Consumer Protection Strategy and Programme, COM(2005)115 Final. (SEC(2005)425, Brussels 6.4.2005

External, Transport and Regional development. Several respondents including France, Ireland, Sweden and Finland emphasized the need for a Health Impact Assessment system.

The need to position health as a driver of economic growth and to disseminate evidence was raised by Ireland, France, the Netherlands, Malta and the UK. Some NGOs and Germany, Ireland and Sweden asked for health to become part of the Lisbon agenda.

Many stressed the need to address health inequalities by increasing funding for health. Respondents also urged the EU to involve stakeholders more closely in policy-making, to support the civil society, to take a stronger role on international health and to step up efforts in the analysis and dissemination of data.

Finally, many respondents also urged the EU to increase resources allocated to health, for the Public Health Programme to better serve policy priorities, to improve dissemination of project results, to cover neighbouring countries and to increase co-funding.

However, the outcome of the (difficult) negotiations on the EU's financial framework for 2007-2013 completed in December 2006 if needed demonstrated the difficulties in obtaining agreement on the ways and means of health policy among the various actors with a stake in the formulation and implementation of EU policies.

### **4.3 The draft Public Health Programme 2007-2013**

On 6 April 2005, the Commission proposed a wide-ranging and ambitious health and consumer protection programme 2007-2013<sup>1</sup> based on the assumption of a €1,203 million budget (out of which €969 million was for health). This proposal foresaw a significant increase in existing Community health action from three to six action strands in order to address cross-border health challenges and to meet stakeholders' expectations.

In its first reading Opinion of 16 March 2006 on the health part of the programme, the European Parliament endorsed the objectives and main actions proposed by the Commission, underlined its preference for a separate health programme, enlarged further the scope of proposed health action and requested a budget of €1,500 million.

However, following the inter-institutional agreement on the Community Financial Framework 2007-2013, the final budget for health action was settled at €365.6 million, i.e. approximately one third of the budget initially foreseen in the Commission proposal of April 2005.

Given these resource constraints, it was considered necessary to take a more focused approach to Community health action. The Commission therefore in May 2006 proposed to refocus the scope of the programme along three broad objectives: to improve citizens' health security; to promote health to improve prosperity and solidarity; and to generate and disseminate health knowledge. It also announced that priority measures would be identified on an annual basis in order to allow the programme to focus its resources on a few carefully selected areas adapted to the political context and emerging needs.

This modified proposal aligned future health action more explicitly with the overall Community objectives of prosperity, solidarity and security and sought to further exploit synergies with other policies, as highlighted by the European Parliament. The modified proposal incorporated to the extent possible the Parliament's concerns on key strategic issues such as the need to promote healthy ageing, to address health inequalities across the EU, to take gender health issues into account and to focus on cross-border issues.

However, in the light of the budgetary constraints, this modified proposal did not include a specific action strand to tackle individual diseases (as in the Commission original proposal which was further strengthened by the European Parliament). Instead, in view of the limited

resources, the Commission stated as the main aim to help reduce the burden of diseases by tackling the most important health determinants. Nevertheless, in cases where important added value could be expected in Community level action on a specific disease (e.g. on rare diseases or mental health), provisions were made under the relevant objectives of the modified proposal. In addition, action on co-operation between health systems (a separate strand in the Commission original proposal) was been considerably streamlined and incorporated into all the three objectives for Community health action.

#### **4.4 The annual Work Plans**

In addition to the framework programme, the European Commission publishes annual work plans in which it outlines each year the specific priority actions on public health.

The work plan for Community public health actions for 2007 is provided in a Commission decision of 12 February 2007 (O.J. L 46/27, 16.2.2007). The total budget for these activities is estimated at close to €42m, of which around €34m to be allocated for financing actions undertaking following a call for proposals issued in February 2007 by the Public Health Executive Agency (a part of DG SANCO). The topics for which calls are invited include:

- Health information
- Response to health threats
- Health determinants.

In general the approach followed by DG SANCO is to issue calls for project proposals from the private and public sector aiming at the pursuit of the stated objectives.

In the field of health information, the work programme aims at developing and operating a sustainable health monitoring system, improving the system for the transfer and sharing of information and health data including public access; developing and using mechanisms for analysis and reporting of information and consultation with Member States and stakeholders on health issues at Community level, improving analysis and knowledge of the impact of health policy developments, other Community policies and activities on health; and supporting the exchange of information on health technologies assessment, including new information technologies and experiences on good practices

With respect to the response to health threats activities aim to strengthen preparedness and to ensure a rapid response to public health threats and emergencies. This will be of particular assistance to cooperation undertaken under the Community network on communicable diseases and other EC legislation in public health and may complement European Research Framework Programme activities.

The detailed objectives include:

- Developing capacity to deal with pandemic influenza and tackle particular health threats;
- Improvement of health sector preparedness for crisis situations and foster intersectoral collaboration (e.g. with civil protection, food and animal sectors) to ensure a coherent response to a crisis and the development of strategies to deal with communicable diseases and safety of blood, tissues and organs.

Finally, the work programme on health determinants will focus on in support of EU policies and strategies on health determinants, notably on mental health, nutrition and physical activity, tobacco, alcohol, drugs and environment. A specific focus will be on projects addressing good practice in conveying health-related life skills, in particular for children and young people, covering both risk and protective factors with an impact on lifestyles and behaviours. Priority

will be attributed to projects showing awareness of wider socio-economic considerations and contribute to reducing health inequalities.

In line with the overall stance outlined in the 2007-2013 programme, the 2007 work programme thus does not provide for measures with respect to specific diseases except where there is clear value-added to be expected from undertaking common initiatives. As a result of the severe budgetary restrictions, and as will be shown below, the funds for public health actions undertaken within the framework of the activities of DG SANCO are tiny, in proportion to the funding of health research under the Communities framework programme (FP7) administered by DG RESEARCH.

Box. EU Treaty Provision concerning Public Health

PUBLIC HEALTH

Article 152

1. A high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities. Community action, which shall complement national policies, shall be directed towards improving public health, preventing human illness and diseases, and obviating sources of danger to human health. Such action shall cover the fight against the major health scourges, by promoting research into their causes, their transmission and their prevention, as well as health information and education.

The Community shall complement the Member States' action in reducing drugs-related health damage, including information and prevention.

2. The Community shall encourage cooperation between the Member States in the areas referred to in this Article and, if necessary, lend support to their action.

Member States shall, in liaison with the Commission, coordinate among themselves their policies and programmes in the areas referred to in paragraph 1. The Commission may, in close contact with the Member States, take any useful initiative to promote such coordination.

3. The Community and the Member States shall foster cooperation with third countries and the competent international organisations in the sphere of public health.

4. The Council, acting in accordance with the procedure referred to in Article 251 and after consulting the Economic and Social Committee and the Committee of the Regions, shall contribute to the achievement of the objectives referred to in this Article through adopting:

(a) measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;

(b) by way of derogation from Article 37, measures in the veterinary and phytosanitary fields which have as their direct objective the protection of public health;

(c) incentive measures designed to protect and improve human health, excluding any harmonisation of the laws and regulations of the Member States.

The Council, acting by a qualified majority on a proposal from the Commission, may also adopt recommendations for the purposes set out in this Article.

5. Community action in the field of public health shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care. In particular, measures referred to in paragraph 4(a) shall not affect national provisions on the donation or medical use of organs and blood.

## 5. Pharmaceutical Forum

### 5.1 Introduction

The Pharmaceutical Forum is a high-level political platform for discussion supported by a Steering Committee and three expert Working Groups. The aim is to improve the performance of the pharmaceutical industry in terms of its competitiveness and contribution to social and public health objectives. The Forum brings together Ministers from all European Member States, Representatives of the European Parliament, the Pharmaceutical industry, health care professionals, patients and insurance funds.

The Forum provides the overall political oversight for the process. The main role of the Forum is to provide strategic direction to the different work streams of the new strategy. It is also designed to provide a political mandate and momentum for the process and a platform for discussion on competitiveness and related public health issues.

The Forum is chaired jointly by Vice-President Verheugen and Commissioner Kyprianou. Ministers from each Member State are invited. In addition to Member States, three representatives from the European Parliament are members. The remaining membership is made up of senior representatives from industry and other stakeholders.

The Forum will meet once a year up to 2008. The first Forum was held on 29 September 2006.

Three expert Working Groups support the work of the Forum and the Steering Committee. The task of the Working Groups is to consider how to make progress on information to patients, pricing policies and relative effectiveness assessments. The Working Groups are composed of representatives of the Member States and the stakeholders. Working Groups are chaired jointly by DG Enterprise & Industry and by DG Health and Consumer Protection.

- Working Group on Information to Patients
- Working Group on Pricing
- Working Group on Relative Effectiveness

The work of the first of these working groups is of importance for the approach to information to patients on asthma issues and asthma management.

### 5.2 Information to Patients

The debate on the issue of advertising and information to patients has become increasingly important in recent years, particularly in light of growing international health websites with uncontrolled content.

The Commission tried to tackle the issue as part of the review of EU pharmaceutical legislation as early as 2002. The proposal included some provisions liberalising information to patients, in particular, a pilot system aimed to ensure the availability of better, patient-orientated information on authorised prescription drugs for three types of long-term and chronic illnesses. In recognition of the crucial role of guided self-management in the treatment of these diseases, asthma was included among them alongside HIV/Aids and diabetes.

The Commission's plans were rejected by the Parliament, as MEPs feared that the proposal would open the door to US-style advertisements for prescription drugs within the EU. The European Parliament's decision against the Commission's pilot project was followed by the rejection of the Member States.

After this failed attempt, it was decided in 2005 to address the issue of patient information in the framework of the Pharmaceutical Forum. The Forum's Working Group on Information was

established to develop a tool to make quality information on diseases and drugs available to all EU citizens, as well as to discuss the legal framework for companies to provide information to patients.

In 2006, the Working Group chose diabetes as model disease to develop an initial information package for patients. Work on the diabetes package and on a draft set of principles on good quality information was finalised and published as part of a consultation in March 2007.

In their responses to the consultation, stakeholders generally welcomed the ideas of developing disease-specific information packages at EU level, as this could serve as a meaningful additional source of quality information for patients across the EU, particularly for patients in smaller Member States which had considerably less online information available than, for instance, English-speaking patients in the EU.<sup>12</sup>

However, the actual format and content of the diabetes package was heavily criticised by most respondents. They pointed out that the language of the document was too complicated and the structure confusing. Moreover, various gaps in the technical and scientific information were identified.<sup>13</sup> In their response, the European Respiratory Society (ERS) pointed out that, according to a 2007 survey among their members, 96.3% of the respondents said that they would like to provide more and better information to patients.

