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**EU ways of governing risks of pharmaceuticals -  
an effective approach to the protection of patients' safety?**

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## 1 Introduction

In the EU medicinal products are governed by a complex system of multi-level public and private regulation. Since 1965 the pharmaceutical industry has been subject to European legislation regarding the whole process of research, development, testing, pricing, marketing, manufacturing, advertisement and retail (Kaufer 1990; Hervey & McHale 2004; Thompson 1994). In this paper we focus on the EU regulatory system that aims at safeguarding the safety, quality and efficacy of medicinal products. More specifically we concentrate on the protection of patients' safety against adverse effects of pharmaceuticals. We discuss the possibilities and limits of governing the assessment and minimisation of risks.<sup>2</sup>

The recent evaluations of this part of EU law indicate problems regarding the protection of patients' safety (Hervey & McHale 2004, 312). These problems refer to the provisions related to the assessment of risks, to the detection of adverse reactions of patients to marketed pharmaceuticals, as well as to the withdrawal of drugs from the market. Important points of critique concern the objectification of risk assessment that is said to be detrimental to the interests of patients, the lack of patients' participation in the authorisation procedures, as well as a lack of transparency of adverse reactions to drugs. Generally, EU law relating to pharmaceuticals is criticised as being piecemeal and *ad hoc*, inappropriate for the protection of fundamental human rights. Since 2004 the EU system governing medicinal products is under revision. Partly due to the new EU policy on better regulation, new combinations of governance instruments have been introduced in this ongoing reform process. More emphasis is laid on particular methods of governance.<sup>3</sup>

In this paper we focus on the interaction between traditional and new EU methods governing pharmaceuticals. We explore whether the present regulatory system provides adequate safeguards regarding patients' safety. More specifically we examine whether the problems we indicated above have been solved.

The central question reads:

*How can the European regulatory system regarding the management of pharmaceuticals' risks to patients' safety be described and evaluated?*

This paper is organised as follows. In the second section we discuss the background of our investigation. First we describe the EU methods and instruments that govern medicinal products. To understand the problems of patients' safety we then discuss the challenges risk assessment and different interests of the various stakeholders imply for the regulatory system. In a third step we develop evaluation criteria. Section three deals with the description of the safety provisions.<sup>4</sup> In the fourth section we evaluate the regulatory system according to our evaluation frame. On the basis of the evaluation we finally draw conclusions regarding the European ways of safeguarding patients' health against risks of pharmaceuticals.

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<sup>1</sup> Comments to b.r.dorbeck-jung @utwente.nl and m.j.vanheffen-oudevrieling@utwente.nl.

<sup>2</sup> To reduce the complexity of our investigation, the legal regime of damage compensation caused by the use of pharmaceutical is not included in this paper.

<sup>3</sup> See White Paper on European Governance, COM (2001) 428; Communication from the Commission, Action plan 'Simplifying and improving the regulatory environment', COM (2002) 278 final, 5 June 2002. In essence, the new regulation policy supports methods that follow a less top-down approach and complements its policy tools with other non-binding coordination mechanisms (Senden 2005, 2; see below).

<sup>4</sup> To reduce the complexity of our investigation the legal regime of damage compensation caused by the use of pharmaceutical is not included in this paper.

## 2 Background of the EU regulatory system governing pharmaceuticals

### 2.1 Methods and instruments of European health care governance

In the EU regulatory system related to pharmaceuticals two general modes of regulation are applied: traditional regulation and 'new governance'. These modes of regulation comprise various methods of coordination. In the domain of health care the modes of regulation involve five major methods:<sup>5</sup>

1. harmonisation 'old style';
2. harmonisation 'new approach';
3. deregulation;
4. 'soft' coordination and;
5. financial incentives.

Of these, the first three are legally binding, whereas the latter two are non-binding mechanisms of coordination. The methods are used to support the integration of markets and the protection of health and safety. The *'old style' harmonisation* is brought about by detailed regulatory EU norms. This method mainly uses mandatory regulation to provide an integrated regulatory system in cases of significant lack of 'fit' or trust between national systems. Once the EU norms are adopted, national authorities are precluded from promulgating provisions in the field, even if these national norms provide greater health and safety protection. By contrast, the *new approach harmonisation* allows a mixture of national and EU norms. On the EU level only minimum standards are established to protect essential health and safety interests. For example, Member States and non-state corporate actors participate in the elaboration of 'European industry standards'. Through a mechanism of mutual recognition Member States can set higher standards at a national level, but must accept lower standards applied by other states as long as these standards meet the EU minimum requirements.

In the European modes of governance *deregulation* involves the reduction or removal of national and European legislation. With respect to national legislation effective deregulatory EU law are the EC Treaty provisions concerning free movement of goods and services.<sup>6</sup> Deregulation in the sense of reduction of European legislation is promulgated in the new European legislative policy.<sup>7</sup> In the European approach deregulation is closely related to harmonisation methods. By excluding national provisions in the field, instruments of 'old style' harmonisation may directly deregulate existing national legislation. In the 'new approach' to harmonisation deregulation appears to take place rather incrementally, as a consequence of the Member States' mutual recognition of certain standards.

*Soft coordination* implies a large range of non-hierarchical instruments and tools. Examples are: resolutions, recommendations, opinions, action programmes, policy papers, and declarations and other instruments of *'soft law'* like codes of conduct and certification.<sup>8</sup> Some examples of soft coordination, amongst which research and policy programmes, provide *financial incentives* that facilitate research and other activities, which are essential to support the integration of the European market.

As indicated above, the five methods of health care governance can be divided in two categories: methods of traditional regulation and methods of 'new governance'.<sup>9</sup> Table 1 provides an overview.

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<sup>5</sup> See Hervey and McHale (2004, 43). Hervey and McHale speak of six methods of governance. They treat mandatory regulation as an extra method. In our view mandatory regulation is a tool of the legally binding methods of EU governance.

<sup>6</sup> Article 95 EC Treaty.

<sup>7</sup> See note 3.

<sup>8</sup> According to Senden, Community soft law is defined as rules of conduct that are laid down in instruments which have not been attributed legally binding force as such, but nevertheless may have certain – indirect-legal effects, and that are aimed at and may produce practical effects (Senden 2004, 111-113). Senden distinguishes between three categories of soft law. These are: 1. preparatory and informative instruments, 2. interpretative and decisional instruments, and 3. steering instruments (Senden 2005, 15). However, soft coordination refers also to non-hierarchical instruments like partnership ('co-regulation'), peer pressures, social dialogue, and the 'open method of coordination' that are not covered by soft law.

<sup>9</sup> L.G Trubek, *The New Health Care Governance*, forthcoming.

**Table 1 Modes and methods of European health care governance**

<b>Modes of governance</b>	<b>Traditional regulation</b>	<b>New governance</b>
<b>Methods</b>	<ul style="list-style-type: none"> <li>- 'old style' harmonisation</li> <li>- 'direct' deregulation</li> <li>- 'soft law'</li> <li>- financial incentives</li> </ul>	<ul style="list-style-type: none"> <li>- new approach harmonisation</li> <li>- 'incremental' deregulation</li> <li>- 'soft' coordination</li> <li>- financial incentives</li> </ul>

According to Table 1, the first mode of European health care governance is comprised of 'old style' harmonisation, direct deregulation, some instruments of 'soft' coordination and financial incentives, whereas the second mode consists of new approach harmonisation, 'incremental' deregulation, 'soft' coordination methods, as well as financial incentives. As we mentioned above, these modes of governance differ significantly regarding the view on how law works. Moreover, they purport different methods of coordination. Traditional governance strongly relies on mandatory rules tied to enforcement and sanctions issued by legislatures and courts. New governance draws attention to more non-legal methods of coordination. The new methods establish norms and achieve compliance by encouraging participation of stakeholders and requiring transparency and accountability of those participating in decision-making processes. In these methods of regulation government still holds a strong position, although a different one. Governmental intervention is required, for private actors cannot be relied on to give appropriate weight to public interests over private ones. But the government no longer is acting on the basis of command and control, but is taking the role of coordinator and facilitator of social action.

