Transparency of authorities: opportunities and restrictions

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List of Abbreviations

AMG	*Arzneimittelgesetz*
AMIS	*Arzneimittelinformationssystem*
ATC	Anatomical Therapeutic Chemical
BDSG	*Bundesdatenschutzgesetz*
BfArM	*Bundesinstitut für Arzneimittel und Medizinprodukte*
BGH	*Bundesgerichtshof*
BVL	*Bundesamt für Verbraucherschutz und Lebensmittelsicherheit*
CAT	Committee for Advanced Therapies
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Co-ordination Group for Mutual Recognition and Decentralised Procedures (human)
CMS	Concerned Member State
COMP	Committee on Orphan Medicinal products
CVMP	Committee for Medicinal Products for Veterinary Use
DIMDI	*Deutsches Institut für medizinische Dokumentation und Information*
EC	European Commission
EEA	European Economic Aria
EEC	European Economic Community
EMEA	European Medicines Agency
EP	European Parliament
EPAR	European Public Assessment Report
EU	European Union
Eudra	European Union Drug Regulating Authorities
EVCTM	EudraVigilance Clinical Trial Module
EVPM	EudraVigilance Post-Authorisation Module
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HMA	Heads of Medicines Agencies
HMPC	Committee on Herbal Medicinal Products
HWG	*Heilmittelwerbegesetz*
ICSR	Individual case safety report
IFG	*Informationsfreiheitsgesetz*
INN	International Non-proprietary Name
MHRA	Medicines and Healthcare products Regulatory Agency
MRRG	*Melderechtsrahmengesetz*
OLG	*Oberlandesgericht*
PCWP	Patients' and Consumers' Working Party
PDCO	Paediatric Committee
PEI	Paul-Ehrlich-Institute
PIP	Paediatric investigation plan
PL	Package Leaflet
PVWP	Pharmacovigilance Working Party
Q&A	Question and Answer
RMS	Reference Member State
SGB	*Sozialgesetzbuch*
SmPC	Summary of Product Characteristics
TRIPS	Trade-related Aspects of Intellectual Property Rights
UK	United Kingdom
URL	Uniform Resource Locator
USA	United States of America
USC	United States Code
VwVfG	*Verwaltungsverfahrensgesetz*

1. Introduction

In the last years transparency of regulatory authorities has become a matter of increasing public interest and has been established as a key policy in the pharmaceutical legislation of the European Union (EU).

Transparency may be classified into administrative and scientific transparency. The rather administrative aspects concern on the one hand the independence of the regulators and experts at the competent authorities that are involved in decision making processes especially regarding financial or other interests in the pharmaceutical industry. On the other hand administrative transparency concerns the public access to information on the daily business, like rules of procedures, agendas and meeting minutes, etc. The public access to medicinal product related information may be understood as scientific transparency. This comprises e.g. information on the grant of a marketing authorisation; product information texts like the summary of product characteristics (SmPC), the package leaflet (PL) and labelling as well as the public assessment report of the marketing authorisation application.

Furthermore transparency may be categorised as proactive or reactive transparency. Proactive transparency describes the automatic provision of information by regulatory authorities e.g. by publication on internet websites, accessible databases or as printed documents and may cover administrative as well as scientific information. In contrast, the reactive transparency describes the access to documents on demand. The reactive transparency approach concerns information held by regulatory bodies including documents prepared by authority members as well as third party documents. While on the EU level the public access to information held by the European Council, Parliament and Commission is ruled by Regulation (EC) 1049/2001, no harmonised legislation on the disclosure of official information held by national authorities exist at present. As a consequence, the access to documents is ruled by individual national provisions. Since the term “commercially confidential” lacks a common legal definition, the understanding differs among the member states on which information may be disclosed and which information need to be protected.

The present thesis deals with the implementation of transparency rules within the European medicines regulatory system. At the beginning, transparency provisions in the current legislation and in upcoming amendments are presented. Than an overview is given about how transparency rules are implemented by key players within the system, like the European Medicines Agency (EMEA), the Heads of Medicines Agencies (HMA), the co-ordination group for mutual recognition and decentralised procedures human (CMD(h)) and the national competent authorities. The following part deals with the commercial use of data disclosed for transparency reasons and the need for restrictions. Finally the advantages of increasing transparency are discussed focussing on the need to keep the balance between transparency and high-quality information for the public on the one hand and protection of intellectual property and commercial interests on the other hand.

2. Legislative framework leading to increased transparency

2.1. European Union

Transparency represents a key policy within the European Union (EU). This is demonstrated by the fact that transparency has already been entered as one of the declarations of the so-called "Maastricht Treaty" establishing the EU that was signed on 7 February 1992 in Maastricht[1]. Declaration 17 of the treaty entitled "on the right of access to information" states that "transparency of the decision-making process strengthens the democratic nature of the institutions and the public's confidence in the administration".

One major step establishing transparency in the general EU legislation was the adoption of Regulation (EC) No 1049/2001[2] on the public access to documents of the European Parliament, Council and Commission. The purpose of this regulation was to define rules and procedures to ensure "on grounds of public or private interest … the widest possible access to documents" of the three institutions (article 1). According to article 2 of the regulation the right of access is granted to all EU citizens and residents (legal or private persons) and may be granted in addition to non-residents by the respective institution. This right refers not only to documents generated by the institution but as well to documents received by it. Article 4 describes exceptional cases in which the access shall be refused. These are mainly cases in which the protection of public interest or of personal data would be undermined. Furthermore commercial interests including intellectual property shall not be violated, "unless there is an overriding public interest in disclosure".

As stated in recital 2 of the regulation, improved transparency especially regarding the decision-making process by granting public access to documents of the institutions "contributes to strengthening the principles of democracy and respect for fundamental rights" as "openness guarantees that the administration enjoys greater legitimacy and is more effective and more accountable to the citizen …". This means that the purpose of the regulation was to increase the trust of the EU citizens in the democratic administration and to improve understanding for decisions made by the institutions.

Besides the more or less general provisions of the mentioned regulation transparency has been established in specific fields of law.

In the last years transparency has become a matter of increasing importance regarding the EU legislation of medicinal products especially by the amendment of the so-called "community code". Starting in 1965 with Council Directive 65/65/EEC[3] several directives entered into force in order to approximate national laws of the member states concerning medicinal products. This process lead to the adoption of "Directive 2001/83/EC on the community code relating to medicinal products for human use" (and Directive 2001/82/EC concerning medicinal products for veterinary use), which assembles the previous provisions in a single text[4]. Meanwhile the community code has been amended by subsequent EC directives. In particular in 2004 the community code has been extensively reviewed and was amended in particular by Directive 2004/27/EC[5].

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[1] *The Treaty on European Union*, OJ **C 191**, 29 July 1992, p. 101.

[2] *Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents,* OJ **L 145**, 31 May 2001, p. 43–48.

[3] *Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products (65/65/EEC),* OJ **022,** 9 February 1965, p. 369–373.

[4] *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use,* OJ **L 311**, 28 November 2001, p. 67–128.

[5] *Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use,* OJ **L 136**, 30 April 2004, p. 34–57*).*

In parallel, Regulation (EEC) No. 2309/93[1] concerning the centralized registration procedure and the establishment of the European Medicines Agency (EMEA) has been replaced by Regulation (EC) No. 726/2004[2]. With this comprehensive review provisions regarding transparency of the EMEA and the competent national regulatory authorities were established.

The main changes of Directive 2001/83/EC regarding transparency are the change of articles 21.3 and 21.4 and the insertion of article 126b. Paragraph 21.3 determines that the competent authority shall make the marketing authorisation and the summary of product characteristics (SmPC) publicly available without delay after granting a marketing licence. Additional documents that shall be publicly accessible after the grant are described in article 21.4. These are the assessment report provided by the authority including the reasons for its decision. Furthermore, separate justifications are to be provided for each indication applied for. Any commercially confidential information has to be removed prior to publication.

Article 126b deals with the integrity and independence of members of the competent authority's staff and consulted experts or rapporteurs involved in the marketing authorisation process and/or in the surveillance of medicinal products. The authority has to ensure that these persons "have no financial or other interests in the pharmaceutical industry which could affect their impartiality". Furthermore they have to declare their financial interests annually.

In addition article 126b details documents of the competent authority for which public access shall be guaranteed. These are the authority's rules of procedures, agendas and minutes of its meetings, the decisions taken, details of votes including explanations and minority opinions.

The provisions regarding transparency in the Regulation (EC) No. 726/2004 exceed the provisions of the community code. First of all the composition of the EMEA's committees detailed in article 56 shall be published together with the individual professional qualification (article 63.1). In line with article 126b of the community code, financial or other interests shall be ruled out and the respective annually declarations of the concerned persons have to be provided. Furthermore the agency shall provide a register of all indirect interests that is accessible to the public on request (article 63.2 (1)). According to the items of the agenda the concerned persons shall declare at every meeting any specific interest "which could be considered to be prejudicial to their independence" (article 63.2 (3)). These declarations shall be made publicly accessible, too.

In line with articles 21.3 and 21.4 of the community code, the SmPC, the assessment report (European public assessment report, EPAR) of the committee for medicinal products for human use (CHMP) or of the committee for medicinal products for veterinary use (CVMP) have to be published as well as the granting, the refusal or the withdrawal of a marketing authorisation application together with the justification of the opinion or decision, respectively.

Article 80 of the regulation describes additional information that should be accessible to the public. Subparagraph 80 (1) defines that the access to "regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products which is not of a confidential nature" shall be ensured. Subparagraph 80 (2) deals with the administrative transparency of the EMEA, stating that "internal rules and procedures of the agency its committees and its working groups" shall be published.

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[1] *Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products*, OJ **L 214**, 24 August 1993, p. 1–21.

[2] *Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, OJ **L 136**, 30 April 2004, p. 1–33.

To define rules for deciding which information shall considered being commercially confidential, the EMEA published principles applying to the disclosure of EMEA documents, which will be discussed below[1]. It is noteworthy to stress that there is no common definition of commercial confidentiality among the member states.

With regard to the surveillance of authorised medicinal products further provisions concerning transparency have been introduced with the review into the community code and into Regulation (EC) No 726/2004. It is laid down that the member states shall establish and operate a pharmacovigilance system to collect and to evaluate information on the safety of medicinal products especially regarding adverse reactions. This information shall be disseminated to the other member states and the EMEA and recorded in a database set up by the agency (article 102 of Directive 2001/83/EC as amended). This database shall provide permanent and full access to the member states (EudraVigilance database, see chapter 3). For healthcare professionals, marketing authorisation holders and the general public an appropriate access shall be granted. Additionally a database (EudraPharm, see chapter 3) shall be established that contains general information on the medicinal product, the authorised product information texts, e.g. the SmPC, the PL and the labelling of the medicinal product, as well as information on conducted or ongoing clinical trials (article 57.1 (b), (d), (f), (l) and article 57.2 of Regulation (EC) No. 726/2004).

A further increase in transparency is reached by the involvement of patients' organisations in the regulatory activities of the EMEA. Starting with Regulation (EC) No 141/2001 on orphan medicinal products[2] the collaboration with patients' organisations was entered into the pharmaceutical legislation. Beside the representatives of each member state and the participants recommended by the agency, the committee on orphan medicinal products (COMP) shall be composed of three members who represent patients' organisations as stated in article 4 (3) of the regulation and according to article 4 (2c), one of the tasks of the COMP shall be to assist the EC in the contact with patients' organisations. The same applies to the paediatric committee (PDCO) which provides as well three representatives of patients' organisations and additional three members who represent healthcare professionals according to article 4 of the Paediatric Regulation[3]. The role of the PDCO and further provisions originating from the Paediatric Regulation will be presented below.