Following the consultation and discussions of the Working Group's progress on information to patients during the Pharmaceutical Forum's second meeting on 26 June 2007, the Commission now appears ready to move away from the 'all-stakeholder' approach and will probably start drafting a first legislative proposal later in 2007. Judging from the process so far, a lengthy adoption process can be expected. Due to the highly political nature of the issue, adoption through the Commission and subsequent legislative debate in European Parliament in Council is likely not to happen until 2009, when both a new Commission and Parliament have been installed.

Whilst considerable time will be taken to find a workable compromise acceptable to the European Parliament, EU policy makers should bear in mind the urgency for additional quality information for patients in light of the wide availability of unreliable and potentially harmful online content. It is evident that the EU can make a significant contribution in this field. Hesitating to do so would be to the detriment of patients, particularly to those suffering from chronic, long-term diseases such as asthma, where better informed patients have been identified as a key factor for improved therapeutic outcomes.

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<sup>12</sup> The European Commission had looked into existing differences between Member States on the issue of information in a draft report that was published as part of a consultation in April 2007. The report sets out possibilities for improving the current legal framework, and reviews the activities carried out by Member States concerning the provision of information on medicinal products in order to respond to the needs of patients and consumers under the current legal scheme. The report concludes that although advertising to the public is prohibited for prescription-only medicines across the EU, rules and practices still vary considerably in Member States. According to the report, this results in unequal access of patients to information on medicinal products. The report also addresses the fact that the quality of available information varied considerably.

<sup>13</sup> [http://ec.europa.eu/health/ph\\_overview/other\\_policies/pharmaceutical/results\\_consultation\\_en.htm](http://ec.europa.eu/health/ph_overview/other_policies/pharmaceutical/results_consultation_en.htm).

## 6. The EMEA and EU market authorisation procedures for medicinal products

### 6.1 Introduction

Contrary to the situation in the public health field, the EU in the pharmaceutical sector has a core competence with respect to the authorisation of drugs in the EU's Internal Market. Indeed via the EMEA, the EU is currently issuing disease specific treatment and research guidelines. This EU competence is Treaty based and clearly has important implications also for the EU's approach to public health policy.

The Treaty of Rome does not contain any specific provisions for the pharmaceutical industry. However, the EU may undertake certain actions within the framework of competition policy (Articles 81-89), the mandate of 30 May 1980, which empowers the Commission to put forward proposals particularly on industrial policy (Article 308), and, in certain cases, on the basis of Article 152 on public health. Article 157 provides for the possibility of coordination by the Commission of Member States' initiatives on EU industrial policy.<sup>14</sup> As far as public health is concerned, by far the most important competence concerns the authorisation of pharmaceutical products within the internal market (Article 95),

### 6.2 Authorisation of medicinal products in the EU

In order to remove obstacles to the internal market in pharmaceuticals while at the same time ensuring a high level of public health protection, the EU has, since 1965, gradually developed a harmonised legislative framework for medicinal products. The current system is based on two separate procedures for marketing authorisation:

- **the centralised procedure** leads to a single marketing authorisation valid throughout the EU based on a scientific evaluation by the committees created within the European Agency for the Evaluation of Medicinal Products (EMA) in London. This procedure is mandatory for certain medicinal products developed by means of biotechnological processes, and optional for certain other categories of medicinal products, such as those containing new active substances, and those presenting a significant innovation.
- For those medicinal products not eligible for the centralised procedure, or where the applicant chooses not to follow the centralised procedure, the system provides for a **mutual recognition procedure**. This procedure has to be used by the applicant whenever an application for marketing authorisation for a medicinal product concerns two or more Member States.

Regulation 2309/93 introduced the centralised procedure, which entered into force in 1995. Within six years, the Commission was obliged to report on the experience acquired in Chapter III of Directive 75/319 on medicinal products for human use and in Chapter IV of Directive 81/851 on medicinal products for veterinary use. The pharmacovigilance chapters of the latter were amended by Directives 2000/38 and 2000/39 respectively. These amendments are now integrated into Directives 2001/82 and 2001/83, which, to improve clarity and rationality, codify and consolidate in a single text all EU legislation on medicinal products for human and veterinary use.

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<sup>14</sup> The preceding and following paragraphs are based on or extracts from European Parliament Fact Sheet, 4.7.5: The chemical and pharmaceutical industries: [http://www.europarl.europa.eu/facts/4\\_7\\_5\\_en.htm](http://www.europarl.europa.eu/facts/4_7_5_en.htm).

In view of the experience gained from 1995 to 2000 and the Commission's analysis report "on the operation of the procedures for the marketing authorisation of medicinal products", the Commission proposed amending Directives 2001/83 and 2001/82. This revision was implemented through Directives 2004/27 and 2004/28.

Alongside this revision, Regulation 2004/726 amended the operation of the European Agency for the Evaluation of Medicinal Products (EMEA) and changed it to the European Medicines Agency. The changes to the centralised procedure (Regulation 2309/93) involve corrections of certain operating methods and adjustments to take account of scientific and technological developments as well as the enlargement of the EU.

### **6.3 The role of the European Medicines Agency (EMA)**

As presented on the home page of the EMA its mission in the context of a continuing globalisation, is to protect and promote public and animal health by developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and non-prescription medicines through a single European marketing authorisation, controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network.

The Agency brings together the scientific resources of over 40 national competent authorities in 30 EU and EEA-EFTA countries in a network of over 4,000 European experts. It contributes to the European Union's international activities through its work with the European Pharmacopoeia, the World Health Organization, and the ICH and VICH trilateral (EU, Japan and US) conferences on harmonisation, among other international organisations and initiatives.

The EMA is headed by the Executive Director and has a secretariat of about 440 staff members in 2007. The Management Board is the supervisory body of the EMA, responsible, in particular, for budgetary matters.

The Agency's work programme for 2007 (<http://www.ema.eu.int>) includes:

- Providing incentives for "orphan medicinal products" (products which for economic reasons are not otherwise developed);
- Providing scientific advice and protocol assistance, in particular with respect to fostering new innovative technologies and therapies (such a paediatric medicines);
- Initial evaluation of human and veterinary medicines;
- The establishment of maximum residue limits for substances used in veterinary medicinal products in foodstuffs of animal origin;
- Post-authorisation activities of human and veterinary medicines
- Pharmacovigilance and maintenance activities, with the aim to ensure the safe use of centrally authorised medicinal products.
- Arbitration and Community referrals
- Medicines for children, with the EMA Paediatric Committee conducting assessment of, agreement on, and verification of compliance with, paediatric investigation plans and waivers and the gradual establishment of a European network for paediatric research and the development of guidelines for transparency of the paediatric clinical-trials database.
- Preparation of scientific opinions on questions relating to herbal medicines and establishment of Community herbal monographs for traditional and well-established herbal medicinal products



Of particular relevance for the present study is the EMEA guidance note of November 2002<sup>15</sup>, which underlines that European and US guidelines recommend a stepped approach to treatment, which is linked to a categorization of the severity of the condition, according to the classification of the GINA workshop report (see below).

Furthermore, as outlined in a note issued in October 2006<sup>16</sup> the Paediatric Working Party (PEG) is working to identify the needs in the different therapeutic areas where there should be research and development of medicinal products for children, either old (i.e. off patent) or new ones (including those under development). The Working Party in this note stresses that there is a need for age-appropriate devices and delivery systems for administration to the bronchial system. Various drug delivery systems are offered (e.g. inhalers, spacers, nebulisers) and training is needed to use the devices appropriately. It also underlines the need for disposition studies including data to link the delivered dose to the actual needed target concentration, for consistency in delivering dose per inhalation and for development / evaluation of patient leaflets and treatment of severe obstruction.

The EMEA and the US Food and Drug Administration (FDA) of the US Department of Health and Human Services have initiated a pilot program to provide parallel scientific advice. The goal of this pilot scheme is to provide a mechanism for EMEA and FDA assessors and sponsors to exchange their views on scientific issues during the development phase of new medicinal products (i.e. new human drugs and biologics). The expected advantages from such interactions are increased dialogue between the two agencies and sponsors from the beginning of the lifecycle of a new product, a deeper understanding of the bases of scientific advice, and the opportunity to optimize product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies. During this pilot scheme, parallel scientific advice efforts should focus primarily on important breakthrough drugs as explained further in this document.

These meetings are conducted under the auspices of the confidentiality arrangement between the European Commission, the EMEA, and FDA.<sup>17</sup>

## **7. The European pharmacovigilance system**

### **7.1 The conceptual and institutional framework**

From a theoretical perspective, Pharmacovigilance is defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effect of medicines. From a more practical standpoint, this translates into, collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological

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<sup>15</sup> Note for guidance on the clinical investigation of medicinal products in the treatment of asthma, Committee for proprietary medicinal products (CPMP), 21 November 2002 (CPMP/EWP/2922/01)

<sup>16</sup> Assessment of the Paediatric Needs Asthma and other Obstructive Chronic Lung Diseases <http://www.emea.europa.eu/pdfs/human/peg/43972706en.pdf>.

<sup>17</sup> An example of the FDA's public guidelines on asthma management: [http://www.fda.gov/FDAC/features/2003/203\\_asthma.html](http://www.fda.gov/FDAC/features/2003/203_asthma.html).

products, herbal and traditional medicines, with a view to identifying new information about hazards associated with medicines, and preventing harm to patients.<sup>18</sup>

Pharmacovigilance is particularly concerned with the so-called Adverse Drug Reactions (ADRs), which are officially described as: “A response to a drug which is noxious and unintended, and which occurs at doses normally used... for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.”<sup>19</sup> The main purpose of such activity stems from the likelihood that, given the impossibility to detect all potential risks during the clinical trials, less common side effects and ADRs become visible only after a drug has entered the market. Even very severe ADRs, such as liver damage, are often undetected because study populations are small. For such reason, post-marketing pharmacovigilance uses tools such as data mining and investigation of case reports to identify the relationships between drugs and ADRs.

As appears straightforward from the above description, pharmacovigilance is thus mostly aimed at protecting human and animal health, more than other important goals such as growth and jobs. It strives to achieve this goal by complementing the *ex ante* risk assessment that leads to a decision to approve the marketing of a given drug. Pharmacovigilance can therefore be also defined as an *ex post* risk assessment of the effects of marketed drugs on patients' health conditions, particularly ADRs. Such *ex post* assessment is made necessary by the asymmetric information that characterizes public administrations and also health practitioners at the time when a new drug enters the market.