It is striking that the present regulatory system on pharmaceuticals makes use of both modes of governance. It combines methods of traditional and new governance. For example, in the authorisation processes of medicinal products the methods 'old style' and 'new style' harmonisation are used, as well as combinations of direct and incremental deregulation. Furthermore, this particular regulatory system makes use of a large variety of instruments like regulations, directives, guidelines, communications, and codes of conduct. In this paper we focus mainly on the legally binding mechanisms of coordination. As the use of 'soft coordination' instruments may have significant effects on the protection of the patients' safety, we include relevant examples of this method in the description and evaluation of the drug regulatory system. Regarding the combination of governance methods we realise that there may be tensions that are created by a hybrid constellation that involves different rationales and logics of governance.<sup>10</sup> For example, the use of hierarchical tools of the old style harmonisation approach in combination with non-hierarchical tools of the new style harmonisation and soft coordination communicates the opposing messages of command as well as of partnership. In our final conclusions we address the question whether the traditional and new modes of regulation are compatible. In the next paragraph we discuss the challenge of conflicting interests and other challenges to the regulatory system.

## **2.2 Challenges to the regulatory system**

To understand the European ways of regulating potential threats caused by medicinal products some basic ideas of risk management should be taken into consideration. The aim of the European risk management strategy is to contribute to the safe and effective use of medicines and to the overall promotion and protection of public health. In view of the increasing demands from patients and the general public for the availability of safe and effective medicines, the Heads of European Medicines Agencies emphasise "that the concept of "zero risk" does not apply to medicinal products. Even with

<sup>10</sup> There is increasing attention to the notion of hybrids in social science (see for example the recent issue of the Dutch Journal of Public Administration, Bestuurskunde, May 2005).

the best knowledge of medicines at the moment of licensing, adverse drug reactions which were not predictable or detectable in the pre-authorisation stage will occur post-licensing when medicines are increasingly used in real life situations".<sup>11</sup> As risks refer to the active ingredients, as well as to the solvents and excipients of drugs, detection and assessment is extremely difficult. Adverse reactions may also be caused by the interplay of other drugs patients take concurrently, and by patients who do not comply strictly to the physician's or pharmacist's instructions. In their risk management policy, the European Agencies state that consumer protection against harmful effects of pharmaceuticals requires high quality scientific expertise, as well as good regulatory practice and good government. To reach an adequate level of safety, scientists have to prove a drug can safely be introduced on the market. Moreover, the acclaimed benefits of the drug must outweigh known risks. Here, the European Agencies take a same stand towards safety as Paracelsus who stated more than four hundred years ago that there is no drug that is harmless and that dose alone determines that the drug is not a poison (see Kaufer 1990, 171). The European risk management strategy includes various tools to detect, assess, minimise and communicate risks. These are: an advanced reporting system, intensive monitoring, peer review, risk management plans provided by pharmaceutical companies and a Code of Conduct which should facilitate communication of risks.<sup>12</sup> According to the Heads of the European Medicines Agencies, by means of these tools risk of releasing pharmaceuticals that may prove to be harmful is reduced to a minimum.

These aspects of risk management involve particular challenges to safety regulation including a need of continuous adaptation to the newest standards of good clinical practices, risk assessment, and good manufacturing practices, as well as to new IT regarding early warning and other information systems. Adaptation and incorporation of the newest state-of-the art requires flexible regulation. This need of flexibility can be opposed to the need of legal certainty, that calls for continuity, transparency, and detailed legal rules (Senden 2005, 7).

Another main challenge to the regulatory system is to balance the interest of pharmaceutical industry in placing their products quickly on the markets against the patients' interest of careful risk assessment and control. As an industry of innovation pharmaceutical industry depends strongly upon investment in research and development.<sup>13</sup> According to the pharmaceutical industry, a company must spend about 500 millions Euro to get a medicine on the market. This is why the drug industry has a strong interest in patent law as well as in public regulation that facilitates the marketing of medicinal products including promotional activities on which the industry heavily relies. Patients have a strong interest in access to effective and safe pharmaceuticals of high quality. As safety requirements may delay the marketing of drugs there can be tensions between the interests of patients and industry.<sup>14</sup> Since pharmaceutical industry has proven to be a powerful stakeholder within the regulatory process effective countervailing powers are of high importance to support the patients' interests.

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<sup>11</sup> See the Report of the ad hoc working group progress on implementation of the European risk management strategy (ERMS 11/05/05), p.3.

<sup>12</sup> According to the policy documents, these instruments are increasingly used with a proactive approach towards the identification and handling of safety concerns in the three stages of the regulatory process. These policy programmes can be regarded as an instrument of soft coordination.

<sup>13</sup> Pharmaceutical innovation, as measured by the number of marketing authorisations applied for and granted, has fallen in the last several years. Against this background, the Enterprise DG of the European Commission commissioned Charles River Associates to undertake a study investigating whether there is a worldwide crisis in innovation in the pharmaceutical sector (see CRA ENTR/03/28, 8<sup>th</sup> November 2004). According to the study, the recent decline in application and authorisation does not reflect a crisis in innovation. The findings of the study suggest that there will be a gradual increase in marketing authorisations regarding new active substance over the next five years. There is also, however, considerable concern regarding the types of product being developed. In the US there is a higher proportion of new biologic products coming onto the market. Moreover, it is clear that global Research and Development expenditure over the past decade has shown a strong upward trend. This is why the study concludes that the 'crisis' is that the number of new products has not increased whilst the overall level of resources being invested has risen dramatically.

<sup>14</sup> Tensions may not arise in cases of serious diseases, in which patients may conceive access to new products as a matter of 'life or death'.

European regulatory action is driven by the need to safeguard patients against risks, but also by the policy goal of creating the 'internal' market. The dynamics of risks, the particular features of the pharmaceutical market and industry, the importance of its products and the potentially harmful nature of pharmaceuticals call for a dynamic regulatory system that is able to balance economic interests and consumer protection. Within this regulation system, the EU institutions are required to balance the need to meet requirements of the various stakeholders involved, in particular those of the governments and health care authorities of the Member States<sup>15</sup>, of patients and of the pharmaceutical industry. In our evaluation we will draw attention to the impact of this hybrid on the effectiveness of the regulatory system in terms of balancing economic interests and consumer protection. Additionally we will regard the hybrid constellation of a flexible regulatory system that as well responds to legal certainty. Since flexibility and dynamics imply uncertainty it is likely that tensions arise in this constellation.

### 2.3 Evaluation criteria

In this paper the European regulatory system regarding the management of pharmaceuticals' risks to patients' safety is described and evaluated. As indicated above, risk management refers to the detection and minimisation of risks. Within risk management strategies the minimisation of risk depends strongly on measures of risk detection (such as risk assessment). Risks can be detected when a drug is developed, tested<sup>16</sup>, marketed and monitored for as yet undetected adverse drug reactions after being finally admitted to the market. Risk detection requires effective surveillance in all stages of the development of a medicinal product. Risk minimisation depends strongly upon a fast withdrawal of pharmaceuticals in cases of serious adverse reactions. It is supported by quality management, which covers development, manufacturing, packaging and advertisement activities. With reference to all these joined activities drug safety is seen as the result of a trade-off between 'pre-marketing' and 'post-marketing' action of risk management (Kaufer 1990, 155).