Regulation (EC) No. 726/2004 foresees additional involvement of patients' and consumers' organisations. According to article 65(1) two members of the EMEA management board shall represent patients' organisations, and one doctors' and one veterinarians' organisations, respectively. Article 78 (1) provides that appropriate contacts with representatives of patients or consumers, industry and healthcare professionals shall be established. These persons may be invited to participate as observers in certain activities of the agency. Furthermore paragraph (2) states that the scientific committees, working parties and scientific advisory groups shall consult "parties concerned with the use of medicinal products", in particular patients' and healthcare professionals' organisations. In addition article 59 (3) of Directive 2001/83/EC determines that patient target groups shall be involved in the creation of the PL of a medicinal product to ensure that the information is clear and understandable. According to article 65 of the community code "interested parties" shall be involved in

[1] *Principles to be Applied for the Deletion of Commercially Confidential Information for the Disclosure of EMEA Documents, 15 April 2007,* Doc. Ref.: EMEA/45422/2006, URL: http://www.emea.europa.eu/pdfs/human/euleg/4542206en.pdf, [accessed on 20 Nov. 2009].

[2] *Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products,* OJ **L 18**, 22 January 2000, p. 1 - 5.

[3] *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 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,* OJ **L 378**, 27 December 2006, p. 1 – 19.

the development of guidance documents on diverse issues like e.g. the legibility of the PL and the labelling.

Additional legal provisions exist regarding public access to information on medicinal products for paediatric use. As laid down in the Paediatric Regulation the paediatric committee (PDCO) evaluates paediatric investigation plans (PIP) for medicinal products resulting in an opinion[1] that is forwarded to the agency. With respect to the final opinion of the PDCO the EMEA issues an opinion that is published after deletion of commercially confidential information on the EMEA website (see below). In addition to the described provisions regarding the publication of opinions and decisions the Paediatric Regulation dictates an even higher degree of transparency. Article 41 lays down that particulars on clinical trials conducted/applied for in line with an approved PIP have to be entered into the respective database on clinical trials (EudraCT, see below) and that parts of this information shall be accessible to the public. This deviates from article 11(1) of the Clinical Trial Directive[2], which determines that only the competent authorities of the member states, the EMEA and the EC shall have access to the respective database. The kind of information on the paediatric clinical trials that shall be made public is set out in a Commission communication[3] published on 4 February 2009 and will be detailed below.

Besides the described public access to information via internet and community databases, provisions have been made concerning the access to EMEA documents following a written request. According to article 73 of the Regulation (EC) No 726/2004, the above mentioned Regulation (EC) No 1049/2001 on the public access to documents of the European Parliament, Council and Commission shall apply to documents of the EMEA or documents in its possession. On 19 December 2006 the EMEA management board adopted revised "Rules for the implementation of Regulation (EC) No 1049/2001 on access to EMEA documents"[4]. In line with the Regulation EC No 1049/2001 the scope of the EMEA management board decision is to ensure the widest possible public access to documents generated or received by the agency.

Regarding the transparency of the marketing authorisation holder towards the general public it is necessary to discriminate between information and advertising. In general, advertising of a medicinal product that is available on medicinal prescription only is prohibited (according to article 88 of the community code). Advertising is defined in article 86 as "any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products." Since the community code does neither contain detailed provisions on information nor on discrimination between information and advertising, the terms are interpreted differently among the member states, leading to an inconsistent legal basis within the community. In Germany, for example, the permission to provide information to the general public by the marketing authorisation holder on medicinal products subject to prescription is limited to answering specific questions[5]. This includes the prohibition for the marketing authorisation holder to disseminate the SmPC and the PL, even though they are scientific documents that have been authorised by the

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[1] *Art. 6(1)a*, *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 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*, OJ **L 378**, 27 December 2006, p. 1 – 19.

[2] *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*. OJ **L 121**, 1 May 2001, p. 34 – 44.

[3] *Communication from the Commission — Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006,* OJ **C 28**, *04 February* 2009, p. 1-4.

[4] *Rules for the implementation of Regulation (EC) No 1049/2001 on access to EMEA documents*, 19 December 2006, Doc. Ref: EMEA/MB/203359/2006, Rev 1, URL: http://www.emea.europa.eu/pdfs/general/manage/mbar/20335906en.pdf, [assessed on 21 Nov. 2009].

[5] *§ 1(5) des Gesetzes über die Werbung auf dem Gebiet des Heilwesens (Heilmittelwerbegesetz – HWG),* BGBl I, 19 Oktober 1994, p. 3068-3072.

respective competent authority. Regarding the public access to product information texts of medicinal products subject to medical prescription on the website of the marketing authorisation holder the legal situation in Germany is ambiguous. The higher regional court in Munich allowed the presentation of scientific information on an internet website, as the internet is characterised as a passive information medium that allows an interested party to search for answers to specific questions and not as an active medium that disseminates unsolicited information to the general public like e.g. television[1]. In contrast, in a comparable case law the higher regional court in Hamburg decided divergently on this matter. In this case the presentation of product information texts on prescription-only medicines in the internet is seen as a prohibited advertisement as it is not limited to healthcare professionals[2]. On 16 July 2009 the Federal court of justice (*Bundesgerichtshof*) decided to refer the matter to the European Court of Justice[3]. In detail the European instance shall clarify whether the presentation of authorised product information texts like the SmPC and the PL of prescription-only medicinal products in the internet is subject to Article 88 (1) a of the community code, concerning the prohibition of advertising to the general public of prescription-only medicinal products.

In contrast to the strict but divergent interpretation in Germany, other member states permit the access to several types of non-promotional information to the general public (see chapter 3.4.2).

To address these discrepancies and to develop a legal framework regarding the information provided by the marketing authorisation holder on prescription-only medicinal products to the general public a proposal for a directive to amend the community code has been published by the European Commission as part of the so-called EU pharmaceutical package[4]. The pharmaceutical package comprises legislative proposals focussing on three main aims: (i) to combat counterfeit of medicinal products, (ii) to improve safety monitoring (pharmacovigilance) and (iii) to provide high-quality information for the general public on medicinal products that are subject to medical prescription[5]. The latter includes a proposal to amend the community code (for national registrations)[6] and in parallel a proposal for a regulation that determines that the respective provisions of the proposed directive shall apply to Regulation (EC) No 726/2004 (for centralized registrations), too. The directive foresees the incorporation of the new Title (Title VIIIa) “Information to the general public on medicinal products subject to medical prescription” into the community code.

The proposal specifies the types of information that may be disseminated indirectly or directly by the marketing authorisation holder to the general public. In particular the SmPC, the PL, the labelling as approved by the competent authorities and the assessment report may be made accessible. In addition, texts that do not exceed these documents but present the information differently are allowed. Furthermore information on non-interventional trials, on accompanying measurements and on the medicinal product in context to the addressed medical need may be disseminated.

The proposal specifies quality criteria regarding the content of the information, that include on the one hand characteristics like being objective, verifiable, evidence-based, in an understandable language to the general public, not misleading, in line with the SmPC, PL and labelling, up-to-date etc. and on the

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[1] *OLG Munich, 13 January 2005, 6 U 2773/04.*

[2] *OLG Hamburg, 23 November 2006, 3 U 43/05.*

[3] *BGH, 16 July 2009, I ZR 223/06.*

[4] *Pharmaceutical Package, Safe, innovative and accessible medicines: a renewed vision for the pharmaceutical sector*, 10 December 2008, URL: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/pharmpack_en.htm, [assessed on 21 Nov. 2009].

[5] *Press release*, 10 December 2008, Doc. Ref: IP/08/1924. URL: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/pharmpack_12_2008/ip-08-1924_en.pdf, [assessed on 18 Nov. 2009].

[6] *Proposal for a Directive of the European Parliament and of the Council amending, as regards information to the general public on medicinal products subject to medical prescription, Directive 2001/83/EC on the Community code relating to medicinal products for human use*, Doc. Ref: 2008/0256, URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0663:FIN:EN:PDF [assessed on 21 Nov. 2009].

other hand mandatory statements regarding among others the prescription only-availability, the origin of the information and a contact address of the marketing authorisation holder.

One major aspect of the proposal concerns the restriction of the channels for the dissemination of information by the marketing authorisation holder to (i) health-related publications as specified by the member states, to (ii) internet websites and to (iii) the responses to requests for information. The active distribution of unsolicited information like particularly on television and radio is prohibited explicitly.

Additional provisions deal with the authorisation and the surveillance of requirements and conditions on the disseminated information to the public detailed in the new title by the competent authorities.

With respect to the second major aim of the pharmaceutical package which is the strengthening of the EU pharmacovigilance system comprehensive proposals to amend the community code and Regulation (EC) No 726/2004 have been developed which contain further transparency measures. In particular the proposal to amend the regulation foresees that the EudraVigilance database shall be strengthened and that a safety web portal shall be established by the Agency in collaboration with the EC and the member states to disseminate pharmacovigilance information on medicinal products authorised within the community[1]. In parallel the directive proposal dictates the establishment of national safety web portals by the member states which are linked to the EMEA web portal as well as the obligatory usage of EudraVigilance database for the adverse event reporting by both, marketing authorisation holders and national competent authorities[2] (see chapters 3.1.1 and 3.1.3).

The legislative proposals have been adopted on December 10th, 2008 and need to be discussed by the EP and by the Council of Ministers as part of the codecision procedure before they may enter into force. Thereafter, the member states shall incorporate the provisions into national laws within 12 months after the publication in the official journal of the EU.

2.2. National Provisions

As stated above, no common EU legislation concerning the disclosure of official information held by authorities exists within the European economic area (EEA) and the majority of member states have individual freedom of information acts in place. However, since the description of the individual provisions of each member state would go beyond the scope of this thesis, the respective German legislation serves as an example and is presented in detail.

In December 2004 the draft of a German freedom of information act has been published. At this time similar laws existed already in more than 50 states, including the majority of the EU member states. The German act has been developed mainly to improve the control and the acceptance of administrative procedures by the public and with respect to the EU treaties and the above mentioned Transparency Regulation[3] to contribute to the European integration process[4].

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1 *Art. 24 and 26 of the Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency,* Doc. Ref: 2008/0257 (COD), URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:EN:PDF, [assessed on 11 Jan. 2010].

2 *Art. 106, 107 (3.) and 107a (1.) and (2.) of the Proposal for a Directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use,* Doc.Ref: 2008/0260 (COD), URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0665:FIN:EN:PDF, [assessed on 11 Jan. 2010].

3 *Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents,* OJ **L 145**, 31 May 2001, p. 43–48.

4 *Entwurf eines Gesetzes zur Regelung des Zugangs zu Informationen des Bundes (Informationsfreiheitsgesetz – IFG),* Bundestagsdrucksache **15/4493**, 14 December 2004, p. 1-17.