There are many actors that make pharmacovigilance possible in the EU. These include:

- **Marketing authorisation holders (MAHs)** are primarily responsible for the safety of their medicinal products, from the start of drug development and throughout the lifecycle of a product. “The MAH has to fulfil various pharmacovigilance system requirements which are either explicitly laid down in legislation or are detailed in supporting guidelines”. The responsibility for the safety of the individual medicinal products rests with the MAH. He is obliged to establish and operate a system, which allows the conduct of all obligations that derive from the ongoing safety monitoring of the medicinal product. Activities that must be performed by MAHs include:
  - expedited reporting
  - periodic safety update reporting
  - responding to requests for information from Competent Authorities
  - handling of urgent safety restrictions and safety variations
  - continuous monitoring of the safety profile of the authorised medicinal product
  - notifying Competent Authorities and health professionals of changes to the risk-benefit profile of products
  - meeting commitments made at the time of authorisation
  - internal audit of the pharmacovigilance system

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<sup>18</sup> The phases of pharmacovigilance are: a) Data collection; b) Data management; c) Signal detection; d) Safety issue assessment; e) Decision-making; and f) Communication and action. See Fraunhofer Institute, *Assessment of the European Community System of Pharmacovigilance* (2006).

<sup>19</sup> Who Technical Report n. 498 (1972).

- **Health care professionals (HCPs)** have direct contact to the patients and they possess medical knowledge. Therefore, they are an important source for the collection of safety data, which arise from the application of medicinal products. Moreover, HCPs are responsible to inform the patients about safety related problems and changes of the application of a medicinal product. Thus, the practical implementation of pharmacovigilance and the prescription of a safe treatment rest with them.
- **Competent authorities at national level** are normally Ministries of Health of special agencies with a specific mandate to promote drug safety in the national territory; these authorities are responsible for nationally authorised products, including products that are not centrally authorised<sup>20</sup>. They must continually monitor the safety profile of the products available on their territory and take appropriate actions where necessary and monitor the compliance of market authorisation holders (MAH) with their obligations with respect to pharmacovigilance.
- **Member states** are obliged to operate a pharmacovigilance system; to encourage (or require) doctors and other healthcare professionals to report suspected ADRs to the competent authorities
- **The EMEA** plays the main coordinating role in the EU pharmacovigilance system. As specified at Article 57.1(c) of Regulation (EC) No 726/2004, one of the tasks of the EMEA is “to coordinate the supervision... of medicinal products which have been authorised within the Community and to provide advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluation, coordination of the implementation of pharmacovigilance obligations and the monitoring of such implementation”. The Agency secretariat coordinates the pharmacovigilance related processes (including Member States’ pharmacovigilance activities), gives advice on necessary safety measures and provides information about adverse reactions through a database. It is also responsible for the communication with the MAHs of centrally authorised products and for coordination of issues relating to the monitoring of the compliance of the MAH with its pharmacovigilance obligations (Moseley 2004).
- Within the EMEA, **the CHMP** is responsible for providing scientific advice evaluating evidence and formulating opinions on emerging safety issues of centrally authorised products and of products that are subject of a referral (Moseley 2004). The principal task of the CHMP’s Pharmacovigilance Working Party (**PhVWP**) is “to provide advice on the safety of medicinal products authorised in the European Union (EU) and the investigation of adverse reactions to enable effective identification, assessment and management of risk, at any phase in the product life cycle. On the basis of such advice the PhVWP will provide, where applicable, recommendations for regulatory action to its stakeholders, i.e. the CHMP/EMEA and NCAs”. According to this document the key responsibilities of the PhVWP are:
  - evaluation of potential signals arising from spontaneous reporting, including those identified from the EudraVigilance database, and all other sources, including epidemiological databases, studies and published literature;

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<sup>20</sup> The NCAs in the Member States are responsible for nationally authorised products including products that are decentrally authorised. For this case the responsibility for the conduct of pharmacovigilance including the implementation of regulatory actions rests with the NCAs of all Member States that have granted a marketing authorisation.

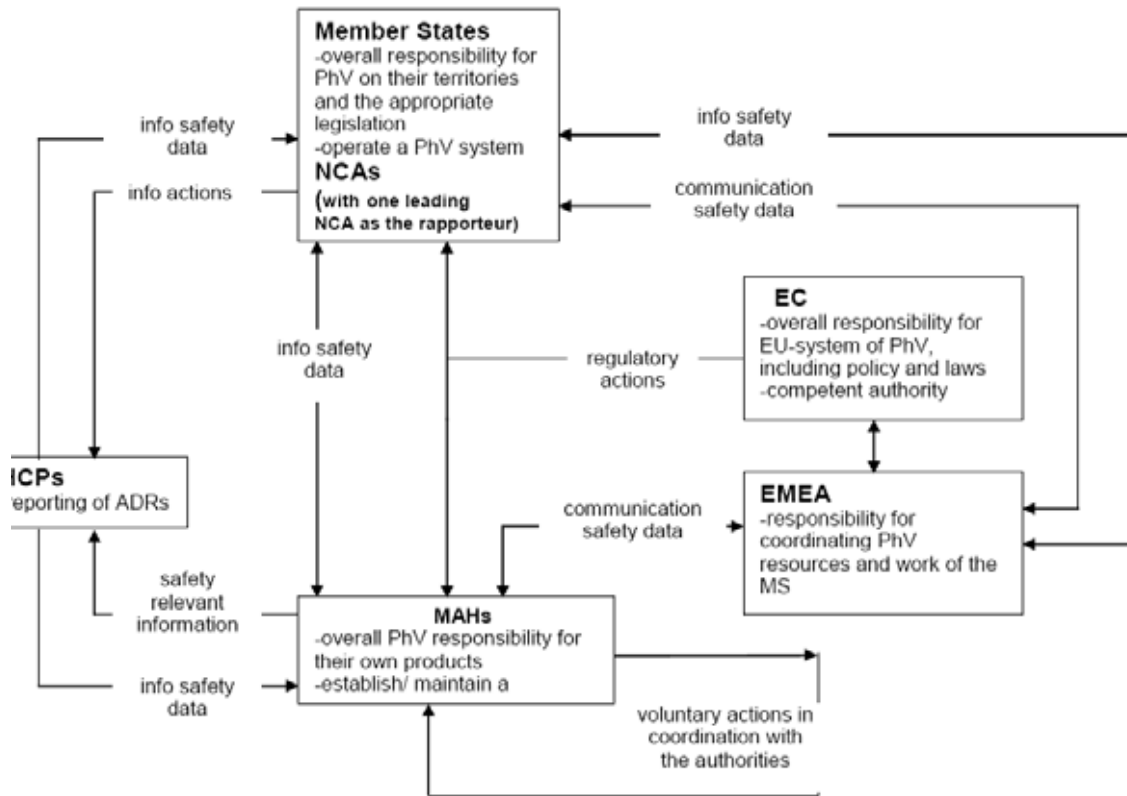
- provision of advice on confirmation and quantification of risk and on regulatory options;
  - risk management by advising on risk management plans;
  - monitoring regulatory action and the outcomes of such action;
  - setting standards for procedures and methodologies to promote good vigilance practice; promotion of communication and exchange of information between the EMEA and NCAs;
  - international cooperation.
- **The European Commission DG Enterprise (Unit F2)** is responsible for the overall pharmacovigilance system in the EU (including policy formulation and lawmaking), and acts as competent authority in case of centrally authorised products.<sup>21</sup> The Commission also issues guidelines on the collection, verification and presentation of ADR reports, including technical requirements for electronic exchange of pharmacovigilance information in accordance with internationally agreed formats.

The required flow of information and the division of competences and responsibilities between the different actors of the EU pharmacovigilance system is depicted below in Figure 1, which relates exclusively to the case of centrally authorised medicines.

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<sup>21</sup> In all other cases (decentrally authorised medicines, mutual recognition) the Commission can adopt decisions based on the opinion of the EMEA Committee for Medicinal Products for Human Use (CHMP) for those products that are subject to the referral procedures.

Figure 2. Pharmacovigilance regarding centrally authorised medicinal products



Source: KKS-UKT/Fraunhofer ISI 2005

As emerges from the picture, a patchwork of actors, roles, responsibilities currently characterises the EU system. Such system is considered to be too complex and often redundant, leading to overall uncertainty, wastage of resources and sometimes to a partially ineffective surveillance and detection of ADRs in Europe.

## 7.2 Division of competences within the European Commission

Pharmacovigilance rules in the EU are included in a directive of the European Parliament and the Council which lays down the rules for manufacture, distribution, authorisation and post-authorisation supervision of nationally authorised products (Directive 2001/83/EC as amended), in a corresponding regulation of the European Parliament and the Council for centrally authorised products (Regulation (EC) No 726/2004), in a Commission Regulation (Regulation (EC) No 540/95) and in Commission guidance (Volume 9A of Eudralex). Although the legislation was reviewed in 2004 (the so-called “2001 Review”) the changes to the pharmacovigilance provisions were relatively minor. Importantly there was no thorough review of the pharmacovigilance provisions and as a result the current provisions have become gradually more complex over time and do not reflect the evolution in science and technology that has occurred, including the opportunities for simplification offered by the full use of modern information technology.

The competences in the field of pharmaceuticals are divided as follows.

- *Health perspective*: DG SANCO is competent for pursuing health care objectives such as patients’ access to the most appropriate use of medicines;

- *Economic perspective:* DG ENTR (Unit F5) is competent for ensuring transparent pricing and reimbursement decisions, and supporting competitiveness, innovation and employment in the EU pharmaceutical sector.
- *Product perspective:* DG ENTR (Unit F2) is in charge of ensuring the quality, safety and efficacy of medicines. This task covers the issue of market authorisations, issued after a scientific (*ex ante*) assessment by the EMEA; Pharmacovigilance – *ex post* assessment; good manufacturing practices and IP protection against the circulation of counterfeited products. Furthermore, this unit at DG ENTR is also in charge of preparing new regulations (e.g. on tissue engineering, paediatric medicines, etc.).

It is in this context of major importance that – given the ‘soft’ provisions for public health actions in the Treaty – the Treaty provisions for pharmacovigilance are, in fact found in articles concerning the functioning of the Internal Market, notably articles 94-96 which, for full information are reproduced in the box below.

#### APPROXIMATION OF LAWS

##### Article 94

The Council shall, acting unanimously on a proposal from the Commission and after consulting the European Parliament and the Economic and Social Committee, issue directives for the approximation of such laws, regulations or administrative provisions of the Member States as directly affect the establishment or functioning of the common market.

##### Article 95

1. By way of derogation from Article 94 and save where otherwise provided in this Treaty, the following provisions shall apply for the achievement of the objectives set out in Article 14. The Council shall, acting in accordance with the procedure referred to in Article 251 and after consulting the Economic and Social Committee, adopt the measures for the approximation of the provisions laid down by law, regulation or administrative action in Member States which have as their object the establishment and functioning of the internal market.

2. Paragraph 1 shall not apply to fiscal provisions, to those relating to the free movement of persons nor to those relating to the rights and interests of employed persons.

3. The Commission, in its proposals envisaged in paragraph 1 concerning health, safety, environmental protection and consumer protection, will take as a base a high level of protection, taking account in particular of any new development based on scientific facts. Within their respective powers, the European Parliament and the Council will also seek to achieve this objective.