Regarding our evaluation of the regulatory system a first conclusion is that effective protection of patients' safety requires adequate provisions with respect to risk management, quality management, and to surveillance issues. A second conclusion concerns the legitimacy and effectiveness of the regulatory system. In the view of the principles of good governance, patients' safety can be supported by a 'good' regulatory system. These conclusions raise the question what we understand by 'adequate provisions' and how the quality of the regulatory systems can be determined.

According to Abraham and Lewis, *adequate risk management* requires a distinct definition of risks, high level evaluation standards, competent evaluators who have a high quality scientific expertise at their disposal, and a fast withdrawal of the drug in cases of serious adverse reactions (2000,115). In the processes of the development and marketing pharmaceuticals *adequate quality management* is based on sophisticated quality assurance systems and good research, manufacturing, packaging and advertisement practices. *Adequate surveillance* requires competent inspectors, as well as safeguards that minimise regulation capture like job rotation and measures with respect to impartiality (see Ayres and Braithwaite 1992, 52). Furthermore, surveillance is facilitated by a sophisticated information system on adverse reactions to pharmaceuticals. As we discussed above, a *good regulatory system* on medicinal products leaves room for the adaptation of procedures and standards to the newest state of scientific and technical knowledge. To safeguard legal certainty a good regulatory system provides for continuity, transparency, and detailed legal rules. Regarding the power relations between patients and pharmaceutical industry we concluded that effective countervailing powers are of high importance to support the patients' interests. Countervailing powers include the participation of patients and their representatives in the regulatory process with respect to the development, marketing and surveillance of medicinal products.<sup>17</sup>

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<sup>15</sup> Regarding the central question of this paper we do not focus on problems regarding the principle of subsidiarity that governs the health care field.

<sup>16</sup> Of course, before this, the drug was tested on animals.

<sup>17</sup> See also White Paper 2001, 11 (COM 2001 428 final). Here, the participation of patients and their representatives are discussed in the context of the principles of proportionality and democracy. To reduce

To summarise, our evaluation of the EU regulatory system regards the aspects and criteria that are shown in table 2.

**Table 2 Evaluation frame**

<b>Aspects</b>	<b>Adequate risk management</b>	<b>Adequate quality management</b>	<b>Adequate surveillance</b>	<b>Good regulatory system</b>
<b>Criteria</b>	<ul style="list-style-type: none"> <li>-distinct definition of risks</li> <li>-high level evaluation standards</li> <li>-competent evaluators</li> <li>- fast withdrawal</li> </ul>	<ul style="list-style-type: none"> <li>-sophisticated quality assurance system</li> <li>-good practices ensured</li> </ul>	<ul style="list-style-type: none"> <li>-competent inspectors</li> <li>-job rotation</li> <li>-safeguards regarding impartiality</li> <li>- sophisticated information system</li> </ul>	<ul style="list-style-type: none"> <li>-flexibility</li> <li>-legal certainty</li> <li>-effective participation of patients</li> </ul>

In the next section we describe the EU provisions that refer to risk assessment, quality management and surveillance. With regard to the central question of this study we describe more specifically the relevant methods and instruments of governance in which these provisions are embedded, as well as the means by which the aspects of patients protections are provided (for example, definitions and activities), including the actors to which the provision are addressed and the actors' rights and duties. Our description focuses mainly on legally binding methods of governance. As far as possible we include relevant examples of 'soft' law. Since the authorisation of a new medicinal product is crucial in the European regulatory system the description is divided into the three stages of pre-marketing, marketing authorisation and post-marketing of drugs.

### **3 Description of the regulatory system**

#### **3.1 Safety regulation in the pre-marketing stage**

In the pre-marketing stage safety regulation refers to clinical trials. In this stage EU regulation makes use of the methods of 'old style' harmonisation, 'direct' deregulation, 'soft' coordination and financial incentives. Important instruments of harmonisation and deregulation are: the EC Treaty establishing the EU and two directives on clinical trials. Instruments of 'soft' coordination include an international declaration and European guidelines on good clinical practices. Financial incentives imply the funding of pharmaceutical research. They concern as well the development of an information system of monitoring adverse reactions occurring in clinical trials.

To respond to the harm that has been caused by clinical trials to patients in the German Nazi regime, a series of international declarations and conventions was produced after the Second World War, with the aim of ensuring ethical practices in clinical trials.<sup>18</sup> The International Conference on harmonisation (ICH) reached a consensus in 1995 to provide a harmonised approach for Good Clinical Practice. The European Clinical Trial Directive of 2001 regulates the conditions under which clinical trials of pharmaceutical products may be conducted within the EU.<sup>19</sup> It is based on Article 95 of the Treaty

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the complexity of our study we do not include aspects of democracy. For the same reason we do not regard aspects of effectiveness like enforceability and acceptance of legal provisions.

<sup>18</sup> An overview is provided by Gevers 2001.

<sup>19</sup> Directive 2001/20/EC. The legal basis of the Directive is Article 95 EC, which provides co-decision procedure.

establishing the European Union. The Directive applies to clinical trials on pharmaceuticals which are in a development stage, and 'investigational medicinal products'.<sup>20</sup> It does not cover particular research relating to gene sequencing or cloning.

In the stage of pre-marketing tools that facilitate *risk management* are inseparably linked with means of *quality management*. Directive 2001/20/EC requires that trials must be undertaken in accordance with 'good clinical practice'. Good clinical practice refers to a set of internationally recognized ethical and scientific quality requirements, which must be observed for designing, conducting, recording, and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected and that the results of the clinical trial are credible. With regard to internationally acknowledged standards the European Commission refers to those contained in the Declaration of Helsinki.<sup>21</sup> Very recently, Directive 2005/28/EC of 8 April 2005 laid down principles and guidelines for good clinical practice as regards investigational medicinal products for human use.<sup>22</sup> Considering risk regulation the principle laid down in Article 2 is of importance. According to this provision, the rights, safety and well being of the trial subjects shall prevail over the interest of science and society. Another tool of risk assessment and quality management is the investigator's brochure that compiles the relevant data of the study. This brochure can also be seen as a means to enable the surveillance of clinical trials. According to Article 8, the information in this brochure shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. Moreover, the brochure shall be validated and updated by the sponsor at least once a year. Member States are required to make publicly available within their territories the documents relating to the adoption of good clinical practice principles.

As regards risk assessment and quality assurance the ethical committees that are established by EU law play an important role. These committees are charged with the evaluation of clinical practices.<sup>23</sup> Article 6 provides that Member States shall take the measures necessary for the establishment and operation of research ethic committees. When assessing proposed clinical trials ethics committees examine the relevance of the trial and its design. They balance any foreseeable risks and inconveniences against any anticipated benefits which may accrue to the subject of the trial and to other present and future patients. The committee considers the adequacy and completeness of written information to be provided and the procedure for obtaining informed consent. It assesses also major amendments to the clinical trial protocol researchers submit later in the course of the trial.

Regarding the quality assurance system the provisions on patient's rights and informed consent are of importance. Directive 2001/20/EC stipulates that a clinical trial may not be undertaken unless the rights of the subjects are protected. These rights include traditional human rights, such as the right to physical and mental integrity, privacy and data protection. In the Directive informed consent is defined as a decision taken freely after being duly informed of its nature, significance, implications and risks. The consent must be given in writing, after an interview with the trial investigator, who explains the objectives of the trial and any consequent risks and inconveniences. Recognizing the various approaches to the interpretation of the informed consent, the Directive leaves the determination of the boundaries of it to the individual Member States. The Directive formulates also specific regulations regarding the provision of minors and incapacitated adults with information. These groups of research

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<sup>20</sup> According to Article 2, investigational pharmaceuticals are defined as 'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packed) in a way different from the authorized form, or when used for an unauthorized indication of where used to gain further information about the authorized form.' The authorization of marketing will be discussed below.