On 1 January 2006 the German freedom of information act (IFG, *Informationsfreiheitsgesetz*[1]) entered into force. This may be seen as a milestone in transparency, as until that date administration procedures and documents were secret and confidential in principle. A right to access data on running administration procedures was generally only granted if disclosure was necessary to protect or defend the rights of a stakeholder of the respective procedure or when the applicant is personally concerned as laid down in § 29 of the administrative procedures act (VwVfG, Verwaltungsverfahrensgesetz), § 25 of the social code (SGB X, Sozialgesetzbuch X), § 19 of the Federal Data Protection Law (BDSG, Bundesdatenschutzgesetz) and § 8 of the law, regulating the tasks and authorities of registry offices (MRRG, Melderechtsrahmengesetz)[2]. Nevertheless, an access to information on demand may have been granted on a case-by-case decision by the competent authority when a legitimate interest of the applicant was given. In contrast, the freedom of information act permits everyone the access to information in principle (§ 1(1)), i.e. without specific requirements. To refuse the access the competent authority now has to justify the exceptional circumstances of its decision.

Like the transparency regulation[1], the IFG determines exceptional circumstances limiting the right of access to information. These circumstances are (i) the protection of public interest (§ 3 IFG), like e.g. the prevention of disadvantageous consequences on international relations, military or safety relevant matters, public safety, etc.; (ii) the protection of the decision-making process of an authority (§ 4 IFG); (iii) the protection of personal data (§ 5 IFG) and (iiii) the protection of intellectual property and trade or company secrets (§ 6 IFG). The competent authority decides about the legitimacy of applications on access to information. In cases when the authority may come to the conclusion that the data concern third party's interests, especially when §§ 5 or 6 may apply, the applicant has to provide a justification for the access and the authority has to consult the concerned third party prior to granting access (§§ 7 and 8). The third party will be informed about the final decision of the authority and its remedies.

In general the impact of the German IFG on existing provisions regarding transparency in specific fields of law is limited. As stated in § 1(3) IFG specific provisions concerning the public access to official documents will overrule the IFG provisions (except § 29 VwVfG and § 25 SGB X). Regarding the German pharmaceutical legislation specific provisions concerning transparency are presently made in the German Drug Law (AMG, Arzneimittelgesetz) and will be detailed below. With respect to § 1 (3) IFG and to these AMG provisions it is noteworthy to stress the fact that the 15th AMG amendment act, which entered into force on 23 July 2009, contains a clause (item 71, expanding § 84a AMG, see below) addressing the IFG. It is stated that in contrast to § 1 (3) IFG the right of access to information in the responsibility of the competent authorities for the granting and surveillance of marketing authorisations for medicinal products exist in parallel to the specific provisions of the AMG. In other words the AMG does no longer overrule the IFG.

In the following part the amendments of the German pharmaceutical legislation according to the provisions regarding transparency of the review of Directive 2001/83/EC will be presented. Prior to the incorporation of Directive 2004/27/EC into national law by the 14th AMG amendment act, the following regulations for public information already applied. § 34 (1) determined the kind of information that has to be published by announcement in the federal law gazette (*Bundesanzeiger*):

- granting or renewal of a marketing authorisation,
- withdrawal,
- revocation,
- suspension,
- expiry of a marketing authorisation

[1] *Gesetz zur Regelung des Zugangs zu Informationen des Bundes (Informationsfreiheitsgesetz – IFG),* BGBl. I, 05 September 2005, p. 2722-2724.

- discontinuation of marketing
- change of the name of a medicinal product
- withdrawal or revocation of the release of a batch of a medicinal product.

In addition, due to the 14th AMG amendment act, the granting of an extension of the data exclusivity period (according to § 24b (1) 3 and (7), respectively) or the granting of a data exclusivity period according to § 24b (6) or (8) has to be published in the federal law gazette.

The subsections (1a)–(1d) of § 34 AMG were introduced with the 14th AMG amendment act, too. They deal with the information that has to be made publicly accessible without delay in an electronic form by the competent authority:

- Information about the grant of the marketing authorisation together with the SmPC
- The assessment report including an opinion concerning the results of preclinical and clinical trials separately for every indication applied for as well as the results of residue limit studies for veterinary medicinal products after removal of commercially confidential information
- In the case of a conditional approval, the conditions including the time limits for fulfilment of the conditions.

This provision concerns as well any changes to the above mentioned information.

§ 84a AMG deals with the right of access to pharmacovigilance information in the context of liability. In cases were a reasonable suspicion exists that a medicinal product caused a serious harm that exceeds an acceptable extend, the aggrieved party may request disclosure of information by the marketing authorisation holder and by the competent authority needed to clarify whether a claim for compensation (pursuant to § 84) exists. In contrast to the IFG, the access to information is limited to the aggrieved party and to the need for disclosure to determine a possible claim for compensation. As mentioned above, this restriction has been removed by the 15th AMG amendment act.

Article 126b paragraph 1 of Directive 2001/83/EC as amended dealing with the transparency and independence of the authority has been incorporated nearly literally into the AMG by the insertion of § 77a (1). This subsection rules out that members of the authority or consultants involved in the approval and supervision of medicinal products have financial or other interests in the pharmaceutical industry undermining their neutrality and determines that these persons have to declare their interests annually (see above).

Subsection (2) of § 77a AMG details that the competent higher federal authorities and the competent authorities shall make publicly accessible their procedural rules as well as the agendas and results of their meetings. It is noteworthy to stress, that in contrast to § 77a (2) AMG article 126b.2 lays down in detail that these meeting minutes shall include details of votes and their respective justifications and especially the minority opinions. Furthermore § 77a (2) AMG restricts the provisions of article 126b in view of the fact that it lays down that manufacturing and business secrets and secrets of the authority shall be protected.

3. Transparency within the European Medicines Regulatory System

As presented in chapter 2, transparency of regulatory authorities and of the approval and surveillance processes of medicinal products has become an issue of major public interest. The following part presents the implementation of transparency by regulatory authorities in the EU.

3.1. Implementation of transparency by the European Medicines Agency (EMEA)

The EMEA adopted in March 2005 the EMEA Road Map to 2010, which summarizes the agency's visions and strategies to address the new challenges resulting from political and legal changes and the substantial scientific progress in the following years[1]. One major objective presented is the access to high-quality information granted to healthcare professionals, patients and the general public. Therefore the analyses of the current transparency practices and initiatives to enhance the access to information leading to an action plan were envisaged.

On 19 June 2009 the EMEA published a draft transparency policy for public consultation which classifies three main transparency objectives[2]. These objectives are (i) increases transparency in the EMEA day-to-day business, (ii) closer collaboration with stakeholders, and (iii) improved cooperation with the national competent authorities on transparency issues. The following part presents the current implementation of transparency by the EMEA as well as major future plans according to the transparency policy.

3.1.1 Transparency in the EMEA daily business

Transparency in the day-to-day operation of the EMEA may be divided in general transparency dealing with administrative and regulatory information and scientific transparency comprising product-related information.

Administrative transparency

The general transparency is mainly implemented by publication of relevant documents on the agency's website. The website of the EMEA (http://www.emea.europa.eu/home.htm) consists of six major categories which are "about us", what's new", "human medicinal products", "veterinary medicinal products", "inspections" and "general reporting". Rather administrative information is mainly accessible in the categories "about us", presenting the organisational structure of the agency, "what's new" informing about the latest publications of the agency (scientific and administrative information) and "general reporting", dealing with information on executive, administrative and general management-related issues.

The category "about us" provides detailed information about the organisational structure of the agency and its committees. In line with article 63 and article 80.2 of Regulation (EC) No 726/2004 the composition of the committees like the management board, the CHMP, the CVMP, the COMP, the committee on herbal medicinal products (HMPC), the PDCO and the committee for advanced therapies (CAT) is available. Besides the composition of the respective committees the "public declaration of interests and confidentiality undertaking of EMEA scientific committee members and experts" is provided for every member of the committees together with the professional profile of the respective member.

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[1] *The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future*. 04 March 2005, Doc. Ref: EMEA/H/34163/03/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/directory/3416303enF.pdf [accessed on 20 Nov. 2009].

[2] *The EMEA Transparency Policy, Draft for Public Consultation*, 19 June 2009, Doc. Ref: EMEA/232037/2009 – rev, URL: http://www.emea.europa.eu/pdfs/human/transparency/23203709en.pdf [accessed on 20 Nov. 2009].

The declaration of the direct and indirect interests consists of a detailed questionnaire. First of all current or previous activities for a company are detailed with respect to the kind of activity (employee, consultant, (principal) investigator, member of a steering committee, advisory board, etc.) and to the date of activity (currently or in the previous year; more than one, but less than 5 years ago or more than 5 years ago). In case of any relevant activity the kind and the period of activity, the company, the concerned products or the therapeutic indication field have to be specified. Then the possible financial interests in a pharmaceutical company are declared (more or less than 50,000 Euro or none) as well as other interests like the ownership of a patent. Finally it has to be declared if the employer of the respective person gets financial support (grant or funding) by a pharmaceutical company. In addition a confidentiality undertaking is part of the declaration.

The scientific profile provides short information on the membership in EMEA committees, on the professional background, on the education and on the areas of expertise and research interests.

Besides the details of the composition and of the declarations of the members the role and responsibilities as well as the rules of procedures of the respective committee are accessible.

The category general reporting provides information of the EMEA directorate and the management board comprising in particular press releases, public statements, status reports, work programmes, annual reports, financial and budgetary reporting and standard operating procedures, which give a comprehensive overview about the EMEA activities.

The mentioned draft of the EMEA transparency policy proposes further "key transparency initiatives" in this field, including the improvement of the user-friendliness of and access to the agency's website; the generation of a register, which displays all publicly available documents (as described in the draft EMEA policy on the practical operation of access to EMEA documents, see below) and quality assurance activities like revisions of external and internal guidance, establishment of performance indicators and training of the EMEA staff according to the implementation of the policy. [1]

A further general aspect that is discussed in the transparency policy is the public awareness of the agency's work and the understanding of its decision making processes. Improvements in this area shall be achieved by yearly workshops with media, workshops with external stakeholders on current topics, special workshops for small and medium sized companies and by the internal assessment and improvement of methodologies and processes like the CHMP benefit risk assessment (initial application and post-marketing experience), the weighing of multiple benefits and risks, the impact of scientific advices on the outcome of an application and the quality of EPARs. In addition, collaborations with universities and researchers on common projects shall increase the visibility of the EMEA in scientific areas. In general the information and guidance on specific fields like orphan, herbal and veterinary medicinal products shall be improved.

Scientific transparency

Scientific transparency of the EMEA encompasses medicinal product related transparency focussing on the assessment, approval and surveillance of medicinal products falling under the scope of Regulation (EC) 726/2004, i.e. centrally approved medicinal products. The central registration procedure aims at a marketing authorisation by the EC which is valid throughout the EU. The scientific assessment and evaluation of the marketing authorisation application is performed by the CHMP or the CVMP, respectively, and results in a scientific opinion recommending the grant or the refusal of the application by the EC.

[1] *The EMEA Transparency Policy, Draft for Public Consultation,* 19 June 2009, Doc. Ref: EMEA/232037/2009 – rev, URL: http://www.emea.europa.eu/pdfs/human/transparency/23203709en.pdf [accessed on 20 Nov. 2009].

The committees meet once a month and the outcome of the meetings is published on the EMEA website as e.g. CHMP monthly report. The information on the concerned medicinal products contained in the report differs depending on the evaluation phase of a medicinal product. In case of adopted opinions (initial applications or post-marketing activities) or of withdrawals, the name and the indications of the medicinal products and the applicant are published together with a link to the summary of opinion (in case of a positive evaluation) or a question and answer document (Q&A document, in case of a negative opinion), respectively. The summary of opinion is a short presentation of the medicinal product informing about the name, the active substance, the indication, the dosage, the benefit and the most common or most serious side effects, as well as the recommendation of the committee.