4. If, after the adoption by the Council or by the Commission of a harmonisation measure, a Member State deems it necessary to maintain national provisions on grounds of major needs referred to in Article 30, or relating to the protection of the environment or the working environment, it shall notify the Commission of these provisions as well as the grounds for maintaining them.

5. Moreover, without prejudice to paragraph 4, if, after the adoption by the Council or by the Commission of a harmonisation measure, a Member State deems it necessary to introduce national provisions based on new scientific evidence relating to the protection of the environment or the working environment on grounds of a problem specific to that Member State arising after the adoption of the harmonisation measure, it shall notify the Commission of the envisaged provisions as well as the grounds for introducing them.

6. The Commission shall, within six months of the notifications as referred to in paragraphs 4 and 5, approve or reject the national provisions involved after having verified whether or not they are a means of arbitrary discrimination or a disguised restriction on trade between Member States and whether or not they shall constitute an obstacle to the functioning of the internal market.

In the absence of a decision by the Commission within this period the national provisions referred to in paragraphs 4 and 5 shall be deemed to have been approved.

When justified by the complexity of the matter and in the absence of danger for human health, the Commission may notify the Member State concerned that the period referred to in this paragraph may be extended for a further period of up to six months.

7. When, pursuant to paragraph 6, a Member State is authorised to maintain or introduce national provisions derogating from a harmonisation measure, the Commission shall immediately examine whether to propose an adaptation to that measure.

8. When a Member State raises a specific problem on public health in a field which has been the subject of prior harmonisation measures, it shall bring it to the attention of the Commission which shall immediately examine whether to propose appropriate measures to the Council.

9. By way of derogation from the procedure laid down in Articles 226 and 227, the Commission and any Member State may bring the matter directly before the Court of Justice if it considers that another Member State is making improper use of the powers provided for in this Article.

10. The harmonisation measures referred to above shall, in appropriate cases, include a safeguard clause authorising the Member States to take, for one or more of the non-economic reasons referred to in Article 30, provisional measures subject to a Community control procedure.

#### Article 96

Where the Commission finds that a difference between the provisions laid down by law, regulation or administrative action in Member States is distorting the conditions of competition in the common market and that the resultant distortion needs to be eliminated, it shall consult the Member States concerned.

If such consultation does not result in an agreement eliminating the distortion in question, the Council shall, on a proposal from the Commission, acting by a qualified majority, issue the necessary directives. The Commission and the Council may take any other appropriate measures provided for in this Treaty.

Thus the directives in the field of public health, such as directive 2004/27 on the Community code relating to medicinal products for human use, routinely refers to article 95 of the Treaty and not to article 152, reproduced earlier in this Report. The use of article 95 is in fact indispensable from a legal point of view: measures aiming at a rather detailed control with and supervision and, indeed, some degree of harmonization of pharmacovigilance measures cannot legally find their justification in concerns with public health but exclusively in concerns concerning the functioning of the Internal Market. So, in the present Treaty context and pending new provisions concerning harmonization in fields of public policy which today remain in the realm of national competences, the pharmacovigilance measures are likely to remain within the competence of DG ENTR as responsible for the implementation of detailed measures concerning the implementation of free movement of goods and services within the EU's Internal Market.

In January 2004, the Commission presented to the Pharmaceutical Committee a proposal for an Assessment of the Community System of Human Pharmacovigilance. The proposed Assessment was justified on the basis of new pharmaceutical legislation, enlargement of the EU and the changing expectations of our stakeholders. Furthermore, the Commission argued that it was our shared responsibility to ensure that public health protection mechanisms continue to be robust. The proposal had three phases:

- An assessment of the current system including site visits to the national competent authorities and the EMEA,
- Identification of strengths and weaknesses, and

- Proposals on how the system might be strengthened.

According to the synthesis of a total of 48 contributions (made available on the web site of DG ENTR) prepared by the Commission services and published in February 2007 the public consultation made clear that the current EU system for pharmacovigilance is complex, duplicative and an impediment to the single market in pharmaceuticals. There is, still according to the Commission, clear evidence of both industry and regulator resources being diverted away from public health protection to meeting duplicative administrative requirements. Furthermore a lack of clear roles and responsibilities combined with slow and cumbersome EU action in response to drug safety alerts puts patient safety at risk. Stakeholders are calling for the EU system to be rationalised and strengthened. Notably there were calls for:

- Modernization of the legal framework, notably for a single Council regulation to replace all existing EU laws, for a renewal of legislation on periodic safety updating reports (PSURs) and, not least, for an increase in resources for pharmacovigilance.
- Simplification of the organization of the pharmacovigilance system, notably for harmonization of requirements and/or for an overall EU system with one single procedure, rather than disparate Member State systems, notwithstanding recognition that the Member States have a crucial role to play in the implementation of the system.
- Streamlining of the adverse drug reaction reporting (ADR), with rationalization and simplification of the ADR requirements for industry and regulators and submission of ADR reports in standardized form to one single point rather than the current multiple reporting system. In addition there were call for measures to stimulate ADR reporting from health care professionals, patients and consumers.
- Rationalization of the post-authorization system with a more European rather than divergent Member State decisions of drug safety issues.
- Reinforcement of risk management plans, with regulators stressing the need for legal requirements for companies to complete the data collection on drug safety and with reconsideration of education and decision support for prescribers, dispensers and users of medicines and for tighter rules for communication by industry to regulators on risks and withdrawals of medicines.

A more thorough study of the various contributions also reveals concerns, expressed in particular by certain NGOs, consumer organizations and a journal, that the pharmacovigilance system practiced in the EU involves an unfortunate concern with purely industrial interests and management of public health risks. For example Health Action International (submission No 7) argues that the pharmacovigilance system is marked by fundamental conflicts of interest, between health priorities and trade imperatives and by the fact that the same agency both approves drugs for marketing and takes responsibility for monitoring their safety in practice. HAI therefore recommends that while DG ENTR should be responsible for drug safety regulation, the overseeing of pharmacovigilance should be assigned to DG SANCO. A journal (*Précrire*) argues that companies cannot substitute themselves for an efficient public pharmacovigilance system and should not be allowed to interfere with either the analysis of drug safety information or the resulting decisions. The combination of health responsibilities with sponsorship of industry within the EU framework was also (as quoted in the contribution by HAI) criticized in a recent UK Parliamentary enquiry, which argued that the combination of these two roles leads to lack of clarity of focus and commitment to health outcomes.

It must be stressed, however, that the criticism put forward by NGOs, consumer organisations and stakeholders from side of health care providers finds many points in common with the



views of industry, as expressed for example in the contribution from the European Federation of Pharmaceutical Industry and Association (EFPIA). According to the EFPIA:

- Pharmacovigilance rules in the EU are found in a wide array of documents that are sometimes contradictory and often unclear. As such, the rules can be both complex and confusing. There is a need for a new approach to pharmacovigilance regulation in the EU that will allow pharmaceutical companies to focus their pharmacovigilance resources on safety evaluation activities instead of on complying with unclear and complex regulatory demands. Such an approach would be in the best interest of public health.
- The legal framework needs to be improved. The legislation should contain clear and concise provisions that would simplify, strengthen and provide legal certainty to the EU legislative framework for pharmacovigilance. Burdensome national discrepancies throughout an enlarged European Union must be eliminated and national regulators should be prohibited from adding national requirements to those provided for in the European legislation applicable throughout the EU so as to avoid inconsistencies between the rules applied in different Member States. Such a prohibition should not, however, limit the powers of EU regulators to regulate across the EU and the EEA in the interest of public health.
- Obligations that are currently unclear or ambiguous, in particular those that are laid down in the Commission guidance on pharmacovigilance, “Volume 9 – Pharmacovigilance: Medicinal Products for Human use and Veterinary Medicinal Products” (‘Volume 9’), should be clarified and made more precise.

The legislation should contain a single set of simplified rules for expedited and periodic reporting of adverse drug reactions (‘ADR’) in the EU and provide for a single reporting point for ADRs within the EEA. The reporting obligations can be further simplified by removing the “unexpected/expected” concept, and requiring the reporting of all serious cases when electronic reporting is implemented. The legislation should contain clear and flexible provisions regarding Qualified Persons (‘QPs’) responsible for pharmacovigilance that allow individual companies to appoint the number of QPs best suited to their respective organizations. Finally, it should also include consistent standards for inspections of company pharmacovigilance departments by the EMEA and EU Member State authorities.

Asthma management is a field of health care where pharmacovigilance is highly important and extremely difficult. Due to the decentralized nature and the importance of management, including management of information, at the level of the patient’s family (or in many cases the parents!), primary health care providers and - in kindergartens and schools - no doubt also increasingly by supervisors and teachers there are important risks of mismanagement and unreported adverse drug reactions. Furthermore, according to many experts a number of the medicines used to treat asthma symptoms carry a significant risk of influencing adversely physical and mental development and consequently, a need for regular surveillance of the collateral effects of drugs notably in children<sup>22</sup> But also in the elderly. As underlined in the contribution from the European Federation of Allergy and Airway Diseases Patients’ Associations (EFA, contribution No. 5), such recording is often haphazard and dependent on a

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<sup>22</sup> This risks of applying certain new asthma therapy to children, without appropriate research into their long-term effects on physical and mental development is underlined, for example, in an article by a specialist in paediatric asthma in *The Lancet* in 2006: Hans Bisgaard: Long-acting Beta2, agonists and paediatric asthma, *The Lancet*, Vol. 367, January 2006. See also, on the same subject, Fernando D. Martinez: Safety of Long-Acting Beta-Agonists – An Urgent Need to Clean the Air, *N. Engl. J. Med.* 353:25, December 2005.

prescribing physician recognising a temporal link between a prescription and an adverse event. According to the EFA such event monitoring would not have picked up less clearly linked events such as cardiac events linked to prolonged prescribing of COX-2 inhibitors or to an increased risk of asthma deaths in association with prescribing of long-acting beta agonists in the absence of inhaled steroids. It is also, according to the EFA, likely to under-report problems associated with use of medicines that are either unlicensed, as is often seen in paediatric practice, or used beyond their licensed dosages e.g. problems seen again in children with use of high and unlicensed dosages of inhaled steroids as well as nasal steroids for infants.

As stressed by the EFA, patients are an underutilised source of adverse event reporting and methods should be developed for them or their representatives to submit adverse event data. Moreover, even if a drug is prescribed predominantly in specialist practices, adverse events may only be noted in primary care settings and combination of primary and secondary care data on adverse events may become particularly important. Therefore, the EFA considers the decision making process as complex with the current divisions between European Medicines Agency (EMA) / Committee for Medicinal Products or Human Use (CHMP) functions and those of regulatory bodies in Member States. The EFA finds that this may lead to real confusion with doctors in certain member countries receiving very differing or no advice and mentions a recent example of salmeterol where the UK Medicines and Healthcare Products Regulatory Agency (MHRA) provided advice, but many other Member States did not, creating confusion with many doctors in Europe turning to the International Primary Care Respiratory Group (IPCRG) or the US Food and Drug Administration (FDA) website for advice.