<sup>21</sup> See the detailed guidelines of the European Commission on the principles of good clinical practice in the conduct in the EU of clinical trials on medicinal products for human use (Brussels, ENTR/6416/01).

<sup>22</sup> The European Commission published this Directive in the Official Journal of 9 April 2005. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 29 January 2006 at the latest.

<sup>23</sup> Approval of these committees is granted within 60 days. In the case of certain issues, such as gene therapy and somatic cell therapy, Directive 2001/20/EC requires that specific written authorisation must be given by the relevant competent body.



subjects are perceived as particular vulnerable. In both cases the investigator is obliged to provide a design that minimises pain, discomfort, fear and any other foreseeable risk. To protect these groups against unreflected consent and risks, the Directive prohibits incentives or financial inducements to minors and incapacitated adults.

In the regulatory system governing the pre-marketing stage, means of *surveillance* are the investigator's brochure, the protocol of the clinical trial, as well as the EU information system on adverse reactions. Directive 2001/20/EC provides a system of monitoring adverse reactions occurring in clinical trials using the Community information system ('*pharmacovigilance*') procedures to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk. In the past three years central EU databases, the EUDRACT database and the Eudravigilance-Clinical Trial Module, have been established.<sup>24</sup> These databases facilitate the communication between competent authorities in Member States, and between the European Commission and the European Medicines Evaluation Agency. They provide information concerning approvals of ethics committees, notifications to the competent authorities where trials are ended for reasons of safety, as well as inspections, which have been undertaken to ensure that the conduct of the trial is in accordance with principles of good clinical practices. With respect to investigational medicinal products, Directive 2005/28/EC requires that all clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected. Member States are obliged to undertake inspections to ensure that the conduct of clinical trials on medicinal products is in accordance with good clinical practice.<sup>25</sup> This Directive requires also that Member States ensure that inspectors, appointed to inspect the sites concerned by any clinical trial conducted, receive appropriate training. Each inspector shall sign a statement declaring any financial or other links to the parties to be inspected.

To support effective surveillance Directive 2001/20/EC obliges investigators to notify serious adverse events or reactions to the sponsor. Investigators are also required to inform the sponsor in relation to 'adverse events and/or any laboratory abnormalities' identified in the protocol as critical to safety evaluation. Detailed records of these events are to be kept by the sponsor, and to be notified to the Member State where the trial is being undertaken. According to the Directive, any suspected unexpected serious adverse reactions which are fatal and life-threatening must be communicated to the national government, as well as the ethics committee. Such information should be given no later than seven days after the sponsor becomes aware of it, and follow-up information should be provided within a period of eight days later. In the case of any other suspected unexpected serious adverse events, these should be notified within a period of 15 days after these first came to the attention of the sponsor.

### **3.2 Safety regulation in the stage of authorisation**

In the stage of the approval of pharmaceuticals the EU uses all traditional and new methods of coordination (new style and old style of harmonisation, incremental and direct deregulation, soft coordination methods and financial incentives). Presently, the focus lies on new governance methods. However, mandatory regulation still plays a large role. Instruments are regulations, directives, guidelines, communications, policy documents, and codes of conduct.<sup>26</sup> EU Law covers marketing and

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<sup>24</sup> See the Detailed Guidance on the European clinical trials database EUDRACT of the European Commission (ENTR/F2/BL, April 2003).

<sup>25</sup> Article 15 of the Directive. These inspections are to be undertaken on behalf of the EU, but are conducted at the Member State Level.

<sup>26</sup> See Regulation 2309/93, which was replaced by Regulation 726/2004 of 31 March 2004 (OJ L 136/1). In 2001 the European Commission issued Directive 2001/83/EC on the Community Code relating to medicinal products for human use that was based on Article 95 of the Treaty establishing the European Union (OJ L-311/67). Recently, the Commission adopted Directive 2004/27/EC (OJ L 136/34), which amended Directive 2001/83/EC. The amendments were formulated on the base of the findings of the evaluation of the marketing procedures that were published in 2001 (Commission, DG Enterprise 2001). This new legislation will be applicable as from 30 October 2005 when implemented in the national legislation by the Member States.

manufacturing authorisation, as well rules regarding as labelling, packaging and advertisement of medicinal products. According to EU Law, no medicinal product may be placed on the market within the Community unless a marketing authorisation has been granted. It is also unlawful to manufacture pharmaceuticals within the EU without appropriate authorisation.<sup>27</sup>As the Community has no competence for harmonising measures in the public health field, the authorisation or approval of new pharmaceuticals is still, in principle, basically a matter of national authorities. However, certain categories of new pharmaceuticals are subject of a different regime. This is the *centralised procedure* of an approval at EU-level. Moreover, for all medicinal products that are to be marketed in a Member State, other than in which they were first authorised, a *decentralised procedure* must be followed. As a consequence national authorities have an exclusive competence only regarding new pharmaceuticals that do not fall within the specific categories of the centralised procedure and for which a first authorisation is asked. The complex regulatory system governing the licensing stage is enforced by EU and national authorities, as well as through self-regulation of the pharmaceuticals sector.

### ***Marketing authorisation - the centralised procedure***<sup>28</sup>

In the opinion of the EU it is necessary to create a centralised authorisation procedure that is compulsory for high-technology medicinal products, particularly those resulting from biotechnological processes, in order to maintain the high level of scientific evaluation of these products in the EU. Other aims are: to preserve the confidence of patients and the medical professions in the evaluation and to ensure the effective operation of the internal market in the pharmaceutical sector.<sup>29</sup>

The centralised procedure includes provisions that facilitate *risk management*. According to Regulation 726/2004 authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. In exceptional circumstances the authorisation may be granted subject to a requirement for the applicant to introduce specific safety procedures.<sup>30</sup>

An authorisation decision is based on a risk evaluation procedure, in which scientific expertise of national and international experts are involved. In this procedure *risk assessment* is based on quality, safety of efficacy grounds. An authorisation is given by the European Medicines Agency (EMA). As an agency of the EU the EMA assists the EU institutions with the scientific and technical aspects of pharmaceutical markets. The EMA Management Board is comprised of two representatives from the Commission, Parliament, each Member State and, quite recently, two representatives from patient organisations respectively. The operational strand of the EMA is effectively its scientific committees. In the EU procedures for authorisation of pharmaceuticals the Committee for Medicinal Products for Human Use (CHMP) is a key actor.<sup>31</sup> In fact it is the CHMP that determines whether new pharmaceuticals fall within the lists of the Annex of Regulation 726/2004. An applicant who seeks marketing authorisation for a new product that falls within the scope of the centralised procedure makes his application directly to the EMA. The CHMP gives an opinion within 210 days of receipt of the application. The EMA must then forward its decision to the Commission within 30 days. After several internal consultations the Commission (DG Enterprise and the Information Society) takes a final decision regarding the marketing of the new product. A product license granted under the centralised procedure is valid in all Member States, and the pharmaceutical is entered on the Community Register of Medical Products. According to Regulation 726/2004, the EMA is required to publish the opinion of the Committee, as well as the assessment report including the reasons for its

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<sup>27</sup> Marketing authorisation must be renewed once five years after the approval. Thereafter, the authorisation is normally of unlimited validity.