In contrast, the monthly report provides no specific information on ongoing assessments, as only the number of adopted lists of questions is indicated. Further information included in the monthly reports comprise mainly referral procedures, reports from the co-ordination group for mutual recognition and decentralised procedures human (CMD(h)) or from CHMP working parties, organisational matters and procedural announcements if appropriate.

The aforementioned summaries of opinions are published without delay following adoption on the EMEA website until the final decision by the EC has been adopted and the application (initial application for marketing authorisation or application for post-marketing activities) has been approved. Following the approval by the EC, the EPAR created by the CHMP or the CVMP, respectively, is published according to article 13.3 of Regulation (EC) No. 726/2004.

The EPAR comprises a summary for the public written in lay language, a table listing all authorised presentations, the scientific discussion, which is the core assessment document reflecting the grounds and conclusions of the assessors and a document describing the procedural steps taken before authorisation. Post-approval activities either will be summarised in a list or will cause amendments of the EPAR. In case of major changes to the EPAR, e.g. the submission of comprehensive new clinical data supporting an application for a new indication or route of administration etc, a separate EPAR may be created rather than an amended version.

As mentioned before the scientific discussion is the core document, which is created out of the CHMP assessment report after removal of commercially confidential information. It provides comprehensive information regarding the clinical and preclinical modules of the marketing authorisation application and rather marginal information on the pharmaceutical quality module, as this is considered as commercially confidential[1] (see chapter 4). In addition to these documents the currently approved product information texts (Annex I-IIIb of the EC decision, displaying the SmPC, the marketing authorisation holder responsible for batch release, conditions of a conditional approval as appropriate, labelling and PL) are available.

The summaries of opinions and the EPAR are published in the category human or veterinary medicines as appropriate on the EMEA website. In addition, this category displays information on withdrawals and refusals, the Q&A documents. These documents give answers to questions addressing the properties, the indication, the mode of action, the supportive documentation submitted, the major concerns of the respective committee, and the consequences for patients in clinical trials or patients treated with the already authorised medicinal product in case of post-marketing activities.

Further important publications regarding the product-related or scientific transparency in the category human medicinal products are the product safety announcements. In this section publications are

[1] *Principles to be Applied for the Deletion of Commercially Confidential Information for the Disclosure of EMEA Documents, 15 April 2007*, Doc. Ref: EMEA/45422/2006, URL: http://www.emea.europa.eu/pdfs/human/euleg/4542206en.pdf, [accessed on 20 Nov. 2009].

listed, which inform about new findings regarding the safe use of medicinal products, e.g. the occurrence of serious side effects that are under investigation by the CHMP, restrictions on the use of a medicinal product, recommendations regarding the inclusion of new safety-relevant information in the product information of a medicinal product, etc.

The category also contains the subsection "Medicines for children". This section strongly contributes to public transparency as it provides the opinions and decisions on paediatric investigations plans according to article 5(1) and article 25(7) of the Paediatric Regulation[1]. Besides the presentation of class waivers in this section, the product-specific decisions are tabulated and thus publicly accessible.

In addition to the "regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products" that is publicly accessible on the EMEA website in line with article 80.1 of Regulation (EC) No 726/2004, the EMEA established different information technology systems to implement the new provisions in the pharmaceutical legislation. In a press release of 6 December 2006 the EMEA announced the launch of the public European medicines register called EudraPharm, which fulfils the articles 57(1)l and 57(2) of the regulation[2]. Currently the database contains information on centrally approved human and veterinary medicinal products comprising general information, like name, pharmaceutical form, strength, approved presentations, route of administration, marketing authorisation holder, legal status, approval procedure (incl. authority) and ATC-code in English language and the product information texts including the SmPC, the PL and the labelling in all (current) EU languages. In contrast to the information available on the EMEA website further development steps of the EudraPharm database aim on the inclusion of medicinal products authorised by national procedures. EudraPharm is intended to be a public database displaying information on all medicinal products approved in the EU.

Further developments of EudraPharm concerning the fulfilment of legal provisions regarding transparency and the information of the public will focus on the inclusion of data on clinical trials received from the EudraCT database, which has been established by the EMEA according to the Clinical Trial Directive[3] and was launched on 1 May 2004. EudraCT is a database granting access only to the member states, the EMEA and the Commission. As laid down in article 57.2 of the Regulation (EC) 726/2004 the EudraPharm database shall include information on ongoing and closed clinical trials. In a Commission communication the EC published guidance on the respective data that shall be extracted from EudraCT and be made publicly available in EudraPharm[4]. The communication mainly deals with protocol-related information that is currently entered into EudraCT. Nevertheless reference is made to the developments of EudraCT according to the Paediatric Regulation[1], which lays down major steps regarding the access to information on paediatric clinical trials as mentioned in chapter 2. In article 41 of the Paediatric Regulation it is stated that the EMEA shall make publicly available even details on results of paediatric trials. Therefore EudraCT needs to be upgraded to enable the integration of results related information. Furthermore paediatric clinical trials that have been presented to the regulatory authorities according to articles 45 and 46 of the Paediatric

[1] *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 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,* OJ **L 378**, 27 December 2006, p. 1 – 19.

[2] *Press Release: European Medicines Agency launches EudraPharm – the European medicines database.* 6 December 2006, Doc. Ref: EMEA/456119/2006, URL: http://www.emea.europa.eu/pdfs/general/direct/pr/45611906en.pdf, [accessed on 20 Nov. 2009].

[3] *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*. OJ **L 121**, 1 May 2001, p. 34 – 44.

[4] *Communication from the Commission — Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006,* OJ **C 28**, 4 February 2009, p. 1-4.

Regulation have to be published, whether or not the studies are part of an agreed PIP (article 41(2)). In other words, information on paediatric trials which were already terminated when the Paediatric Regulation entered into force and which concern medicinal products approved in the EU shall be included in the database.

Subsection 3 of article 41 determines that the Commission develops a guidance giving detailed advice on which information shall be included in EudraCT and/or be published. The final guidance has been published in form of a Commission communication on 4 February 2009[1]. This document differs between protocol-related and results related information on the clinical trial and concerns all paediatric clinical trials (i) having at least one trial centre within the EEA and/or (ii) trials which are part of an agreed PIP.

The protocol related information has to be supplied and entered into EudraCT prior to the start of the trial either when the clinical trial application at the national competent authority is valid (in case of investigation sites within the EEA) or at the latest one month after the EMEA decision on the PIP and the approval of the trial by the third-country authority and the positive ethics committee vote are granted. The publication takes place automatically after the approval by the national competent authority. In case of a negative vote of the concerned ethics committee, the protocol related information remains public and the reason for the ethics vote will be indicated. As listed under item 3.1 of the communication the protocol related information that has to be entered into EudraCT and to be made available to the public comprises details on:

- identification of the clinical trial and its protocol,
- sponsor,
- source of funding,
- contact point for public use,
- identification and description of the treatment arms of the study to be used,
- therapeutic objective of the trial (disease under investigation),
- major objectives and endpoints,
- trial design including the countries in which it is to be conducted,
- trial population,
- inclusion/exclusion criteria,
- trial status (per country or region as applicable), and if refused for ethical reasons the reasons for refusal.

In general, results related information has to be supplied six months after termination of the study; in exceptional circumstances 12 months after completion. The results related information represents a summary of the study outcomes and the respective conclusion drawn. Item 3.2 of the communication provides the following list of information that has to be entered into EudraCT and to be made public:

- administrative information and trial identification,
- trial design,
- scientific background and explanation of rationale for the trial,
- participants in the trial; information on the subject population including inclusion and exclusion criteria and demographic information,
- the treatments used,
- objective(s) of the trial,

[1] *Communication from the Commission — Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006.* OJ **C28,** 4 February 2009, p. 1-4.

- outcome measures,
- randomisation implementation,
- blinding,
- statistical methods,
- patient disposition,
- protocol deviations,
- recruitment,
- baseline data,
- trial interruption,
- outcomes and estimation,
- ancillary analysis,
- adverse events,
- trial termination,
- discussion and interpretation of study results (interpretation of trial results by sponsor, if available and by competent authority, if available),
- a declaration of the submitting party on liability for the accuracy of the submitted information.

In addition to the Commission communication setting out the nature of information which shall be included in EudraCT and which shall be made public, the EC published on 4 February 2009 two guidelines which list the concrete data fields to be inserted in EudraCT, one dealing with clinical trials in general (implementation of article 57 (2) of Regulation (EC) No 726/2004) and the other dealing with paediatric clinical trials according to the Paediatric Regulation[1, 2]. The additional or differing data fields concerning the protocol-related information are presented in table 1 (see next page) in bold letters. The main discrepancies between the two lists result from the higher degree on transparency required in case of paediatric clinical trials, since additional kinds of studies have to be included. In particular this comprises the entry of phase I trials, of trials without investigation centres in the EEA, of prematurely terminated trials or of prohibited trials due to a negative Ethics Committee opinion, and the retrospective entry of already completed trials presented to the authorities according to articles 45 and 46 of the Paediatric Regulation.

Regarding results related information the two guidelines only tabulate the items listed in the Commission communication that are shown above, with short explanations. The main reason for this is that until then EudaCT did not contain results related information. It is stated that the public access to the clinical trial results is planned as soon as the integration of this data in the database has been realised. Beside the technical objections, guidance on standardised presentation of the results is needed and still in preparation.

[1] *List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006 and its implementing guideline 2009/C28/01*. Eudralex, **Vol 10**, Chapter V, URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf [accessed on 20 Nov. 2009].

[2] *List of fields contained in the EudraCT clinical trial database to be made public , in accordance with Article 57(2) of Regulation (EC) No 726/2004 and its implementing guideline 2008/C168/02.* Eudralex, **Vol 10,** Chapter V, URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf [accessed on 20 Nov. 2009].

Table 1: Differing EudraCT data fields for general and for paediatric clinical trials: sections (highlighted in grey) and data fields (bold letters) with different requirements for adult and paediatric clinical trials[1, 2] are listed in table 1.