There are strong and convincing indications that the horizontal and vertical complexity of the EU's pharmacovigilance system results in considerable delays in the handling, synthesising and dissemination of the emerging on adverse drug reaction and also of the systemic integration of findings and decisions from the front line of the FDA. The treatment of asthma management issues, in fact, provides an example of the comparatively low reaction coefficient within the EU. For example, the FDA on 18 November 2005 requested manufacturers of three asthma medicines, Advair Diskus, Foradil Aerolizer, and Serevent Diskus to update their existing product labels with new warnings and a Medication Guide for patients to alert healthcare professionals and patients that these medicines may increase the chance of severe asthma episodes, and death when those episodes occur. As indicated by the FDA, all of these products contain medicines belonging to the class known as "long-acting beta 2-adrenergic agonists" (LABA), which are long-acting bronchodilator medicines. Further, bronchodilator medicines, such as LABAs, help to relax the muscles around the airways in the lungs and wheezing (bronchospasm) happens when the muscles around the airways tighten. The FDA stressed that even though LABAs decrease the frequency of asthma episodes, these medicines may make asthma episodes more severe when they occur.

Possibly in reaction to the concerns expressed by the FDA the EMA's Paediatric Working Party in October 2006 in an opinion listed needs for data on inter alia the safety in long term use of Salmeterol and on its safety with or without concomitant inhalation of glucocorticoids. However, apart from this announcement the web site of the EMA does not as per the date of drafting provide any further updating on the pharmacovigilance status for this and the two other products classified as "questionable" by the FDA. This can no doubt be considered a good example of the complexity of the EU's PhV system and of an illustration of the needs for a streamlining the procedures as, in fact, called for by the Commission as lately as in early 2007.

### **7.3 The Commission's pharmacovigilance strategy**

The recent consultation run by the Commission highlighted two main problems as regards the decision-making process on pharmacovigilance in the EU:

- The complexity of the system; and
- The potential conflict of interest between the mandate of the European Commission, DG ENTR – to promote competitiveness, innovation and employment in the EU – and the need to protect the health of EU citizens, .

### 7.3.1 *Tackling complexity*

As regards the first critique, the European Commission has recently announced that it plans to cooperate with the EMEA and other stakeholders to strengthen and rationalise the current EU system of pharmacovigilance, with the aim of proposing changes to the current legal framework in 2008. This includes initiatives such as:

- funding of studies together with DG Research to strengthen the knowledge on the safety of medicines as well as methodologies used to conduct pharmacovigilance;
- working with the Member States to identify and resolve implementation issues, including and administrative practices that interfere with the single market.
- Working with the EMEA to strengthen its coordinating role including supporting full compliance and maximum utilisation of the EU pharmacovigilance database (**Eudravigilance**).
- Clarify the boundaries between the competences of member states and the EMEA, in order to avoid duplications.
- Strengthen the rules on transparency relating to pharmacovigilance data, assessment and decision-making and involve stakeholders (e.g. patient and healthcare professional groups) in the processes including reporting (including patient reporting).
- Establish clear standards ('Good Vigilance Practices - GVP') for the conduct of pharmacovigilance by both the industry and regulators.
- Free up resource by rationalising and simplifying the reporting of suspected adverse drug reactions (ADRs), both expedited and periodic reporting, making best use of current information technology (including Eudravigilance) and matching the reporting requirements with the level of knowledge about the safety of a specific product.
- Stimulate innovation by establishing a clear legal requirement to conduct post-authorisation safety studies including those in risk management systems.
- Rationalise EU decision-making on drug safety issues to deliver fast, robust decisions that are equally and fully implemented for all relevant products and across all markets.

### 7.3.2 *Pharmacovigilance elsewhere*

In the United States, pharmacovigilance is the responsibility of the Center for Drug Evaluation and Research (CDER), part of the Food and Drug Administration (FDA) which again is a division of the US Department of Health and Human Services. The budget of the FDA as a whole for fiscal year 2008 amounts to a little more than \$2bn. Through the years, responsibilities within FDA for drug regulation have undergone major changes. Most of these came as a result of innovations in drug development and additions to legislative authority. As of 1994, CDER was the largest headquarters component of FDA, consisting of almost 1500 men and women working in several buildings. The complexity and challenges of drug review are multiplying as the sophistication of drug design and manufacturing increases, which speaks to the importance of maintaining a well-trained and adequately supported group of agency drug officials, for the good of the public health.

Various laws and policies of the 1980s have had an important impact on drug approval and distribution. For example, the agency strengthened reporting requirements for adverse reactions in 1985. The new requirements addressed all prescription drugs, including older pharmaceuticals that predated FDA approval. New regulations for investigational drug development also went into effect in 1985. The new rules increased the availability of experimental drugs, including compassionate use of drugs under research for patients with serious and/or life-threatening conditions. In 1988 FDA promulgated treatment IND regulations. These allowed desperately ill patients to receive promising new drugs before full approval had been completed. Congress passed the Prescription Drug Marketing Act in the same year. This law prohibited the purchase, sale, trade, and -- with exceptions -- re-importation of drug samples. It also required drug wholesalers to register with states.

On October 6, 1987, the Center for Drugs and Biologics was split into the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research (CBER). This split was necessary because of the increasing volume of NDAs, to provide proper high-level attention to the growing problem of AIDS, and to address other issues in drug and biologic evaluation.

In the UK the Medicines and Healthcare products Regulatory Agency (MHRA), a government agency, is responsible for ensuring that medicines and medical devices work, and are acceptably safe. The Agency uses a variety of methods of collecting information on medicines. Healthcare professionals, as well as patients, are encouraged to report suspected adverse drug reactions and there is a legal requirement for companies to report such reactions to their products to us (SIC!). A register of these suspected adverse reactions is maintained which helps provide early warnings of potential drug hazards. The Defective Medicines Report Centre (DMRC) receives and assesses complaints and reports of actual or suspected defects in medicines. The MHRA also runs an information service, EURODIRECT, a data base which provides downloading options of both UK and EU documents and specifications relevant for pharmacovigilance.

Like in the UK, the Medicines Control Agencies around in the EU in general depend upon the Ministry of, or are part of, the Ministry of Health or Social Affairs or in some cases are fully independent institutes. This is the case (as reported on the web sites of the agencies<sup>23</sup>) in Austria, Belgium, Bulgaria (specialised agency), Czech Republic (State Institute for Drug Control), Denmark (Danish Medicines Agency, under the Ministry of the Interior and Health), Estonia (State Agency of Medicines, under the Ministry of Social Affairs), Finland (National Agency for Medicines), France (AFSSAPS), Germany (BfArM), Greece (National Organization for Medicines), Hungary (National Institute for Pharmacy), Ireland, Italy, Latvia, Lithuania, Luxembourg, the Netherlands (the Medicines Evaluation Board and Agency), Poland, Portugal, Romania, the Slovak Republic, Spain, Sweden and, as indicated above, the United Kingdom.

It goes without saying that, as stated in a number of contributions to the public consultation and as illustrated above with respect to recent questioning of certain asthma medicines by the FDA, the final result is an extremely complex institutional setting and which is likely to significantly reduce the efficiency of the defence of the interests of public health in general and of the consumers and patients in particular.

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<sup>23</sup> As reported on the International Society for Pharmaceutical Engineering web site ([http://www.ispe.org/cs/root/regulatory\\_resources/regulatory\\_agencies\\_contacts/regulatory\\_agencies\\_europe](http://www.ispe.org/cs/root/regulatory_resources/regulatory_agencies_contacts/regulatory_agencies_europe) )

### 7.3.3 Is There a Conflict of interest?

The second main critique addressed to the EU pharmacovigilance system is the potential conflict of interest within DG ENTR, which plays at once the role of promoting competitiveness, innovation and growth; and that of issuing decisions on pharmacovigilance for the protection of the health of EU citizens.

In this respect, it cannot be ignored that:

- Competent authorities in all member states are either Ministries/Departments of Health or, in any case, agencies endowed with an overarching mandate to pursue the protection of citizens' health. The same applies also to the *US* (where the Food and Drug Administration is responsible for post-authorisation surveillance); *Japan* (Ministry of Health, Labour and Welfare); *Canada* (the Marketed Health Product Directorate of Health Canada); *Australia* (Therapeutic Goods Administration); and *New Zealand* (the Centre for Adverse Reactions Monitoring (CARM), the Medicines Adverse Reactions Committee (MARC) and Medsafe).
- Against this background, DG ENTR has a fairly different mandate, namely to “ensure that EU policies contribute to the competitiveness of European enterprises and facilitate job creation and economic growth”; and in doing so, it pays “particular attention to the needs of manufacturing industry and small and medium-sized enterprises”.

Based on this evident contrast, as indicated above, one association that contributed to the recent consultation proposed that the competence for issuing regulations and decisions on pharmacovigilance be moved to DG SANCO, whose explicit role is to “help make Europe's citizens healthier, safer and more confident”.

As reported, the Health Action International, HAI-E, concluded that DG SANCO:

*“should assume responsibility for overseeing pharmacovigilance activities. That would both help to soften the impact of conflict of interest, and bring badly-needed fresh thinking to what post-marketing drug safety appraisals should involve ... We emphatically believe that DG Enterprise should concern itself strictly with trade and commercial imperatives and play no primary part in medicines regulation that affects consumer health and safety”.*