<sup>28</sup> The centralised procedure was set up by regulation 2309/93/EC (OJ 1993 L 214).

<sup>29</sup> According to the Annex to Regulation 726/2004, certain biotechnological products, medicinal products for human use for which the therapeutic indication is the treatment of certain diseases, as well as orphan medicinal products are to be authorised by the Community. Optional access to the centralised procedure is provided for medicinal products, although not belonging to the before mentioned categories, are nevertheless therapeutically innovative.

<sup>30</sup> Article 14 (8) Regulation 726/2004.

<sup>31</sup> The CHMP has a total of 32 member, including also three members of the EEA-EFTA States (Iceland, Liechtenstein and Norway).

opinion in favour of granting authorisation. The European Public Assessment Report shall include a summary written in a manner that is understandable to the public.

### ***Marketing authorisation - the decentralised procedure***

Since January 1998 the decentralised procedure has been compulsory for all new pharmaceutical to be marketed in a Member State, other than that in which they were first authorised. A producer who has obtained approval in one Member State (the 'Reference Member State') may seek approval in another Member State (the 'Concerned Member State'). The Reference Member State is required to provide an assessment report for the relevant product. The Concerned Member State must make a decision on approval within 90 days. The approval may be refused only on grounds of risk to public health. In this procedure *risk assessment* is based on quality, safety of efficacy grounds. If the Concerned Member is minded to refuse, the matter is submitted to the CHMP for arbitration. The CHMP opinion then is forwarded to the Commission who makes the final decision. The Commission's decision is binding on the Member States. If there is a serious disagreement among Member States, the matter is resolved by the Council. According to Gardner, the CHMP provides an institutional forum which fosters the convergence of national approval systems (1996, 59).

In 2004 the decentralised procedure was revised in order to improve the opportunities for cooperation between Member States.<sup>32</sup> A coordination group was set up for the examination of any question relating to marketing authorisation of a medicinal product in two or more Member States. Within the coordination group, all Member States are required to use their best endeavours to reach agreement on the action to be taken. In order to promote harmonisation of authorisations Member States shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics must be drawn up. Directive 2004/27/EC requires also that guidelines providing a definition of a potential serious risk to public health must be established.<sup>33</sup> This revision indicates that there is a movement from the equilibrium of 'old' and 'new' harmonisation measures to more measures of the latter approach.

### ***Manufacturing authorisation***

Manufacturing authorisation is bound upon provisions on *quality management*. Article 41, 48 and 49 of Directive 2001/83/EC set out the requirements that must be met by an applicant seeking manufacturing authorisation. Requirements concern the specification of the medicinal products and the place in which they are to be manufactured. The manufacturer must have at its disposal suitable premises, equipment and control facilities, and a 'qualified person'. The requirements for such a person are at least a university-level course for at least four years in pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, or biology; and at least two years of practical experience in a relevant field. The qualified person is responsible for checking each batch of product manufactured to ensure compliance with national laws and the requirements of the marketing authorisation.

To reduce the risks of undue manufacturing the Commission has enacted detailed rules laying down the principles and guidelines of good manufacturing practice for medicinal products and investigational medicinal products.<sup>34</sup> According to Directive 2003/94/EC the manufacturer is obliged to ensure that manufacturing operations are carried out in accordance with good manufacturing practice and in accordance with the information provided in the application for marketing authorisation. Good manufacturing practice can be attested by a particular certificate. The manufacturer is required to establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and personnel. Other safety measures concern the competence and qualification of personnel, hygiene programmes, premises and equipment, documentation, production, quality control, work contracted out, complaints, product recall, emergency unblinding, and self-inspection. For the interpretation of the principles and guidelines of good manufacturing practice, the manufacturers and the competent authorities are obliged to take into account the Guide the

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<sup>32</sup> See Chapter 4, Directive 2004/27/EC.

<sup>33</sup> Article 29 (2) Directive 2004/27/EC.

<sup>34</sup> Directive 2003/94/EC (OJ L 262/22).

Commission produced.<sup>35</sup> According to EU Law, manufacturing authorisation is to be granted by national authorities.<sup>36</sup>

### **Labelling and packaging**

Incorrect use of pharmaceuticals can have harmful effects. This is why the EU has taken measures of *quality management* regarding the labelling and packaging of pharmaceuticals. Directive 2001/83/EC specifies mandatory information that must be included on the packaging, about matters, such as the active ingredients, method and route of administration.<sup>37</sup> They also require a warning to keep the product out of the reach of children, an expiry date, any special storage precautions, the name of the holder of the marketing authorisation and the number of the marketing authorisation. According to the Directive, the pharmaceutical company must give particulars in the official language or languages of the Member State where the product is placed on the market. Package leaflets must include information about contra-indications, precautions for use and interactions with other medicinal products and alcohol, tobacco and foodstuffs. A description of side-effects must be provided.<sup>38</sup> In the case of an investigational medicinal product, labelling shall be such as to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product.<sup>39</sup>

### **Advertisement**

Advertisements of pharmaceutical may be misleading or positively harmful, if they result in inappropriate use of medicinal products. EU provisions relating to the advertisement of drugs include measures that can facilitate *risk and quality management*. According to Directive 2001/83/EC, Member States shall prohibit the advertising to the general public of medicinal products available on prescription only, certain psychotropic or narcotic substances, and the mentioning in advertising of certain therapeutic indications, such as sexually transmitted diseases, cancer, diabetes and other metabolic illnesses. Certain misleading, or potentially misleading, material is prohibited. This includes material, which suggests that the effects of taking the medicine are guaranteed, or suggests that the health of the subject could be affected by not taking the medicine, could lead to erroneous self-diagnosis, or suggests that the safety or efficacy of the product is due to the fact that it is 'natural'. Some articles of the Directive apply also to advertising to medical professionals, defined as 'persons qualified to prescribe or supply' pharmaceuticals. Specific rules govern matters such as sales promotions, hospitality, and provision of free samples. In this context the principle is that such inducements must be inexpensive and relevant to the practice of medicine or pharmacy. According Directive 2004/27/EC, at sales promotion hospitality being offered by the pharmaceutical industry must always be strictly limited to the main scientific objective of the event. It must not be extended to persons other than health-care professionals. To enable the European Commission to set out an information strategy to ensure good-quality, objective, non-promotional information Directive 2004/27/EC requires an evaluation of current practice with regard to information provision – particularly on the Internet – and its risks and benefits for patients.

### **3.3 Safety regulation in the post-marketing stage**

In the post-marketing stage the EU uses all traditional and new methods of coordination we described in the second section of this paper. Instruments are regulations, directives, guidelines,

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<sup>35</sup> Directive 91/356/EEC, preamble. This measure of 'soft law' concerns quality management, personnel, premises and equipment, documentation, production, quality control, contracted-out work, complaints and product recall, and self-inspection.

<sup>36</sup> Article 40 of Directive 2001/83/EC.

<sup>37</sup> This Directive covers the labelling and packaging of medicinal products, as well as the leaflets inserted in such packaging. The new Directive regarding good clinical practice with respect to investigational medicinal products requires authorisation for the processes of packing or presentation (Article 9 (1) Directive 2005/28/EC).

<sup>38</sup> According to Article 59, these are undesirable effects which can occur under normal use of the medicinal product.

<sup>39</sup> Article 15, Directive 2003/94/EC.

communications, policy programmes, agreements, and a code of conduct. In this stage safety regulation refers to certain measures of *risk management* and *surveillance*. Measures of risk management concern here the withdrawal of licenses. Member States are required to take all appropriate steps to ensure that supply of the medicinal product is prohibited and that it is withdrawn from the market. This is the case, for example, if the pharmaceutical appears to be harmful, the risk-benefit balance is not favourable under the authorised conditions of use. Generally, withdrawal is executed by the Commission. Where urgent action is essential to protect patients' safety, a Member State may suspend the use of a medicinal product.