Data fields for paediatric clinical trials (art. 41/ Reg. (EC) No 1901/2006)	**Data fields for clinical trials in general (art. 57/ Reg. (EC) No 726/2004)**
B Identification of the sponsor	B Identification of the sponsor
Name of organisation: Country **Status of sponsor – Commercial or non-commercial** Source(s) of Monetary or Material Support: Name of Organisation Country Contact point designated by the sponsor for further information on the trial	Name of organisation: Country Source(s) of Monetary or Material Support: Name of Organisation Country Contact point designated by the sponsor for further information on the trial
E.7 Trial type and phase	E.7 Trial type and phase **(Phase I clinical trials are not made public)**
Human pharmacology (Phase I) **First administration to humans** **Bioequivalence Study** **Other** **If 'other', please specify** Therapeutic Exploratory (Phase II) Therapeutic Confirmatory (Phase III) Therapeutic Use (Phase IV)	 Therapeutic Exploratory (Phase II) Therapeutic Confirmatory (Phase III) Therapeutic Use (Phase IV)
G4 Clinical trial sites/investigators in the member state or country concerned	(section not contained)
Networks to be involved in the trial **Name of Organisation:** **Country**	
N Review by the Competent authority or Ethics Committee in the country(ies) concerned	N Review by the Competent authority or Ethics Committee in the country(ies) concerned
Clinical Trial Authorised (**for EEA and third countries where a clinical trial authorisation is required**) Date of authorisation **Or For third country trials if a clinical trial authorisation is not required a statement that it has been notified to the local competent authority or that this is not required as applicable**	Clinical Trial Authorised (for EEA countries) Date of authorisation
Ethics committee opinion – positive **or negative** or pending Date of opinion **In the case of a negative ethics committee opinion based on ethical concerns a brief statement of the reasons**	Ethics committee opinion – positive, or pending Date of opinion
Recruitment status of the trial (not commenced, active, completed) End of trial status (Completed, **prematurely terminated, or prohibited**)	Recruitment status of the trial (not commenced, active, ended) End of trial status (ended)
Date of the global end of the trial Anticipated date of the availability of results **no more than six months** after the trial has ended, only **in exceptional circumstances at the latest within twelve months.**	Date of the global end of the trial Anticipated date of the availability of results (no more than the end of trial date **plus twelve months)**

[1] *List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006 and its implementing guideline 2009/C28/01*. Eudralex, **Vol 10**, Chapter V, URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf, [accessed on 20 Nov. 2009].

[2] *List of fields contained in the EudraCT clinical trial database to be made public , in accordance with Article 57(2) of Regulation (EC) No 726/2004 and its implementing guideline 2008/C168/02*. Eudralex, **Vol 10,** Chapter V, URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_02_04_guideline.pdf, [accessed on 20 Nov. 2009].

As mentioned in chapter 2, article 57.1 (d) of Regulation (EC) No 726/2004 determines that it is one of the duties of the EMEA to ensure dissemination of information on side effects of medicinal products approved in the EU to the member states via a database granting access in an appropriate extend to healthcare professionals and the public.

The EudraVigilance database has been created to manage the dissemination and exchange of information on suspected adverse events to medicinal products in the pre- and post-authorisation phase of their life-cycle between the EMEA, national competent authorities, marketing authorisation holders and sponsors of clinical trials. Information contained in EudraVigilance is related to medicinal products authorised in the EEA or to medicinal products which are subjects to clinical trials conducted in this area. The database shall facilitate the early identification and evaluation of potential safety risks related to the use of a medicinal product. With respect to the life-cycle phase of the product the EudraVigilance database of two reporting platforms, the EudraVigilance post-authorisation module and the EudraVigilance clinical trial module (EVPM and EVCTM, respectively).

At present the EudraVigilance access is limited to the EC, the EMEA, and the national competent authorities. To fulfil the above mentioned legal requirements regarding the "appropriate levels of access"[1] to the healthcare professionals and the general public, the EMEA has published on 19 December 2008 the "Draft EudraVigilance Access Policy for medicinal products for human use" for discussion and to be commented by the stakeholders[2].

In this document created by the EudraVigilance expert working group (EVEWG) the stakeholders are divided in three different groups with divergent access categories: (i) the authority group (national competent authorities of the EEA, EC and EMEA), (ii) healthcare professionals and general public group, and (iii) marketing authorisation holders and/or sponsors in case of clinical trials, respectively. One important general principle of the policy is that concerning the access for the latter two groups, the protection of personal data needs to be guaranteed. Regarding the data the policy differs between spontaneous reports (individual case safety reports, ICSR) and reports from interventional or non-interventional trials. Table 2 displays the access categories for the three groups in detail. In summary, the authority group has full access to all data entered in EVPM and EVCTM, whereas the other groups receive graduated access. Marketing authorisation holders (category III) receive access to all ICSRs entered in EVPM but in contrast to the access category I, the displayed data fields are limited to guarantee personal data protection. With respect to ICSRs from clinical trials (EVCTM) the sponsor has only access to his own reports. The most limited access will be granted to healthcare professionals and the general public (category II). This group will only receive access to so-called "drug-analysis prints", which contain aggregated EVPM data (including all ICSR) included in tables and figures and which will be published after the termination of the quality review of data. They will be published on the EudraVigilance website together with general guidance documents explaining the informative value of the data. This guidance informs about the following facts:

- adverse reaction reports build only a part of the information necessary for a valid evaluation of the safety, further measures like the conduction of post-marketing trials and further pharmacovigilance data like sales and prescription data and pharmacoepidemiological data are usually taken into account for the safety assessment.

[1] *Art. 57 (1) d, Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, OJ **L 136**, 30 April 2004, p. 35.

[2] *Draft EudraVigilance access policy for medicines for human use*, 19 December 2008, Doc. Ref: EMEA/187439/2006/Final, URL: http://www.emea.europa.eu/pdfs/human/phv/18743906en.pdf, [accessed on 20 Nov. 2009].

- the causality assessment of an individual case strongly depends on the quality of information supplied and may not always be appropriate.
- adverse reaction data are carefully monitored and routinely evaluated; the detection of potential safety issues results in regulatory actions and appropriate communication (e.g. update of the SmPC, healthcare professional information letters, etc.)

The proposed subset of accessible data fields for marketing authorisation holders are provided in Annex II of the draft policy. The implementation plan for granting the respective access levels will commence with the access to centrally approved medicinal products for healthcare professionals and the general public and in parallel with granting the access to the currently registered marketing authorisation holders and sponsors. In a further step, the category II access will be extended to all products and to all marketing authorisation holders and sponsors.

Table 2: comparison of the access categories of the stakeholder groups according to EudraVigilance modules for individual case reports related to authorised medicinal products (EVPM) and to medicines which are subjects to clinical trials (EVCTM)[1]

Stakeholder group	EVPM (EudraVigilance post-authorisation module)	EVCTM (EudraVigilance clinical trial module)
"**authority group**" – **category I** (EC, EMEA and national competent authorities)	**Category IA:** Full access to all types of medicinal products and the complete information in the ICSRs	**Category IB:** Full access to all individual cases and full and the complete information in the ICSR (interventional and non-interventional trials, authorised or investigational medicinal products)
Healthcare professionals and general public – category II	**Category IIA** Access includes all ICSRs that are presented as drug analysis prints which will be published after the data quality review	**Category IIB** No access (results of clinical trials will be accessible to the public via EudraPharm)
Marketing authorisation holders or sponsors – category III	**Category IIIA** Access to all ICSRs with a limited set of data fields accessible, usage of data analysis and signal detection tools possible	**Category IIIB** Access restricted to "their own" individual cases that have been transmitted by themselves

At present, the EudraVigilance access policy is a draft that is likely to be modified in the course of the public discussion.

As mentioned in chapter 2, the upcoming review of Regulation (EC) No 726/2004 with respect to pharmacovigilance issues as part of the EU pharmaceutical package foresees the strengthening of the

[1] *Draft EudraVigilance access policy for medicines for human use*, 19 December 2008, Doc. Ref: EMEA/187439/2006/Final, URL: http://www.emea.europa.eu/pdfs/human/phv/18743906en.pdf, [accessed on 20 Nov. 2009].

EudraVigilance database. According to Article 24 of the proposal[1] the database, which serves to collect pharmacovigilance information on medicinal products authorised in member states of the EU, shall allow national competent authorities the immediate and simultaneous access to and the common usage of the entered information. EudraVigilance shall comprise information on adverse events, on overdose, misuse, medication errors and trials. As proposed in the EudraVigilance access policy (see below in detail) the public access to EudraVigilance data shall be realised by the presentation of aggregated data. In addition, the general public may request individual case safety reports, which shall be provided by the EMEA or the competent national authority within 90 days according to article 24 (3) of the proposal.

In contrast, the public access to data from the EudraGMP database has already been realized since 30 July 2009[2]. The EudraGMP database shall provide data on pharmaceutical manufacturers both within the EEA and in third countries including the manufacturing and import licenses and GMP (good manufacturing practice) certificates, as well as information on inspections (e.g. planning, results, etc.), on GMP non-compliance and on quality alerts. EudraGMP was originally designed for the information of the competent surveillance authorities within the EEA. In line with the general efforts to increase transparency in the regulatory activities of authorities, it was decided to grant access to EudraGMP data to the general public. At present, information on GMP certificates, manufacturing and importation licenses is available after deletion of personal (e.g. information on qualified persons) and commercially confidential information.

Beside the information provided in databases and on internet websites transparency may be granted on demand. According to article 73 of Regulation (EC) No 726/2004 the Transparency Regulation on access to documents[3] also applies to EMEA documents as described in chapter 2. To outline general principles regulating the access to documents of the agency, the EMEA management board adopted implementation rules which shall "ensure the widest possible access to the documents the agency produces or receives and has in its possession"[4]

In line with Regulation (EC) No 1049/2001 (article 4) these implementation rules define in article 3 three exceptional circumstances under which the agency shall refuse the access to a specific document:

1. disclosure would undermine the protection of public interest or of privacy and integrity of the individual (with regard to the protection of personal data)
2. disclosure would undermine the protection of commercial interests, including intellectual property; or of court proceedings or of the purpose of inspections
3. disclosure of documents in the context of ongoing procedures which could influence the decision-making process; in some cases (e.g. preliminary internal documents) even the disclosure after the decision shall be refused if it may undermine the process

Further provisions of article 3 are that (i) in case of doubt the originator of the document shall be consulted; (ii) in case of documents generated by a member state the authoring member state may

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[1] *Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, Doc. Ref: 2008/0257 (COD), URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:EN:PDF, [assessed on 11 Jan. 2010].

[2] *EudraGMP 2.0 gives public access to information about good manufacturing practice (GMP), Press release*, 04 August 2009, Doc. Ref: EMEA/494112/2009, URL: http://www.emea.europa.eu/Inspections/docs/49411209en.pdf, [accessed on 20 Nov. 2009].

[3] *Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents*, OJ **L 145**, 31 May 2001, p. 43–48.

[4] *Rules for the Implementation of Regulation (EC) No 1049/2001 on access to EMEA documents*, 19 December 2006, Doc. Ref: EMEA/MB/203359/2006 Rev 1, URL: http://www.emea.europa.eu/pdfs/general/manage/mbar/20335906en.pdf, [accessed on 20 Nov. 2009].

request non-disclosure without its agreement and (iii) if the exceptions apply only to parts of the documents, the respective parts shall be removed prior to disclosure of the remaining document.

Following a request for access to documentation the EMEA shall carefully analyse if the respective information is covered by one of these exceptions. In case of documents prepared by a third party, i.e. by any legal or private person or entity outside the agency, the EMEA will refuse access or will disclose the respective documents without consultation of the originator (unless a member state document is concerned) if the above mentioned exceptional circumstances clearly do or do not apply, respectively.

In cases of doubt when the third party originator of the requested documents has to be consulted, the agency may decide to grant access even if the concerned third party explicitly disagrees. In this case the third party has to be informed about the decision and its possible remedies.

Article 4 classifies three categories of documents, namely the categories public, restricted and confidential, which are defined in the annex of the document:

Public: Any document that is not considered to be "restricted" or "confidential" is a public document.

Restricted: Documents covered by the exceptions made in article 3 of the implementing rules are classified "restricted", if disclosure could be disadvantageous at present, but will be acceptable at a later stage of the respective procedure.

Confidential: Documents falling under the exceptions of article 3 will be classified as "confidential", if disclosure could harm essential interests of the EU Institutions, the member states and the agency.