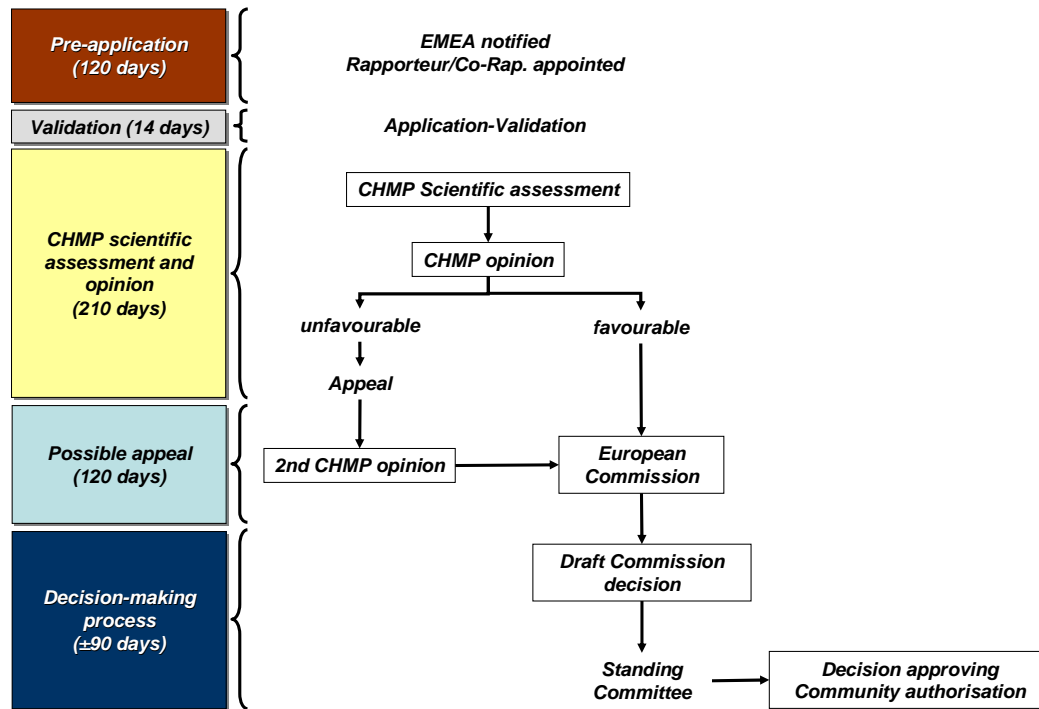
However, when compared with the UK Parliament's review of the relative inefficiency of the Department of Health and the MHRA, the alleged “conflict of interest” at the European Commission seems quite different, for the following reasons:

- The MHRA' primary objective is indeed to safeguard public health by ensuring that all medicines on the UK market meet appropriate standards of safety, quality and efficacy. In other words, the conflict of interest would stem for a “capture” of the Department of Health by the industry, not by a conflict between two different “missions” within the same institution;
- The main problems identified by the UK Parliament are a lack of transparency, accountability and adequate skills, which pave the way for a degree of complacency towards the interests of powerful industry players;
- The problem identified by the UK Parliament leads to a suggestion to move “responsibility for representing the interests of the pharmaceutical industry ... into the remit of the Department of Trade and Industry to enable the Department of Health to concentrate solely on medicines regulation and the promotion of health”. The Parliament's proposal, in other words, calls for a clear division of responsibilities, but does not affect the cycle between *ex ante* assessment and *ex post* surveillance, which would remain in the hands of the DH.

Furthermore, at EU level, the following differences can be highlighted:

- The system is organised on a multi-level basis, where DG Enterprise acts on the basis of information reported by patients, HCPs, MAHs, Member states and the EMEA;
- Within DG ENTR, two different units are responsible for promoting the competitiveness of the pharmaceutical sector (F5) and for pharmacovigilance (F2);
- In the EU Pharmacovigilance system, EMEA plays a key role in the subsequent monitoring of the safety of authorised products, in close cooperation with HCPs and the MAHs. EMEA was actually established following requests by the BEUC and the European Parliament in 1995. The CHMP must closely monitor reports of ADRs and, when necessary, issue recommendations to the European Commission regarding changes to a product's marketing authorisation or the product's suspension/withdrawal from the market.
- The HAI-E acknowledges that DG ENTR should remain responsible for drug safety regulation. However, DG ENTR is also responsible for the *ex ante* approval of medicines, also after the scientific advice of the EMEA's CHMP. Figure 2 below shows the role of DG ENTR and EMEA in the marketing authorisation procedure. The proposal by HAI-E, thus, would entail either moving both responsibilities to DG SANCO (authorisation and *ex post* surveillance) or splitting the two in two different DGs.
- The decision to monitor drug safety is closely linked to responsibility for drug safety regulation. Moving responsibility for pharmacovigilance into the remit of DG SANCO may create inefficiencies and organisational redundancies in the policy formulation/evaluation cycle.
- Finally, within the European Commission, DG ENTR also holds a key responsibility for *ex ante* impact assessment and *ex post* evaluation: this also justifies the attribution of responsibility for pharmacovigilance to this DG (with the support and advice of a technical body such as EMEA).

Figure 3. The centralised procedure for marketing authorisation



Source: Elaboration on European Commission, DG Entr (2007) at <http://ec.europa.eu/enterprise/pharmaceuticals/>.

### 7.3.4 Pharmacovigilance and asthma management

Based on the previous sections, it is fair to conclude that the problems related to the lack of effectiveness and efficiency of the pharmacovigilance system in the EU – which have been recognised by the Commission also in recent documents – do not lie in the alleged conflict of interest within the two units (F2 and F5) of the Enterprise Directorate-General. The role of DG Enterprise as both contact point for businesses and body in charge of pharmacovigilance can be justified in many respects, and does not seem to have created significant shortcomings in the evaluation process to date. Indeed, the alleged conflict of interest was raised only by HAI-E in the consultation, and on rather shaky grounds.

That said, of course the overall system can be improved, and the Commission seems to have committed to a number of promising changes in the current governance of the process, which have the potential to increase transparency and accountability of public administrations.

Perhaps the most urgent problem to be solved in the months ahead is improving the approval process and information sharing on respiratory diseases, in particular asthma.

In Europe, around 1.5 million people reportedly live in fear of dying from an asthma attack. In Western Europe, as reported by the World Health Organisation, every hour one person dies as a result of asthma, around 30 million people have asthma, and 6 million suffer from symptoms

which are characterised as severe. Overall, the total cost of asthma care in Europe is €17.7bn per year, and productivity lost every year because of poor asthma control is estimated at €9.8bn.<sup>24</sup>

Accordingly, asthma management is probably the most challenging task for EU health policy in the years to come. A recent survey – published on *Allergy* in February 2007 – estimated that 90% of deaths for asthma in Europe could be prevented with a more efficient asthma management system. Important initiatives on asthma have been undertaken at EU level in the past years to tackle the problem.

More recently, the European Parliament voted a draft resolution on the Council common position for adopting a regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Asthma is indeed particularly widespread amongst children, and the treatment of asthma in early years can prove particularly important.<sup>25</sup>

But are there current flaws in the EU pharmacovigilance system which jeopardise the efficient management of asthma in the EU? The recent “Brussels Declaration” discussed at the *Summit for Change in Asthma Management* hosted by UK Liberal Democrat MEP Liz Lynne in the European Parliament on October 19, 2006 called, *i.a.*, for making asthma a political priority, spreading information amongst patients, HCPs and policymakers, promoting best practices on asthma management (e.g. the Finnish case), updating the EMEA Guidance note on Asthma and improve pharmacovigilance on asthma.<sup>26</sup>

This recent proposal, once again, seems to point at EMEA as the key actor in charge of ensuring that clinical trials currently being undertaken on drugs for respiratory diseases adequately take into account the magnitude and complexity of the asthma phenomenon. The current EMEA Guidance note, issued in 2002, reportedly did not lead to significant changes in the way clinical trials are run. Trials remain unrepresentative of the asthmatic population, and the *Summit for Change in Asthma Management* concluded that drugs are often tested on only 2% of the type of people affected by the disease.<sup>27</sup> A review of the Guidance Note should therefore be considered in order to stimulate better clinical trials on the side of MAHs.

In addition, the transparency of activities carried out by EMEA both within the EU pharmacovigilance system and as regards the pre-authorisation assessment phase can be made more transparent. In line with widely acknowledged principles of good regulation, the publication of decisions adopted by EMEA and the consultation on principles adopted in the assessment of the health impact of new drugs can significantly increase the accountability and efficiency of the overall process. For example, publishing detailed press releases such as the ones published by the US FDA could substantially contribute to the transparency of EMEA and disseminate information as to “who does what” in the EU pharmacovigilance system.

Another important step would be the publication of the methodology followed by EMEA in assessing whether to grant authorisation to new drugs, as well as to assess *ex post* the impact of

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<sup>24</sup> European Respiratory Society, *The European White Lung Book: The First Comprehensive Survey in Respiratory Health in Europe*, 2003.

<sup>25</sup> See, e.g. Pohunek, P., *Paediatric asthma: How significant it is for the whole life?*, Paediatric Respiratory Reviews, Vol. 7, pp. S68-S69, Elsevier Science, 2006.

<sup>26</sup> The Brussels Declaration is attached as an appendix to the present Report.

<sup>27</sup> See, *i.a.*, *Asthma: The growing gap between scientific understanding and clinical practice*, Report of a Master Class held in Brussels in July 2006, available at <http://www.summitforchange.eu>.



a given pharmaceutical product on the market. Such methodological documents could be subject to public consultation, and this would in turn enable all stakeholders to contribute to improving the methodology currently being adopted by EMEA, and to check whether such methodology is actually followed in the *ex ante* and *ex post* evaluation phases.

Moreover, the *Summit* has stressed the systemic nature of the asthma disease: it is heavily affected by the environment and its treatment and prevention requires a “holistic approach”, not solely based on the prescription of medication. In this respect, important recent initiatives are the following:

- Addressing asthma and respiratory diseases in children was one of the pillars of the Commission’s 2003 Communication on a European environment and health strategy and the 2004 Action Plan on Environment and Health;
- Reducing exposure to fine particles and ozone as the main outdoor culprits for the adverse effects on children's respiratory symptoms is addressed in the 2005 Thematic Strategy on Air Pollution;
- Tobacco legislation sets out a list of 14 health warnings about smoking during pregnancy and smoking around children, and the Commission is in the final stages of adopting a Green Paper on smoke-free environments;
- Full implementation of existing Community legislation addressing air pollution, such as Integrated Pollution Prevention and Control (IPPC), national emission ceilings and air quality is necessary to secure healthy outdoor air for our children.
- The Council and Parliament recently agreed new vehicle emission standards EURO 5/6(5) that will dramatically reduce emissions of fine particles from cars.
- In 2007 the Commission will propose a related EURO VI proposal for heavy duty vehicles, and the revision of the National Emission Ceilings Directive, limiting national emissions of particles and ozone precursors.
- The proposed Directive on ambient air quality and cleaner air for Europe, currently in co-decision, is introducing further environmental objectives for fine particles.
- The recently launched Seventh Framework Programme for Research included respiratory diseases as one of the key priorities for European research in the years to come.

In this context and perspective it is highly relevant to take stock of the work programme and priorities in the field of health research in the EU’s Framework Programme for Research now adopted for the seven-year period 2007-2013.

## **8. EU funding of health research on asthma**

### **8.1 The EU’s Seventh Research Framework Programme (FP7)**

The 7<sup>th</sup> Framework Program will provide funding for research activities in the EU and some non-EU countries for a total of €50.5 bn over a period of seven years, 2007 to 2013. The first calls were issued on 22 December 2006, with April-May 2007 as the first deadlines for project submissions, the specific dates varying from one theme to another.

As shown in Table 1 FP7 will provide funding for five main areas of research and activities:

- Cooperative research projects and various coordination and support activities. These projects in general must include at least three partners from at least three different EU countries.