Surveillance is performed by the European Medicines Agency, national authorities, as well as by self-inspection of the holder of the license. The EMEA is charged with the supervision of pharmaceuticals authorised through the centralised procedure. The Agency coordinates the supervision of the quality of medicinal products placed on the market by requesting testing of compliance with their authorised specifications. Regarding medicinal products authorised by the decentralised procedure and manufactured within the Community, the supervisory authorities are the competent authorities of the Member States. Additionally, the EMEA is given an important role in the surveillance activities regarding these products. According to Regulation 726/2004, the holder of a marketing authorisation is required to check whether the medicinal product concerned is corresponding to the technical and scientific progress. Directive 2003/94/EC requires that manufacturers conduct repeated self-inspections as part of the quality assurance system in order to monitor the implementations and respect of good manufacturing practice and to propose any necessary corrective measures. To enable public control, manufacturers are required to maintain records of such self-inspections and any corrective action subsequently taken. Coordination of the execution of the various supervisory responsibilities vested in the Member States is entrusted to the Commission.

Regarding the issue of *competence of inspectors* recent EU regulation has taken measures to ensure the provision of high scientific and technical expertise within the scientific committees and working groups of the EMEA. Members and alternates of the EMEA are chosen for their role and experience in the evaluation of medicinal products. The EMEA is responsible for coordination the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance activities. Moreover, the Agency is required to provide Community institutions and Member States with the best possible scientific opinions, as well as to apply the highest possible standards in its evaluations addressing the quality, safety and efficacy of high-technology pharmaceuticals. According to Regulation 726/2004, the field of activity of the EMEA's Scientific Committees is enlarged and their operating methods and composition are modernised. This Regulation stresses that scientific expertise constantly must be renewed. It stipulates that greater depth of scientific advice for future applicants is required. The scientific role of the EMEA's committees is supported by the setting-up of a permanent technical and administrative secretariat. The expertise of national authorities and inspectors is primarily a matter of national concern. Additionally, EU law states that national inspectors must possess the appropriate qualifications.<sup>40</sup> Their surveillance reports are made available to the Commission, the Member States and the CHMP.

To prevent *regulatory capture* the concerned EU Law provides measures of job rotation, safeguards regarding the impartiality of officials, as well as organisational safeguards. With respect to job rotation one measure is that members of the EMEA's CHMP are appointed for a three-year-term which may be renewed. The Executive Director is appointed for a period of five years which may be renewed once. In order to guarantee independence and transparency, members of the Management Board of the EMEA, member of the committees, rapporteurs and experts, as well as all members of staff of the competent authority of the Member States are required to have no financial or other interests in the pharmaceutical industry which could affect their impartiality.<sup>41</sup> These persons are obliged to make an annual declaration of their financial interests. Persons involved in EMEA activities mentioned beforehand who participate in meetings or workings groups of the Agency must declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence.

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<sup>40</sup> See Regulation 726/2004.

<sup>41</sup> Article 126b, Directive 2004/27/EC.

These declarations are made available to the public. Regarding the activities of the EMEA, all indirect interests, which could relate to the pharmaceutical industry must be entered in a register held by the Agency which is accessible to the public, on request, at the Agency's offices. The Agency establishes a code of conduct with particular reference to the acceptance of gifts. In addition to that Regulation 726/2004 requires that the database on medicinal products is managed independently of pharmaceutical companies. To guarantee the independence the management of funds intended for activities connected with this database, the operation of communication networks and market surveillance permanent control of the competent authorities is established.<sup>42</sup> Regarding organisational safeguards at the EMEA a permanent technical and administrative secretariat has been set up to support the independence of the Agency.

In the EU surveillance is based on an overall *information system*. Above we mentioned the decentralised information system and the central EU databases that were established to provide information for risk control. EU law obliges Member States to operate a pharmacovigilance system to ensure the adoption of appropriate and harmonised decisions concerning the medicinal products authorised within the Community, having regard to information obtained about adverse reactions to medicinal product under normal conditions of use.<sup>43</sup> This system is used to collect information useful in the surveillance, and to evaluate such information scientifically. In this system information about misuse, serious abuse and risks coming to light through the use of the relevant products over time is registered and communicated. To get insights into the severity of risks the Directive makes a distinction between 'adverse reaction', 'serious adverse reaction', and 'suspected unexpected adverse reaction'. The latter category is defined as one the nature, severity, and product outcome of which is not consistent with the summary product characteristics, which are a key part of the authorisation process. These definitions can be regarded as a contribution to *risk management*.

EU law requires Member States to take all appropriate measures to encourage doctors and other health care professionals to report suspected adverse reactions to the competent authorities. The marketing authorization holder is required to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country. He must submit a periodic safety update report to the competent authority of the Member State. This report includes a scientific evaluation of the risk-benefit balance of the medicinal product. Directive 2004/27/EC obliges the holder to ensure that such information is presented objectively and is not misleading. Furthermore, the holder is required to have an appropriately qualified person responsible for pharmacovigilance at his disposal.

For products authorised under the centralised procedure, the EMEA is charged with the operation of pharmacovigilance. Member States and pharmaceutical companies are required to convey immediately all suspected serious adverse reactions occurring within their territory to the EMEA. The EMEA then informs all the other authorities of other national pharmacovigilance systems. In cases of a potential serious public health risk information is directly conveyed to the CHMP, which then advises the Commission, whose final decision is binding on all Member States in which the product is marketed. For medicinal products authorised under the decentralised procedure, the EMEA is also given an important role. The CHMP is required to give opinions in situations where the marketing of a medicinal product originally authorised in more than one Member State is suspended in one of those Member States, due to information coming to light through pharmacovigilance procedures. The EMEA sets up a data-processing network to facilitate the exchange of pharmacovigilance information. According to Regulation 726/2004, the database is accessible to the general public. Through the 'EUDRA' projects, run by the Commission's Pharmaceutical Unit speedy and accurate information exchange on pharmacovigilance matters is ensured. The EU and WHO, working jointly have developed a computer assisted system for the entire authorisation, renewal, follow-up and inspection process. This system - 'SIAMED 2000'- is available, free of charge, to national competent authorities in the Member States.

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<sup>42</sup> Article 102a, Directive 2004/27/EC.

<sup>43</sup> Title IX Directive 2001/83/EC and Article 102 Directive 2004/27/EC.

## 4 Evaluation

In the remaining part of this paper the regulatory system will be evaluated by means of secondary analysis. We use the following evaluation frame we developed above.

Aspects	Adequate risk management	Adequate quality management	Adequate surveillance	Good regulatory system
Criteria	-distinct definition of risks -high level evaluation standards -competent evaluators - fast withdrawal	-sophisticated quality assurance system -good practices ensured	-competent inspectors - effective safeguards against regulatory capture - sophisticated information system	-flexibility -legal certainty -effective participation of patients

In the evaluation we explore whether EU provisions respond adequately to the requirements of risk management, quality management, and surveillance. We will as well regard the quality of the regulatory system. The evaluation of the European ways of governance are left to the final conclusions.