The original version of the implementation rules was adopted by the EMEA management board in May 2004 and it was revised twice in 2006, thus meanwhile four full years of operation of this decision have passed. The years have shown a drastic increase of the amount of requests as stated in the annual reports of the EMEA. Detailed information is given in the reports of 2006, 2007 and 2008 and is illustrated in figure 1. In 2006, the EMEA received 55 requests on access to documents[1]. About half of them (52.7 %) were granted either fully (25 requests) or partially (4 requests). In this second operative year of the implementation rules the main reasons for refusal of access were either the protection of the decision–making process of the EMEA or the protection of commercial interests, both accounting for about one half of the refusals, respectively.

In 2007 the number of requests increased by over 67 % to 92 requests[2]. Again about 50 % of the requests were refused due to the protection of commercial interests, further 33 % concerned the decision–making process and 17 % were refused to protect personal data, inspection purposes or international relations. In 2008 a total number of 124 requests were submitted, 31 of those were refused[3]. Figure 1 illustrates the growing number of requests and the respective number of refusals taken from the EMEA annual reports of the respective years.

[1] *Annual report of the European Medicines Agency 2006*, Doc. Ref: EMEA/MB/24167/2007/EN/FINAL, URL: http://www.emea.europa.eu/pdfs/general/direct/emeaar/EMEA_Annual_Report_2006_full.pdf [accessed on 20 Nov. 2009].

[2] *Annual report of the European Medicines Agency 2007*, Doc. Ref: EMEA/MB/17464/2008, URL: http://www.emea.europa.eu/pdfs/general/direct/emeaar/AnnualReport2007.pdf. [accessed on 20 Nov. 2009].

[3] Annual report of the European Medicines Agency 2008, Doc. Ref: EMEA/330566/2009, URL: http://www.emea.europa.eu/pdfs/general/direct/emeaar/AnnualReport2008.pdf. [accessed on 20 Nov. 2009].

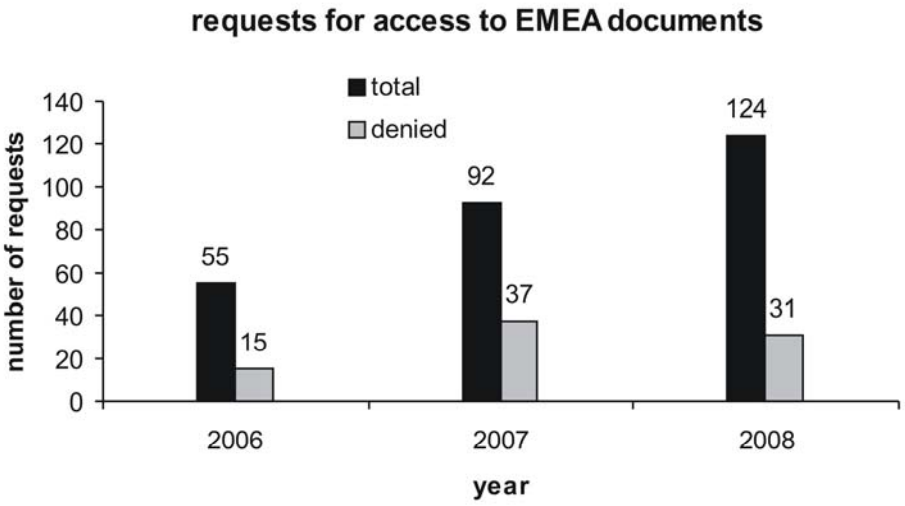

Figure 1: The increasing number of requests for access to EMEA documents in the years 2006, 2007 and 2008 is displayed in figure 1. The black bars indicate the total numbers of requests received by the EMEA whereas the grey bars show the number of refused requests according to the agency's annual reports[1, 2, 3].

Due to the increasing number of requests for access to EMEA documents, the agency decided to establish operation principles to address the demands in a robust, efficient and consistent way. Therefore the EMEA developed a draft policy on the handling of the access to the agency's documents which has been published for discussion on 18 December 2008[1]. It defines two prerequisites for operation which are (i) formal procedures for the classification of the documents and (ii) formal procedures to guarantee the protection of commercial confidentiality and personal data. For the first prerequisite the available EMEA documents need to be classified according to the EMEA implementation rules. This resulted in an output paper which tabulates and classifies various regulatory documents, either generated by the agency or by third parties including applicants and marketing authorisation holders[2]. The output table reflects the general and specific principles which shall apply to the EMEA documents in accordance with the legislation and which are detailed in the policy as follows:

- Provision of widest possible access taking into account the protection of commercial confidentiality, personal data and commercial interests of concerned third parties
- Non-disclosure of working documents and non-disclosure of documents prior to the finalisation of the decision making process, unless an exceptional overriding public interest exists
- Redaction of documents prior disclosure as appropriate to guarantee protection of personal data, commercial interests and commercial confidentiality (in accordance with the respective EMEA principles discussed below[3])
- Strongest efforts will focus on the decision whether a third party document may be disclosed, consultations of third parties will be reduced to a minimum, unless the third party is a member

[1] *Draft EMEA policy on the practical operation of access to EMEA documents*, 18 December 2008, Doc. Ref: EMEA/110196/2006/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/11019606en.pdf [accessed on 20 Nov. 2009].

[2] *Output of the Draft EMEA policy on the practical operation of access to EMEA documents in the context of the authorisation and supervision of medicinal products for human and veterinary use*. Doc. Ref: EMEA/659316/2008/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/65931608en.pdf, [accessed on 20 Nov. 2009].

[3] *Principles to be Applied for the Deletion of Commercially Confidential Information for the Disclosure of EMEA Documents, 15 April 2007*, Doc. Ref: EMEA/45422/2006, URL: http://www.emea.europa.eu/pdfs/human/euleg/4542206en.pdf, [accessed on 20 Nov. 2009].

state, a (non-)community institution/body or a third country. In these cases prior agreement is always needed.

The output table provides a classification of various documents associated with the registration and post-marketing activities into the categories public, restricted and confidential according to the implementation rules and gives advice upon (i) if the document is considered to be a third party document, (ii) if access may be granted or, if not, according to which provision and (iii) if redaction is needed prior to disclosure. In general, all documents submitted by applicants including in particular application dossiers, periodic safety update reports, applicants' responses etc. are considered to be confidential and shall therefore not be disclosed. The output table represents a working document which will be extended or modified when more experience and new types of EMEA documents are available. For the practical operation the access to documents advisory group (ADAG) is set-up.

To guarantee the protection of personal data, commercial confidentiality and commercial interest specific criteria defined in the legislation (with respect to the protection of personal data) or in EMEA documents will be taken into account by the agency. This will be realized mainly by redaction of the respective documents prior to disclosure. Due to the lack of an appropriate legal interpretation of commercial confidentiality, guidance on which information has to be considered to be confidential and needs to be removed is provided in the EMEA document "Principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents"[3].

This document divides commercially confidential information into two main classes. One class comprises intellectual property, specialized knowledge and trade secrets, the second class concerns more commercial secrets and interests, like e.g. business development plans. As a basic principle it is stated that the EMEA will not disclose commercially confidential information when the interests of a natural or legal person might be impaired. The practical implementation of these principles in case of CHMP (or CVMP, respectively) assessment reports is exemplified in detail in the annex of the document. The information of the reports is separated into the following four sections:

- Pharmaceutical quality and manufacturing:
  Most parts <u>are</u> considered to be commercially confidential, especially detailed descriptions; only general statements are acceptable, unless the information is otherwise publicly accessible like e.g. the qualitative composition (SmPC), structure of the active substance
- Non-clinical and clinical information
  In general information associated with the clinical and non-clinical investigation of the medicinal product and its assessment <u>is not</u> considered to be commercially confidential. Exceptions may be made in case of specific details of studies which could be regarded as trade secrets or in case of a development plans
- Information on the outcome of inspections
  In general this information <u>is not</u> considered to be confidential
- Outcome of the scientific discussions
  With the exceptions described in the other categories, the outcome of the discussions including minority opinions and concerns <u>are not</u> regarded as confidential.

The implementation of the draft policy on access to EMEA documents is planned as a two-step-procedure. The first step addresses the reactive disclosure of documents upon written requests. This step includes the disclosure of EMEA documents in an electronic register which are already publicly available on the EMEA website and in addition of any EMEA document which has been disclosed on demand.

The second step deals with the stepwise extension of the electronic register to all EMEA documents, for which public access may be granted.

In this context the draft EMEA transparency policy[1] further suggests to achieve a common definition of the term commercially confidential together with the national competent authorities. This should be done taking into account the results of the public consultation of the draft EMEA access to documents policy and the associated output document.

Further key proposals of the draft EMEA transparency policy deal with the increasing access to information on pharmacovigilance data throughout the lifecycle of a medicinal product. Besides the implementation of the draft EudraVigilance Access policy[2], the proactive publication of several documents is suggested like pharmacovigilance working party (PVWP) monthly reports, pharmacovigilance newsletters/safety bulletins in case of urgent safety issues, direct healthcare professional communications by the marketing authorisation holder and information on the assessment of periodic safety update reports and related variations (mainly by updating the EPAR).

3.1.2 Direct interaction with stakeholders

As dictated by the Regulation on Orphan Medicinal Products[3] and the Paediatric Regulation[4], representatives of patients' associations are involved in the scientific work of the COMP and the PDCO, respectively, having equal rights like the members representing the member states. In line with article 65 of the Regulation (EC) No. 726/2004, the EMEA management board members include to representatives of patients' and one representative of doctors' organisations.

Further involvement of representatives of patients' and consumers' organisations may take place in the decision making process by the scientific committees of the EMEA, i.e. the CHMP, the COMP and the HMPC, thereby implementing the provisions of article 78 of Regulation 726/2004. The scientific work of the committees is supported by several working groups on specific fields which are composed of respective experts, like e.g. the biologics working party, the PVWP, the safety working party, the efficacy working party and the patients' and consumers' working party (PCWP). The CHMP may consult these expert working parties during the decision making process on applications for marketing authorisation and on the development or revision of guidance documents or instructs the working parties with certain tasks. The PCWP consists of representatives from patients' and consumers organisations which fulfil eligibility criteria defined by the EMEA[5]. In general the PCWP deals with all matters of interest to patients regarding medicinal products, like transparency and dissemination of information, product information, pharmacovigilance and interaction between the agency and its committees and patients' associations[6].

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[1] *The EMEA Transparency Policy, Draft for Public Consultation*, 19 June 2009, Doc. Ref: EMEA/232037/2009 – rev, URL: http://www.emea.europa.eu/pdfs/human/transparency/23203709en.pdf [accessed on 20 Nov. 2009].

[2] *Draft EudraVigilance access policy for medicines for human use*, 19 December 2008, Doc. Ref: EMEA/187439/2006/Final, URL: http://www.emea.europa.eu/pdfs/human/phv/18743906en.pdf, [accessed on 20 Nov. 2009].

[3] *Art 4 (2c), (3) of Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products*, OJ **L 18**, 22 January 2000, p. 1 - 5.

[4] *Art. 3 (1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 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*, OJ **L 378**, 27 December 2006, p. 1 – 19.

[5] *Criteria to be fulfilled by Patients' and Consumers' Organisations involved in EMEA Activities*, 7 February 2005, Doc. Ref: EMEA/14610/04/Final, URL: http://www.emea.europa.eu/pdfs/human/pcwp/1461004en.pdf [accessed on 20 Nov. 2009].