- Projects considered presenting a particular scientific interest and which will be selected by a specially nominated Council.
- Mobility of researchers through various versions of the Marie Curie program;
- Development of research infrastructures;
- Non-nuclear actions of the Joint Research Centre.

*Table 1. Overall budget for FP7, €mn*

|                               |        |
|-------------------------------|--------|
| Cooperation (research)        | 32 292 |
| Ideas (scientific excellence) | 7 460  |
| People (mobility)             | 4 727  |
| Capacities (infrastructures)  | 4 291  |
| Non-nuclear actions of JRC    | 1 751  |
| Total                         | 50 521 |

The largest part of the budget, 64%, will be allocated to research projects within a total of 10 different themes (health, food and agriculture, ICT, nano-sciences, energy, environment, transport, socio-economic sciences and humanities, space and security).

Among these themes ICT receives the largest budget attribution with €9050mn. Health comes second with a total attribution of €6100mn. It should be noted, in passing, that research on the introduction of ICT in the health sector is included under the former theme and therefore does not “weigh” in the budget for health research.

## **8.2 General objectives of health research in FP7**

As presented in the work program for the health theme the objectives of research for the whole period is:

Improving the health of European citizens and increasing the competitiveness and boosting the innovative capacity of European health-related industries and businesses, while addressing global health issues including emerging epidemics. Emphasis will be put on translational research (translation of basic discoveries into clinical applications including scientific validation of experimental results), the development and validation of new therapies, methods for health promotion and prevention including promotion of child health, healthy ageing, diagnostic tools and medical technologies, as well as sustainable and efficient health care systems.

The selection of research projects is, as in preceding framework programs made on the basis of projects submitted in response to calls. The first of these calls was issued on 22 December and with a total budget of € 628mn distributed as shown in Table 2, on four categories: biotechnology and tools, basic research and actions “across the theme”. The call includes a fourth category, “optimizing the delivery of health care”, addressing mainly, as suggested in the title, research into the functioning of the health care sector and the interfacing with the recipients of health care. These latter issues will be the subject of the second bunch of research projects to be submitted in the autumn of 2007 but for which the budget is not yet specified.

Table 2. Health research: budget for first call

|   |          |
|---|----------|
|   | 19 April |
| 1. Biotechnology, generic tools and Medical technologies for human health | 138      |
| 2. Translating research for human health                                  | 472      |
| 3. Optimising the delivery of health care                                 | -        |
| 4. Actions across the theme   | 18       |
| Total   | 628      |

### 8.3 Allocation of resources for respiratory diseases

The allocation of these amounts on specific research topics is not specified but can to some extent be deducted from the break-down of the main subjects on detailed topics for which calls are invited. Thus, within item 2, “Translating research for human health” the work program specifies, for the first deadline, a total of 63 topics, of which 11 in the field of biological data integration, 11 in the field of brain research, 14 in the field of infectious diseases and 27 in a heterogeneous group of “other major diseases. The latter group includes 8 topics in the field of cancer research, 3 topics in the field of cardiovascular diseases, 5 in the field of diabetes and obesity, 2 in the field of “rare diseases” and 9 on other chronic diseases. Among the latter, the work program specifies one research topic on “chronic obstructive pulmonary disease with the following specific work program:

***Innovative concepts in chronic obstructive pulmonary disease pathogenesis (COPD).*** Support will be given to multidisciplinary projects investigating innovative concepts and critical gaps in the pathogenesis of COPD in order to increase the knowledge of the pathology of the disease. The research should focus on the translational aspects with integration of biological data with clinical data and on the identification of biomarkers and molecular targets in order to pave the way for better diagnostics and treatment of the disease. User friendly and cost effective diagnostic should be considered. **Funding scheme:** Collaborative projects (Small or medium-scale focused research projects).

As indicated the call is for “small or medium-scale focused research projects” implying a budget up to but probably somewhat below €4mn.

The second part of this call, comprising topics to be submitted in September 2007, includes a total of 49 research topics within item 2, of which 9 topics on biological and medical data, 8 topics on research on brain diseases, 12 topics within infectious diseases, and 20 within other major diseases. Among the latter a topic specifies research on “early processes in the pathogenesis of chronic inflammatory diseases” in the following terms:

***Early processes in the pathogenesis of chronic inflammatory diseases.*** Translational research to obtain mechanistic insights into the early processes underlying chronic inflammatory diseases, such as asthma, rheumatoid arthritis and autoimmune conditions. Emphasis should be placed on identifying and validating molecular networks involved in the establishment and persistence of the chronic inflammatory reaction, with the aim of developing novel and specific anti-inflammatory treatments. A multidisciplinary approach (immunologists, cell biologists, molecular biologists, bioinformaticians) and the use of animal models amenable to genetic testing and manipulation are required. **Funding scheme:** Collaborative project (Large-scale integrating project).

In this case the call specifies a “large-scale integrating project” which can be assumed to involve a budget of up to €10mn.

#### **8.4 Other potentially relevant topics**

Apart from the two research topics specifically addressing respiratory diseases, this call includes topics of a general nature but which might be of some relevance also for asthma research. These topics, for which more details are provided in the annex, cover the following fields:

- Immunotherapy of human food allergies;
- Novel approaches to reconstitute normal immune function at old age;
- Implementation of research into health care practice;
- Self-medication and patient safety;
- Patient safety research network;
- Improving clinical decision making;
- Better use of medicines;
- Continuity of clinical care; and
- Patient self-management of chronic diseases.

In particular the last item in this list could be relevant for research into the approach to self-management of treatment of asthma, frequently implemented outside the normal framework of health care.

#### **8.5 Conclusions on EU funding of asthma research**

Contrary to declared EU objectives and (certain) anticipations, respiratory diseases have not been specified as a high priority in the 7<sup>th</sup> Framework Program. In the selection of priorities in the first call, issued on 22 December, only two topics out of a total of 103 (the total of the two deadlines) concern specifically respiratory diseases as compared to, notably, 15 topics in the field of brain disease, 33 topics in the field of infectious diseases, 13 topics in the field of cancer, 7 in the field of cardiovascular diseases and 9 in the field of diabetes and obesity. However, there would seem to be scope for the formulation of research proposals both within the context of the April deadline (small-scale project) and of the September deadline (large-scale project).

However, as asthma is a disease involving a broad interfacing between the health care sector and the patient, with a considerable amount of self-management, there would seem to be scope for undertaking research on these aspects also within the number of topics of a more general nature. Consequently, researchers in the field of asthma management should clearly consider the scope for formulating research projects in these areas as well.

### **9. Summary – Towards better management and regulation of asthma in the EU**

Asthma is a common life-long chronic inflammatory disorder of the airways that affects children and adults of all ages and whose prevalence is rising in a number of the most-developed countries. Although the understanding of many aspects of asthma has improved over the past two decades, the fundamental causes of asthma are still not known. Various genes have been associated with an increased risk of developing asthma and increased susceptibility to

asthma. Environmental influences are also likely to play a part in the initiation of asthma by interacting with the genetic predisposing factors.

As stressed, for example in the GINA Report quoted above, during the past two decades, we have witnessed many scientific advances that have improved our understanding of asthma and our ability to manage and control it effectively. However, the diversity of national health care service systems and variations in the availability of asthma therapies require that recommendations for asthma care be adapted to local conditions throughout the global community. In addition, public health officials require information about the costs of asthma care, how to effectively manage this chronic disorder, and education methods to develop asthma care services and programs responsive to the particular needs and circumstances within their countries.

At the same time, the Global Initiative for Asthma (GINA) was implemented to develop a network of individuals, organizations, and public health officials to disseminate information about the care of patients with asthma while at the same time assuring a mechanism to incorporate the results of scientific investigations into asthma care.

Publications based on the GINA Report were prepared and have been translated into languages to promote international collaboration and dissemination of information. To disseminate information about asthma care, a GINA Assembly was initiated, comprised of asthma care experts from many countries to conduct workshops with local doctors and national opinion leaders and to hold seminars at national and international meetings. In addition, GINA initiated an annual World Asthma Day (in 2001) which has gained increasing attention each year to raise awareness about the burden of asthma, and to initiate activities at the local/national level to educate families and health care professionals about effective methods to manage and control asthma.

In spite of these dissemination efforts, international surveys provide direct evidence for suboptimal asthma control in many countries, despite the availability of effective therapies. It is clear that if recommendations contained within the GINA report are to improve care of people with asthma, every effort must be made to encourage health care leaders to assure availability of and access to medications, and develop means to implement effective asthma management programs including the use of appropriate tools to measure success.

In this respect the Finnish experience already referred to above would seem to contain important lessons for other Member States and for the approach to asthma management at the level of the EU. The success of this program was attributable in the main to an important effort at the grass-root level taking full account of local and professional conditions and mobilizing not only the medical staff but all stakeholders, including the civil society actors with a potential for establishing the necessary links with, and promoting an efficient management by the patient.

Despite the repeated expressions of concern by the Council, emphasizing in particular, the need to focus in children's health, asthma management and care seems still to be sub-optimal in most EU Member States. In this context note should be taken, however, of the large disparity between EU Member States with respect to prevalence of asthma and, thus, the perception of this as a public health problem.

Understandably, some professionals may feel a high degree of impatience with respect to the speed with which the latest results of asthma research are channelled into the sphere of prevention and care at the national and EU level. However, Europe is now into the 21<sup>st</sup> century facing a number of threats to health and environment and the fixing of priorities as between, say, cancer, cardiovascular diseases, respiratory diseases, mental disorders, arthritis and multiple sclerosis is a particular difficult exercise, notably at the level of the 27 Member States. In addition, and given also the need to act within the framework provided by the Treaty

provisions, Community policies, as formulated by the Commission and the Council and implemented by the Directorate-General for Health and Consumer Protection, have in general focused more on general public health risk factors, such as indoor and outdoor air pollution, dangerous chemicals and tobacco consumption, and not on specific diseases.

The emphasis on risk factors and broad actions for health across sectors, moreover, appears to have been strengthened by the recent decisions by the Council and the Parliament to take more account of the impact on health of all policies.

In addition, the implication of the GINA recommendations and the Finnish experience is that asthma management, probably even more than other public health issues, depends strongly on local conditions and that national and local authorities must be the principal actors in any endeavours aiming at a better control with asthma at the level of the individual.

However, there would nevertheless appear to be a larger scope and need for a strengthening of the EU's implications in this field of public health. An important element of consideration for EU decision makers would seem to be the particular nature of the disease:

- The prevalence is rising in a number of EU countries but is higher the higher the degree of urbanization and income;
- There is a need for further and deeper studies of the costs to the economy of asthma but available estimates suggest that the indirect social and economic costs are very high in proportion to the direct costs for the health care system: asthma does not provoke high costs of surgery or medical treatment.
- There is still a high degree of uncertainty with respect to the causes and the scope for treatment and there would seem to be strong arguments in favour of providing adequate resources to further asthma research in future calls for proposals in FP7;
- In particular, there may be a possibility for treatment through vaccination but research in this field is still in the starting blocks and results can hardly be expected in the short and medium term;
- In the short and medium term asthma management consequently is an issue reaching out beyond the medical profession and into the interfacing between the individual patient and the socio-economic framework and institutions, including schools and work places.