### ***Adequate risk management?***

#### *- Definition of risks*

In the Directives on clinical trials the term ‘risk’ is not defined. The same holds for the authorisation procedure. Rather implicitly a definition of risks is supported by the explanation of the term ‘serious adverse reaction’. However, this explanation does not provide a distinct description. On the EU level the evaluation of risks of pharmaceuticals is framed in terms of an ‘objective scientific basis’. Quality, safety and efficacy are considered as objective criteria. Objectification seems to be an appropriate way to accommodate potential conflicts between the different interests. On this assumption critical comments have been made. One argument against this approach is that in forcing the assessment of pharmaceutical to be framed in the so-called ‘neutral’ terms of the EU regulatory system, it suppresses political debate (Abraham & Lewis 2000; Hervey & McHale 2004, 317; Kaufer 1990). However, the regulation of medicines involves political and social judgements, with respect to national traditions, medical practice, as well as cost containment. Regarding medicinal products a full scientific discussion about the benefits and risks is regarded as absolutely necessary to protect patients.

#### *- High level evaluation standards?*

Under the centralised procedure EU law aims at providing a high level of risk assessment standards. As the decision-making in the scientific committees and working groups of the EMEA is governed by the effort of reaching consensus, it depends on the majority of opinions whether high assessment standards will be adopted. It is questionable whether delegates of Member States supporting high standards will feel closely bound in a climate of consensus and compromise. There is evidence that this is not the case if national experts are delegates to special scientific commissions. According to Kaufer, in this commissions national delegated take views rather independently of partisan considerations and loyalties to specific interest groups (Kaufer 1990, 163). The network of Member States’ experts involved in the EU’s centralised procedure seems to be a good mechanism to utilise the best scientific knowledge available.

Considering the decentralised procedure, there is more evidence for the risk that the least demanding regulatory system sets the standards. A company seeking marketing license may withdraw approval if the Concerned Member State was perceived to have higher assessment standards than other Member States and try to obtain authorisation in one of this ‘weaker’ States. National agencies, reliant

on industry fees, may compete to be chosen as the 'Reference Member State'. Faster agencies are more popular with industry. According to some commentators, such a 'race to the bottom' is not appropriate for pharmaceuticals, where risks to human life and health are fundamental if regulatory mechanisms are not properly applied and enforced (Abraham & Lewis 2000, 94; Hervey & McHale 2004, 297).

*- Competent evaluators?*

In the centralised authorisation procedure risk assessment is performed by scientific committees that are comprised of high-qualified experts. Moreover, the scientific committees of the EMEA are supported by working groups and other input of expertise. Regarding the competence of assessing the risks of clinical trials it is questionable whether the ethics committees have the necessary expertise at their disposal. The Directive does not prescribe the composition of ethics committees. It requires only that researchers must contact a specific 'competent authority' concerned with the regulation of clinical trials at Member State level. Since there is considerable diversity in the Member States (Megone 2001), it is plausible that the quality of the committees' risk assessment varies significantly.

*- Fast withdrawal?*

In the past, critics argued that the EU's regulatory system does not provide a quick solution regarding adverse reaction on medicinal products. As Abraham and Lewis show, in some examples the period during which patients were exposed to a potentially dangerous pharmaceutical product is extended by the EU system (2001, 148). For example, the UK withdrew the sleeping pill Halcion from the British market in 1991, on the grounds that the risk of serious adverse psychiatric reactions outweighing the potential benefits. The scientific commission of the EMEA did not request the other relevant national regulatory authorities to withdraw the Halcion until its investigation was finished. It will to be seen whether the recent regulatory measures of the EU to speed up withdrawal of pharmaceutical from the market turn out to be more effective.

***Adequate quality management?***

*- Sophisticated quality assurance system?*

Regarding the detailed, overall provisions we described above it seems that the EU has created the requirements of sophisticated quality assurance systems related to manufacturing processes, as well as to activities concerning labelling, packaging, and advertisement of pharmaceuticals. As concerns clinical trials, however, detailed standards of good clinical practices are not given. What is missing in this part of the regulatory system is an attempt fully to coordinate emergent legal and ethical principles. According to some criticism, the EU fails to take the ethical elements of the field sufficiently seriously (Hervey & MacHale 2004, 281).

*- Good practices ensured?*

According to the regulatory system good practices are enforced by the investigator, sponsor and ethical committee (clinical trials), the producer, national inspectors (manufacturing, labelling and packaging process, advertisement), and the Member States (all processes). Until now, there is no evidence whether these ways of enforcement are effective. Effectiveness is still to be proved on the base of an evaluation of the practices, including the effects of manufacturing certificates. Regarding the significant influence of pharmaceutical industry on the prescription practices of doctors has been revealed very recently in the Netherlands<sup>44</sup>, it is questionable whether the EU provisions on the promotion of medicinal products are effective. Hence, an evaluation of the provisions concerned as provided in Directive 2004/27/EC seems to be of high importance. As EU provisions on promotion activities are closely linked to national rules the evaluation should include the national level. Regarding the enforcement of good practices another question is whether the financial penalties the EU is establishing to enforce certain obligations connected with marketing authorisations for medicinal products will be effective.<sup>45</sup>

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<sup>44</sup> See the Dutch newspaper *Trouw* of June 26, 2005, p. 6, as well as recent decisions of the Committee that settles disputes concerning advertisement.

<sup>45</sup> See draft regulation laying down the maximum amounts and the conditions and methods for collection of financial penalties imposed by Regulation EC/726/2004.



### ***Adequate surveillance?***

#### *- Competent inspectors?*

Regarding the effort the EU made to enhance the expertise within the European surveillance system we can assume that a high level of scientific, technical and organisational competence is provided in the EU.<sup>46</sup>

#### *- Effective safeguards against regulatory capture?*

The EU has taken a number of measures to prevent and to minimise regulatory capture. It is striking, however, that the appointment of the members of the Management Board of the EMEA can be renewed more than once. Regarding the fact that the EMEA depends on the fees industry must pay for marketing and manufacturing licenses there is a permanent risk of capture. Cases of patient organisations being sponsored by the pharmaceutical industry that were reported very recently in the Dutch newspapers point to an overall risk of regulatory capture that has to be brought under attention of regulatory authorities.<sup>47</sup>

#### *- Sophisticated information system?*

The EU information system on pharmaceuticals, which has been continuously renewed and improved, also in cooperation with the WHO, seems to provide optimal information to detect and minimise risks. This overall information system is comprised of various databases with respect to clinical trials, authorisations and adverse reactions on pharmaceuticals. Though more access to relevant information is granted according to recent regulation, it is questionable whether sufficient transparency of risks is provided. Much of the information stored in the EU databases is only partly accessible to doctors, patients and other stakeholders. Apart from that the question arises whether this information is understandable to the public. It will to be seen whether the measures the EU took recently to improve the databases and communication of risks will provide more transparency in the future.

### ***A good regulatory system?***

#### *- Flexibility and legal certainty provided?*

Considering the recent adaptation to the newest state of risk assessment and quality management, as well as to recent insights into organisational facilities and professional support, the EU regulatory system appears to be rather flexible and dynamic. Regarding the recent amendment of the centralised authorisation procedures with respect to innovative and high technology pharmaceuticals and medicinal products with high therapeutic effects, the regulatory system seems to facilitate innovation. The recent amendments indicate as well that continuity of the regulatory system is not provided. Regarding the extreme complexity and large amount of various regulatory measures it occurs to us that the degree of legal certainty is low. This conclusion is put in perspective, however, by the large amount of detailed provisions that may enhance legal certainty.