[6] *Mandate, objectives and rules of procedure for the EMEA human scientific Committees working party with patients' and consumers' organizations*, 07 September 2006, Doc. Ref: EMEA/208157/2006, URL: http://www.emea.europa.eu/pdfs/human/pcwp/pcwpmandate.pdf, [accessed on 20 Nov. 2009].

Involvement of stakeholders with the agency is furthermore implemented by the organisation of workshops on specific issues, like e.g. the development of a new guidance. The EMEA invites interested parties, like e.g. representatives of the pharmaceutical industry, of patients' and consumers' associations, of healthcare professionals etc. to workshops on a current topic giving them the opportunity to present their respective points of view on the matter of interest. Thereby the EMEA may take into account the different interests of the stakeholders when developing the new guidance document. Furthermore, the EMEA usually publishes the drafts of the respective guidance documents for public consultation to give the interested parties the opportunity to submit their comments.

The EMEA transparency policy suggests a revision of the current interaction activities between the agency and the patients' and consumers' organisations in order to intensify such interactions. Key transparency initiatives in this field include the involvement of representatives of the respective organisations into the PVWP, the creation of a stakeholder database, which is intended to simplify the identification of the relevant stakeholders to be informed in case of emerging topics, the development of a framework regarding the interaction with healthcare professionals, the creation of the European medical information network, which shall be used to disseminate medical information on medicinal products approved by the EMEA to healthcare professionals and to the general public, the organisation of workshops on emerging technical and regulatory topics[1].

3.1.3 Cooperation within the European Medicines Regulatory System

The third main objective of the EMEA transparency policy deals with the strengthening of the collaboration on transparency issues within the European medicines regulatory system, including the various national competent authorities of the EEA, the EMEA and the EC. Openness and transparency among the regulatory bodies of the EU and the member states have been facilitated by the stepwise development of information technologies, i.e. the implementation of the EU telematics projects EudraNet, EudraVigilance, EudraCT, EudraPharm and EudraGMP. "Eudra" abbreviates for "European Union drug regulating authorities". As presented above, EudraVigilance, EudraCT and EudraGMP are EU databases that administrate medicinal product related information on pharmacovigilance issues, on clinical trials and on pharmaceutical manufacturers, respectively, granting different levels of access to authorities and stakeholders, whereas EudraPharm administrates general information on medicinal products (see chapter 2) accessible to the general public.

EudraNet is a communication platform serving for the secure exchange of regulatory information between national competent authorities, the EMEA and the EC. Furthermore, EudraNet is used for the confidential communication with the pharmaceutical industry, especially for the submission of applications and it hosts community databases like e.g. EudraVigilance.

At present national legislations on freedom of information and transparency differ among the member states as no harmonised EU legislation is applicable. The draft EMEA transparency policy identifies the harmonisation of key transparency elements as a necessary step to increase the efficiency of the European medicines regulatory system. A further key initiative suggested to strengthen the transparency within the system is the prior announcement of scheduled scientific committee meetings on the recommendation of regulatory actions in case of safety concerns. In parallel, the general public shall be informed on the planned discussion. More general suggestions like the publication of agendas and minutes of the scientific committees' meetings, the implementation of public access to community databases EudraVigilance, EudraCT and EudraGMP (which administrate data that are partially

[1] *The EMEA Transparency Policy, Draft for Public Consultation,* 19 June 2009, Doc. Ref: EMEA/232037/2009 – rev, URL: http://www.emea.europa.eu/pdfs/human/transparency/23203709en.pdf [accessed on 20 Nov. 2009].

provided by national competent authorities), increasing transparency on safety issues with respect to periodic safety update report data, the information on meetings of the PVWP shall simultaneously increase public transparency and are therefore presented in detail above.

The cooperation within the European medicines regulatory system is as well subject to the legislative proposals of the pharmaceutical package. As mentioned in chapter 2 the pharmaceutical package comprises proposals amending the community code and Regulation (EC) No 726/2004 with respect to pharmacovigilance issues which stipulate the establishment of an EMEA safety web portal providing links to national safety web portals[1]. The web-portal shall serve as a communication platform for the dissemination of pharmacovigilance information within the European medicines regulatory system and to the general public. This includes composition of committees, meeting minutes, risk management systems, list of intensively monitored medicinal products (established according to article 23 of the regulation proposal), listing of pharmacovigilance system master file sites for all approved medicinal products within the community including contact details, information on how to report adverse events and online reporting forms for patients or healthcare professionals, due dates for periodic safety update reports, outcomes of post-authorisation safety studies, as well as results of assessments and decisions taken by the respective committees and the competent national authorities. Furthermore the platform shall inform about the initiation of pharmacovigilance procedures according to articles 107i to 107l of the directive proposal (amending the community code) [2]. These procedures shall be started by a member state in case of serious safety concerns like e.g. considerations to suspend or revoke an authorisation, not to renew an authorisation, to dictate new contraindications or reduced doses, etc. The information provided via the safety web portal shall include on the one hand the addressed active substance or medicinal product and the concern under examination, and on the other hand information on scheduled public hearings and on how to participate in the hearings and how to submit relevant information.

[1] *Art. 26 of the Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, Doc. Ref: 2008/0257 (COD), URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0664:FIN:EN:PDF, [assessed on 11 Jan. 2010].

[2] *Proposal for a Directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use*, Doc.Ref: 2008/0260 (COD), URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0665:FIN:EN:PDF, [assessed on 11 Jan. 2010].

3.2. Implementation of transparency by the Heads of Medicines Agencies

The Heads of Medicines Agencies (HMA), which represent the leaders of the competent regulatory authorities of the EU member states, intend to facilitate a common approach of the authorities regarding transparency as they recognise discrepancies in the implementation of the provisions of Directive 2001/83/EC and different national legal provisions concerning the access to documents and the disclosure of information[1].

As a complementary document to the EMEA road map[2], the HMA developed a strategy paper for the European medicines regulatory network, which addresses the challenges of the evolving regulatory environment the network is facing, focussing on the mutual recognition and decentralised procedure[3]. The paper is based on the outcome of six working groups on special themes. One of them was concerned with communication and information and the strategy paper presents general views on transparency and the dissemination of information. It is considered to develop a communication strategy for the network to avoid the realisation of different approaches on transparency and information by the member states. The need for a communication strategy is justified by the provisions of the new legislation, by an increased demand for timely high-quality information by stakeholders and the general public and by the missing knowledge of media and the general public on regulatory processes and on the responsibilities of the different participants. The working group identified the need for a harmonised view and implementation of the member states on five fundamental questions. These are:

- What means the term "making publicly available"?
- How much information shall be contained in agendas and records of meetings?
- When shall they be made publicly available?
- Shall refusals and withdrawals be made publicly available?
- What has to be considered being commercially confidential and deleted prior publication?
- How may the pharmacovigilance communication be optimised with respect to the involvement of all relevant member states?

One major issue stressed in the document is the identification of the stakeholders of the authorities. A communication strategy shall take into account the requirements, the expectations and the knowledge of the different stakeholders and address them in an appropriate way, regarding the content i.e. relevance, confidentiality, clarity and accuracy and the way of communication, i.e. timeliness and communication mechanisms.

The strategy paper contains as well general reflections on the new legislation (see chapter 2), i.e. the implementation of articles 126b and 21,4 of the community code by the member states dealing with the obligation to "make publicly accessible" rules of procedures, agendas, meeting records and assessment reports after deletion of commercially confidential information. It is stressed, that only assessment reports are to make accessible without delay (article 21, 4), whereas article 126b contains no time specification. This is seen as crucial, since flexibility in this point may avoid that premature public access to agendas and meeting records may influence the decision or harm the applicant as competitors get informed and may react. Flexibility is as well suggested in the interpretation of the term "making publicly accessible". In contrast to the term "publishing", the term making publicly

[1] *Recommendations on transparency*, 20 Nov. 2008, Doc. Ref: EMEA/623107/2008, URL: http://www.hma.eu/uploads/media/Recommendations_on_transparency.pdf, [accessed on 20 Nov. 2009].

[2] *The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future*. 04 March 2005, Doc. Ref: EMEA/H/34163/03/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/directory/3416303enF.pdf [accessed on 20 Nov. 2009].

[3] *The Heads of Medicines Agencies, Strategy Paper, Developing the Heads of Medicines Agencies Strategy for the European Medicines Regulatory Network – A Discussion Document*, Revision November 2007, URL: http://www.hma.eu/74.html, [accessed on 20 Nov. 2009].

available includes access on demand and depending on practical considerations like the workload, authorities may decide on their own how the access shall be granted.

In this context a common understanding of the term "commercially confidential" is seen as crucial. As a general strategy it is suggested to analyse two questions prior disclosure:

- Is disclosing the only source for third parties to receive the particular information and may disclosure be beneficial to a competitor?
- May disclosure negatively impact the commercial interests of an applicant?

In general it is stated that the originator of the information (applicant) should be consulted prior disclosure, however, the competent authority shall outweigh the company's commercial interest and the public interest and finally make a decision. In this context timing of disclosure is again crucial, since many kinds of information are confidential during the decision-making process but will be public after the final decision on the application is made.
Taken together, in their strategy paper the HMA promote a common approach for the access to information and the applying principles especially with respect to the classification of information as commercially confidential. In particular regarding the implementation of article 126b of the community code, dealing with the publication of agendas and minutes of scientific committees they noticed discrepancies among the member states' authorities practice which they intend to assimilate with the "recommendations on transparency" published on the EMEA and HMA website on 20 November 2008. They focus on ongoing procedures and determine which information may be disclosed in agendas and minutes of meetings of scientific committees during the procedure. This comprises the name of the active substance (in case of generics only the active moiety shall be stated), the authorisation procedure type and the therapeutic class. After the closure of the procedure access to the minutes may be granted after deletion of commercially confidential information[1].

[1] *Recommendations on transparency*, 20 Nov. 2008, Doc. Ref: EMEA/623107/2008, URL: http://www.hma.eu/uploads/media/Recommendations_on_transparency.pdf, [accessed on 20 Nov. 2009].

3.3. Implementation of Transparency by the Co-ordination group for Mutual Recognition and Decentralized Procedures (CMD(h))

The co-ordination group for mutual recognition and decentralized procedures (CMD(h)) was set up according to the revision of the community code in 2004. The CMD(h) is a superior group composed of representatives of the EEA member states and deals with topics related to the marketing authorisation of human medicinal products in two or more countries. The main goals of the CMD(h) are to provide a common interpretation of the relevant legislation ensuring a consistent, high-quality standard in the decision-making process and to support the member states in reaching agreement in the mutual recognition and decentralized procedures. Furthermore, the CMD(h) is occupied with the harmonisation of existing marketing authorisations across the community.

The transparency measures of the CMD(h) are outlined in a position paper published in February 2007[1]. In principle, the CMD(h) practices transparency in two different ways. These are on the one hand the internet publication of documents like the press releases, Q&A documents and guidance documents and on the other hand the European product index or mutual recognition index (MRI product index).