In this perspective there would appear to be an increasing need for EU Member States to consider the scope for a common integrated approach to the asthma problem. It would, in particular, appear attractive to embark into a discussion with Member States as to the benefits of opening an exchange on asthma treatment and management over a wide front within the framework of the Open Method of Coordination.

The advantages of a common approach to asthma management could, in fact, be quite important on condition of involving not only ministries of health but also, possibly, ministries of education and social affairs in addition to the NGOs implied in respiratory diseases and offering services to asthma patients and, naturally, the EMEA and the scientific community.

The work of an OMC activity in the field of asthma could also obtain support from ongoing research and new research projects addressing, in particular, on one side the genetic aspects of asthma and on the other side the correlation of asthma with socio-economic and regional factors. There would as suggested above seem to be good arguments for actively exploring, within the framework of FP7, the scope for combating at least certain categories of asthma through vaccination (an issue already raised in the work programme of the US FDA).

But further progress would presumably require further and deeper research on the socio-economic and environmental aspects of asthma through, notably, longitudinal studies of health profiles. This might best be achieved within regular survey with a more general thrust, aimed, notably, at following the evolution of health (not only asthma but also obesity and other basic health features) of children, adolescents and adults according to education, income and other socio-economic characteristics.

However, the specific issues concerning asthma control must be assessed in the general context of the EU's approach to public health problems and, notably, ex-post control with the market for pharmaceutical product and the reporting on adverse reactions to medicines.

Is already underlined, evidence presented in this report suggests that the asthma management is sub-optimal in a number of EU member states. In fact, we have identified serious problems of disparities between countries as regards pharmacovigilance leading to waste of scarce resources and serious aggravation of the risks of insufficient control with the use of medicines and also a lack of clinical control with adverse long-term effects of the use of certain drugs, notably in children.

With respect to the assignment of responsibilities within the European Commission our conclusions are as follows:

- There seems to be no actual basis for claiming that competence for pharmacovigilance should be moved to the remit of DG SANCO instead of DG ENTR. The current situation actually mirrors the situation in many member states inasmuch as the competence for protecting the interest of consumers and for acting as contact point for the industry is concentrated in the same administrative body.
- To the contrary, the need to adopt a holistic approach in combating asthma, the leading role played by EMEA in the pharmacovigilance system, and the need to leave *ex ante* risk assessment and *ex post* evaluation in the same hands all call for a strengthening of the current system, without such a major change.
- Nonetheless, the advocacy role of EMEA could be strengthened and clarified both as regards pre-authorisation control and post-authorisation surveillance, and the Guidance Note on Asthma should reflect the current mismatch between clinical trials and the emerging complexity of asthma phenomenology.
- Overall, the transparency of activities being undertaken by EMEA should be improved, in order to foster the accountability of professionals working for this important advisory body. In particular, assessment reports – both pre-authorisation and post-authorisation – should be made public.
- Moreover, the role of patients' (and patients associations') self-reporting should be strengthened within the current system, possibly through the establishment of a forum with HCPs, DG SANCO and the EMEA.
- Finally, the procedures and methods of EU impact assessments were strengthened and enhanced as late as in 2006 and there are good reasons to expect these measures to lead to improvements of the health impact assessments as this new approach is being implemented.

## Glossary

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|                     |   |
|---------------------|---|
| AIRE                | Asthma Insights & Reality in Europe   |
| BIA                 | Business Impact Assessment  |
| CHMP                | Committee for Medicinal Products for Human Use of the European Medicines Agency                               |
| CODP                | Chronic obstructive pulmonary disease   |
| DALY                | Disability-Adjusted Life Year   |
| DG ENTR             | Enterprise and Industry Directorate-General of the European Commission  |
| DG SANCO            | Health and Consumer Protection Directorate-General of the European Commission                                 |
| ECRHS               | European Community Respiratory Health Survey  |
| EHFG                | European Health Forum Gastein   |
| ELF                 | European Lung Foundation  |
| EMA                 | European Medicines Agency   |
| ENBR                | European Network for Better Regulation  |
| EPHIA               | European Policy Health Impact Assessment  |
| ERS                 | European Respiratory Society  |
| FP7                 | Seventh Research Framework Programme of the EU  |
| GABRIEL             | Multi-disciplinary study to identify the genetic and environmental causes of asthma in the European Community |
| HIA                 | Health Impact Assessment  |
| HiAP                | Health in All Policies  |
| HPCs                | Healthcare professionals  |
| GA <sup>2</sup> LEN | Global Allergy and Asthma European Network  |
| GINA                | Global Initiative for Asthma  |
| IgE                 | Immunoglobulin E  |
| IMCA                | Indicators for monitoring chronic obstructive pulmonary disease (COPD) and asthma in the EU                   |
| IMPACT              | International Health Impact Assessment Consortium   |
| ISAAC               | International Study of Asthma and Allergies in Childhood  |
| NGO                 | Non-governmental organization   |
| OMC                 | Open Method of Coordination   |
| SPT                 | Skin prick test   |
| US FDA              | United States Food and Drug Administration  |



## Appendix: The Brussels Declaration

### The Brussels Declaration

# TEN POINT PLAN TO REVOLUTIONISE ASTHMA MANAGEMENT IN EUROPE

*"Together we can defeat the burden of asthma."*

#### Asthma is a public health issue with a massive impact

- 32 million people have asthma in Europe<sup>1</sup>
- Every hour one person dies of asthma in western Europe<sup>2</sup>
- Asthma is the cause of one in every 250 deaths in the world<sup>3</sup>
- Asthma is a respiratory manifestation of systemic inflammatory processes<sup>4</sup>
- The total cost of asthma in Europe is approximately €17.7bn per year<sup>5</sup>
- The economic and social costs of asthma are largely due to uncontrolled disease: they are likely to rise as asthma severity and prevalence increase<sup>6</sup>
- Improved diagnosis and management saves lives and saves money as shown by the Finnish Asthma Program<sup>7</sup>
- Children require specific and tested approaches in asthma management – they are NOT little adults<sup>8</sup>
- Patient and professional groups urge authorities to support partnerships between patients and their healthcare professionals

It has been shown by the Juniper Asthma Control Questionnaire that less than one third of patients are well controlled.<sup>9</sup> It is clear that guidelines on their own are not enough. It is the diagnosis, assessment, and consistent management of asthma, working with the patient, that will allow individuals to be fully active and achieve everything that a citizen of Europe deserves.

We have identified ten points for change that we believe must be addressed to reflect the current understanding of asthma and its impact on the individual and society. We also addressed the management of asthma from a political and policy aspect, as well as the approach needed by clinicians dealing with the everyday patient. The needs and perspectives of patient groups, the patient with asthma, their families and care givers are a central focus within this Declaration.

The ten key points identified in the Declaration will only make a difference if they produce real change in action with all colleagues involved in the care of people with asthma, as well as the organisations that represent their needs.

<sup>1</sup>GINA Global Initiative for Asthma. *The Global Burden of Asthma Report*, 2006

<sup>2</sup>World Health Organization. [www.who.int/mediacentre/factsheets/fs206/en/](http://www.who.int/mediacentre/factsheets/fs206/en/)

<sup>3</sup>Masoli M, Fabian D, Hoit S, Beasley R. *The Global Burden of Asthma Report*, 2004

<sup>4</sup>Brussels Declaration. [www.summitforchange.eu](http://www.summitforchange.eu)

<sup>5</sup>European Federation of the Allergy and Airway Diseases Patients Association (EFA). [www.eafa.org](http://www.eafa.org)

<sup>6</sup>Stephen T, Holgate ST, Price D and Valovirta E. *Asthma out of control? A structured review of recent patient surveys*. *BMC Pulmonary Medicine* 2006;6 (Suppl 1):S2

<sup>7</sup>Haastela et al. *Thomaz 2006*. Finnish Asthma Program

<sup>8</sup>Brussels Declaration. [www.summitforchange.eu](http://www.summitforchange.eu)

<sup>9</sup>William M, Vollmer et al. *Association of Asthma Control with Health Care Utilisation and Quality of Life*. *Am. J. Respir. Crit. Care Med.*, Volume 160, Number 5, November 1999, 1647-1652

#### Ten Point Plan of Action

1. Asthma must be recognised as a serious public health issue by society and asthma care should be made a political priority.
2. Policy makers and Professional Bodies, including European Patients' Associations must respond now to the developing understanding of asthma including recognition of asthma as a respiratory manifestation of systemic inflammatory processes.
3. The medical community, guided by its Professional Bodies, should also agree that asthma is different in adults, children and different ethnic groups and needs to be managed in different ways.
4. There should be an immediate update of the European Medicines Agency (EMA) Regulatory Guidance Note on asthma, which is essential to ensure that asthma treatment and diagnosis responds to the latest scientific knowledge, clinical and real world experience.
5. Guidelines should continue to be based on clinical trial evidence, but also take into account health economic and outcomes studies that reflect 'real-world' patient care and family life, including studies that particularly address the child/infant.
6. Those responsible for funding studies at EU level must consider research which helps to answer questions about the impact of other diseases on asthma, how to promote adherence to optimal treatment by both professionals and patients and advance patient-centred care, effective prevention strategies and prevalence studies.
7. Policy makers, politicians, doctors and third parties must explore variation in asthma care across Europe and distinguish between normal variation due to differences in healthcare systems and cultures, and variation that can be reduced through policies that improve organisation of care and clinical practice.
8. National policies should incentivise the organisation of care so that patient groups and people with asthma can actively participate in and make choices about their care.
9. The EU and national governments must liaise with other agencies to understand and reduce the impact of environmental factors on asthma such as smoking, air pollution, hazards in schools, day care, the work place and home, as well as other environmental triggers.
10. National policies should set targets for healthcare providers to keep registries, reduce hospitalisations, emergency healthcare use, days off work and days off school experienced by people with asthma and encourage use of tools/instruments to assess asthma control and reasons for poor control where it exists in the individual.

#### Declaration Faculty

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#### Summit for Change in Asthma Management

The Brussels Declaration captures the key conclusions of the 'Summit for Change in Asthma Management' meeting held in the European Parliament on the 18th and 19th of October 2006. Hosted by Member of the European Parliament Liz Lynne and Professor Stephen Holgate from the University of Southampton, the Summit brought together senior politicians, clinicians, regulatory experts and patient representatives. The Brussels Declaration addresses the management of asthma from a public health policy aspect, as well as the approach required by clinicians and healthcare professionals in dealing with the everyday patient. The needs and perspectives of the patient with asthma, their families and care givers are given a central focus.

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