#### *- Effective participation of patients?*

In the stages of the regulatory system governing pharmaceuticals there are hardly any provisions laying down active participation of patients. In the pre-licensing stage patients' participation is limited to the informed consent. As the interpretation of the boundaries of informed consent is left to the Member States, difficulties can arise in multi-state trials regarding the scope and depth of information about the trial's risks that must be conveyed to the participant to obtain his or her informed consent, due to different interpretations of how deeply risks must be explained and how understanding of risks must be assured. Quite recently the participation of patients in the regulatory system governing the authorisation stage has been encouraged by the membership of two representatives of patients' organisations in the Management Board of the European Medicine's Agency. Apart from this development the European regulatory approach appears to be rather dismissive to participation of patients. An indication to this conclusion is the definition of the patient's position in the Directives on clinical trials. It is striking that the Directives use the word 'subject' rather than that of 'participant'. As the term 'subject' connotes a more passive role in the clinical trial than that of participant, the use of it

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<sup>46</sup> To reduce the complexity of this study the evaluation of the competence of national inspectors who are in charge of surveillance on behalf of the EU was not included.

<sup>47</sup> See the Dutch newspaper *Trouw* of 14/06/05, p. 5.

might also indicate a reluctant approach to patients' participation in the regulatory process (Hervey & McHale 2004, 252).

## 5 Conclusions

In this paper we focused on European ways of governing risks of pharmaceuticals. More specifically we asked whether the European approach appears to be effective regarding the protection of patients' safety. In our evaluation we assumed that the protection of patients' safety requires adequate systems of risk management, quality management and surveillance. With reference to principles of good governance we secondly assumed that patients' safety is supported by a 'good' regulatory system.

According to our evaluation, the regulatory system governing pharmaceuticals the EU developed in the past 30 years shows a comprehensive and dynamic overall approach. Various instruments of European governance are regulating the three stages of pre-licensing, authorisation and post-licensing of medicinal products. Recently this regulatory system has been widely amended and replaced by a new regulation to improve the operation of the authorisation procedures and to adapt the system to the newest technical and scientific knowledge. The analysis of the development of the present regulatory system indicates that the European Commission took earlier evaluations seriously. The dynamic approach in this part of EU law seems to respond adequately to the dynamics of the development and research process of pharmaceuticals. On the other hand, the regulatory system that is still under revision appears to be an extremely complex and open-ended system that does not respond adequately to the needs of legal security and to the requirement of patient participation. The large amount of legal provisions that are compounded within a handbook of nine volumes are not accessible to patients and their representatives, if they are not trained in this particular field of EU law. Regarding patients' participation we observed that there was not much attention for this topic until quite recently. As we discussed above, in the EU law governing the pre-licensing stage the patient is treated rather as a passive subject than as an active person who is entitled to contribute to risk assessment and control. However, the EU consumer model implies that patients are enabled to exercise their own choices. Presently, there appears to be a very gradual movement towards more participation. To begin with, the new EU Regulation regarding the authorisation of medicinal products provides that two representatives of patients' organisations shall be members of the Management Board of the European Medicine's Agency. This Regulation stresses also the need for adequate involvement of civil society, and with particular reference to patients' representatives. Furthermore, in March 2005 the EMEA/CHMP Working Group with Patient Organisation, which was created in 2002, issued recommendations and proposals for action regarding transparency, dissemination of information, product information and *pharmacovigilance*.<sup>48</sup> In April 2005 the European Commission (DG Health and Consumer Protection) published the Luxemburg Declaration on Patient Safety in the health sector.<sup>49</sup> This Declaration recommends the EU institutions to establish an EU forum with participation by relevant stakeholders to discuss European and national activities regarding patient safety and to work in alliance with WHO Alliance towards a common understanding on patient safety issues, and to establish an 'EU solution bank' with 'best practice' examples and standards.<sup>50</sup>

With regard to adequate risk and quality management, the present development of the regulatory system reveals a strong movement towards increasing influence of the EU. In the new Regulation laying down Community procedures for the authorisation and supervision of medicinal products provisions on scientific risk assessment and surveillance are formulated more explicitly than in the past. Through a system of attracting the best experts to the European Medicines Agency and various committees the European authorities may be the most competent ones in the future to safeguard patients' safety. Regarding the critical remarks on the 'devaluation' of high safety standards of the Member States in the European authorisation procedures it is questionable whether the European standards will provide an adequate level of safety. As the European decision-making explicitly stresses the need of consensus it is plausible that Member States opting for less demanding standards can exert considerable influence on the level of standards. Until now considerable difficulty

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<sup>48</sup> <http://www.emea.eu.int/pdfs/human/patientgroup>.

<sup>49</sup> See website of the EMEA (risk management strategy).

<sup>50</sup> Other recommendation concern action of National Authorities and health care providers.

remains over the question whether the appropriate site for risk assessment is national or EU level. With respect to the adequate level of safety another problem may arise by the EU effort to speed up the authorisation procedure. Here the question is whether faster authorisation procedures are detrimental to the protection of patients' safety. Comparing the present situation with the situation about five years ago we conclude that today more transparency is provided regarding the risks of pharmaceuticals. In this respect a critical point is that patients do not have access to the information system *pharmacovigilance*. As regards adequate surveillance the impartiality of inspectors appears to be vulnerable to the influence of pharmaceutical industry. Hence, a final conclusion is that the problems to patients' safety we indicated in the introduction of this paper only partly seem to be solved. In our evaluation we encountered additional problems that call for more research.

As regards the challenges to the European regulatory system governing pharmaceuticals we concluded in the second section that the tensions caused by three hybrid constellations have to be solved. In this respect we assumed that tensions arise from the combination of hybrid modes of governance ('traditional' and 'new' methods), from the connection of conflicting principles ('flexibility' versus 'legal certainty'), as well as from the accommodation of conflicting interests ('patients' versus 'pharmaceutical industry'). A central issue of this paper is whether the European ways of governance relating to medicinal products provide adequate solutions to these tensions. Regarding the tensions between the interests of pharmaceutical industry and consumers it is argued that the authorisation procedure tend to favour the industry's interests, since they are centrally concerned with the single market in pharmaceuticals, but only peripherally concerned with protection of health (Hervey and McHale 2004, 296). One indication for more attention for the industry's interest may be the fact that the DG Enterprise is the driving force behind regulating pharmaceuticals, while the DG Consumer and Health Protection is hardly involved. As regards various interests it is claimed that the EMEA over-emphasises time-to-market for new pharmaceuticals, at the expense of protecting health (Mossialos and McKee 2002, 113). One argument for this claim might be that the focus of the present regulation lies explicitly on speeding up the approval procedures.

As regards the tensions between the needs of flexibility of the regulation system and legal certainty the evaluation indicated that EU law does not provide an appropriate solution. As these principles are difficult to reconcile, the evaluation raises the question by which means an acceptable balance between flexibility and legal certainty can be found. Probably, a regulatory system that provides more deliberation and transparency than the present one would be a good step forward.

As concerns the tensions between traditional and new modes of governance that are combined in the regulatory system regarding pharmaceuticals it occurs to us that the EU has minimised the tensions by integrating them within a sophisticated and powerful approach of concentrating scientific expertise and control at the EU level. As far as we can see the present EU methods of harmonisation and incremental deregulation used in this regulatory system are rather successful. However, there is some evidence that there is extreme reluctance of Member States to accept the combination of new and old style harmonisation within the decentralised procedure.<sup>51</sup> In practice, many national authorities do not follow the principle of mutual recognition. They effectively re-evaluate cases, and the medicinal products authorised by other Member States are not actually recognised. In sum, with regard to the reluctance of Member States and the growing dissatisfaction of patients with the regulatory system governing pharmaceuticals it still has to be shown how effective the pro-active and interventionalistic approach<sup>52</sup> of the EU really is.

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<sup>51</sup> Commission, DG Enterprise, COM (2001) 606 final.

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