The MRI product index is a database that is operated by the member states. It comprises all medicinal products approved within the EU via the mutual recognition or decentralized procedure. The two procedures both include a 90-days recognition period in which the concerned member states (CMS) consider the assessment report of the reference member state (RMS). During this period, the information exchange between the member states is managed by a restricted database, the EudraTrack tracking system. The 90-days period may end with the acceptance of the product by all CMS (if necessary, the CMD(h) gets involved to support a consensus decision, see below. If no consensus is reached, the matter is transferred to the CHMP for arbitration) and the member states shall grant a marketing authorisation within 30 days, i.e. until day 120. At day 120, the following information is transferred from EudraTrack to the publicly available MRI product index: the involved RMS and the CMS, the application type, active substance, pharmaceutical form and strength, the date of day 90 and the marketing authorisation holder. Furthermore, the entry shall provide links to the public assessment report, the SmPC and the PL.

In cases of disagreement of at least one CMS due to a potential serious risk to public health during the mutual recognition period, the issue is referred to the CMD(h) according to article 29(1) of the community code. Detailed information on completed referrals is published in the CMD(h) press releases after the respective meetings. These include the involved member states, the name of the medicinal product, the active ingredient, the pharmaceutical form, the legal basis of the application, the reason for the referral and its result.

[1] *Position Paper on the present transparency policy of the co-ordination group for Mutual Recognition and Decentralized Procedures (CMD(h))*, Feb. 2007, URL: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/About_CMDh/Transparency_measures/CMDh_transparency%20policy.pdf, [accessed on 20 Nov. 2009].

3.4. Implementation by the regulatory authorities of the EU member states

In the following part the implementation of proactive and reactive transparency provisions by the competent regulatory authorities in the EU member states will be presented. The practice of the German higher federal authorities will be exemplified in detail and finally particularities of single member states' authorities will be summarised.

3.4.1 Implementation in Germany

While the German law on medicinal products (AMG) contains provisions concerning the proactive disclosure of information, the German freedom of information act (IFG) deals with the reactive disclosure, i.e. the disclosure of information on request. As provided by the AMG, proactive transparency of the German regulatory authorities is mainly implemented in three ways, (i) by publication in the federal law gazette according to § 34 (1) AMG (see chapter 2), (ii) by publication on their respective websites according to §§ 34 (1b) and 77a (2) AMG and (iii) by publication in the public part of the AMIS-database (above all according to § 34 (1a). AMIS abbreviates for "*Arzneimittelinformationssystem*" and represents a common database of the competent higher authorities federal institute for drugs and medical devices (BfArM, *Bundesinstitut für Arzneimittel und Medizinprodukte*), the Paul-Ehrlich-Institute (PEI), and the federal office of consumer protection and food safety (*BVL: Bundesamt für Verbraucherschutz und Lebensmittelsicherheit*). The database provides specific parts for the respective user groups, like (i) the federal ministry of health, the competent federal authorities and the single authorities of the federal states, (ii) the medical service of the health insurances, and (iii) the general public, including healthcare professionals and the pharmaceutical industry as well as private persons. Access to information contained in the AMIS database is granted at present in two ways, (i) via the German Institute of Medical Documentation and Information (*Deutsches Institut für medizinische Dokumentation und Information,* DIMDI, see below) (ii) and via a recently established federal and state internet portal, the so-called PharmNet.bund portal. The DIMDI portal offers a simple AMIS search that is free of charge and that lists general information on the medicinal product like name of the medicinal product, the pharmaceutical form, the applicant, the registration number and status and the active ingredients (name and amount)[1]. Furthermore it is possible to perform queries which are subject to fees that provide more comprehensive information especially focussing on regulatory information like indication, administrative data on the registration procedure and the regulatory lifecycle like variations, marketing authorisation holder, manufacturing sites (responsible for drug release), composition, pack sizes, legal status etc.

As presented in chapter 2.2, according to 14th AMG amendment act the SmPC and the public assessment report should be provided electronically after granting the marketing authorisation, which is done in the AMIS database. In addition to this provision, the database is created to contain the respective PLs. Different AMIS queries addressing the implementation of this provision have been performed and the results are listed table 3 (see annex I for details of the query). The parameters of the first query were chosen to give the number of granted national marketing authorisations (including national authorisations, mutual recognition and decentralized registration procedures, excluding centralized and parallel distribution licences) in the four years between the entry into force of the 14th AMG amendment act (6 September 2005) and the 6 September 2009. 93 % (9253 of 9983) of the registrations were granted by the BfArM, compared to 3 % (313) and 4 % (417) by the PEI and the

[1] Access to AMIS database via DIMDI, URL: https://portal.dimdi.de/websearch/servlet/FlowController/SelectNggApplication?_changebranch=false&uid=0&name=&mode=&appName=&baseInfo_id=AJ29&magicrequestid=0.10678221237771501&tomcatsessionid=E9EE2DACAF25074DEDEFF4C7C8AFFBB4.joey&stationid=AppList&_stationbranch=_DEFAULT

BVL, respectively. A second group of queries was performed to find out, how many of the documents associated to the respective registrations were available in the database. For the majority (74 %) of the BfArM registrations which were granted since the entry into force of the 14th AMG amendment act the SmPC and the PL are accessible but only 2 % of the respective public assessment reports. For the registrations granted by the PEI during this period (313) 30 % of the respective SmPC and PLs are provided, compared to only 5 % of the respective public assessment reports. In contrast, the BVL provides 60 % of the product information texts and 16 % of the public assessment reports for the licences granted. These results are listed in table 3.

Table 3: Results of AMIS queries investigating registrations granted between 6 September 2005 and 6 September 2009 in Germany by the higher regulatory authorities. Columns list the number of entries in AMIS that provide the indicated documents (SmPC: Summary of Product Characteristics, PL: Package Leaflet, PAR: Public Assessment Report).

Competent authority	Total number of registrations	SmPC/PL available	PAR available	SmPC/PL and PAR available
BfArM	9253	6857 (74 %)	231 (2 %)	231 (2 %)
PEI	313	93 (30 %)	15 (5 %)	7 (2 %)
BVL	417	250 (60 %)	66 (16 %)	66 (16 %)
together	9983	7200 (72 %)	312 (3 %)	304 (3 %)

Taken together, the data demonstrate that neither the product information texts nor the public assessment reports are completely available and that the implementation process is still ongoing.

One of the main duties of the DIMDI is to provide high-quality information on medical and healthcare issues for politicians, healthcare professionals and the general public by the development and the operation of database-supported information systems[1]. The institute allows a comprehensive scientific research on healthcare, medical and drug related information contained in about 70 international and national databases. In cooperation with the national higher regulatory authorities and the Robert-Koch-Institute the DIMDI is building up the PharmNet.bund portal which shall serve as central information system on medicinal products providing the official information available. It shall comprise information on the authorisation, on clinical trials and on medical matters. Furthermore the portal allows the electronic submission of variation applications to marketing authorisations and provides a public register of sites authorised for importation, manufacture or marketing of human blood stem cell preparations according to the § 9 of the German transfusion law. In addition public access to GMP data like manufacturing or importation licences and GMP certificates is planned. Besides becoming a central national source of high-quality information, the portal shall serve as an interface to the correspondent EU databases like EudraPharm and EudraGMP.

Transparency on scientific matters is implemented in particular regarding the safety of medicinal products for human use. Comprehensive information on safety concerns are published on the websites of the competent higher federal authorities BfArM and PEI according to § 34 (1b). The section pharmacovigilance of the BfArM website comprises on the one hand routine information on more general and administrative matters like the protocols of routine sessions and committees' meetings (expert advisory committees for pharmacy-only and for prescription-only issues, respectively) and on the other hand information on serious safety issues and the respective authorities measures. This include in particular sections that provide information on graduated plans, on safety-

[1] *DIMDI, Medical knowledge online*, URL: http://www.dimdi.de/static/en/index.html, [accessed on 21 Nov 2009].

relevant announcements and on so-called *Rote-Hand-Briefe*, which are equivalent to dear healthcare professional letters. The section risk information presents an additional chronological overview.

The website of the PEI provides as well information on serious safety issues like graduated plans and *Rote-Hand-Briefe*. Furthermore the website provides a database on suspected adverse events following immunisation which grants access to the general public. The database is accompanied by comprehensive information for the public on the kind of data contained in the database, especially with respect to the fact that the database contains all reported suspected cases. The user has to confirm that the information is read and understood before the access is granted.

In contrast, no information is found on the realisation of the IFG on the websites of the German competent authorities BfArM, PEI and BVL. According to this German freedom of information act, access to information held by authorities shall be granted on request[1]. The IFG entered into force on 1 January 2006. By now, no guidance or information for applicants on how the request shall be made and in particular on which kind of information may be disclosed or which kind is considered to be commercially confidential is given on the authorities' websites. According to presentations on the authorities' experiences shown by representatives, the BfArM received about 200 requests for information in the first half year of implementation and the PEI received about 100 requests in 2006[2, 3]. Upon arrival of a request for information held by the BfArM as competent authority, it is checked whether the requested documents contain information that need to be protected according to §§ 3-7 IFG. This covers (i) the protection of public interest e.g. ongoing lawsuits, (ii) confidentially submitted information of third parties, (iii) personal data and (iiii) intellectual property and commercially confidential information/commercial secrets. Like the European legislation the German law does not provide a legal definition on the term "commercially confidential". Therefore it is the authority's decision which kind of information may be disclosed. In cases when confidential information is concerned, the authority informs the concerned third party about the request and asks to comment on it. Nevertheless, the final decision about the full or partial disclosure of the information is made by the BfArM taking into account the EMEA principles on commercially confidential information[4]. This information is based on the mentioned presentation[2]; however, there is no official confirmation of this procedure on the institute's website.

[1] *§1(1) Gesetz zur Regelung des Zugangs zu Informationen des Bundes (Informationsfreiheitsgesetz – IFG),* BGBl. I, 05 September 2005, p. 2722-2724.

[2] *Völkel, H., Informationsfreiheitsgesetz (IFG) – Erfahrungen und Verfahren des BfArM,* DGRA Mitgliederworkshop, 20.11.2006, Bonn.

[3] *Wiegelmann, B., Verfahren und Erfahrungen des Paul-Ehrlich-Instituts,* DGRA Mitgliederworkshop, 20.11.2006, Bonn.

[4] *Principles to be Applied for the Deletion of Commercially Confidential Information for the Disclosure of EMEA Documents,* 15 April 2007, Doc. Ref: EMEA/45422/2006, URL: http://www.emea.europa.eu/pdfs/human/euleg/4542206en.pdf, [accessed on 20 Nov. 2009].

3.4.2 Other EU member states

The individual communication traditions of the competent regulatory authorities of the EU member states differ regarding the proactive as well as the reactive disclosure of information held by the authorities. Like described for the current situation in Germany, most of the member states provide product information texts, i.e. the SmPC and the PL, through the internet. Table 4 is based on a survey performed by the EC on the information practices in the member states in 2006[1]. As listed in table 4, only a few member states' authorities grant no access at all to the SmPC and the PL, like Austria and Cyprus. In Greece for example the PL is available, but there is no access granted by the competent authority to the SmPC, neither for the general public nor for healthcare professionals and in Latvia the access to the SmPC is limited to healthcare professionals. In contrast to the product information texts access to the public assessment reports via internet is fully implemented only by five countries according to the replies to the 2006 survey.

Table 4: Results of a survey performed by the European Commission on access to the package leaflet, the summary of product characteristics and the European public assessment report granted by the authorities of the member states in 2006[1]. The table summarises the given answers.

Countries	Package Leaflet	Summary of Product Characteristics		Public Assessment Report
		Free access	Healthcare professionals only	
Austria	**No**	**No**	**No**	
Belgium	Yes	Yes	Yes	Yes
Cyprus	**No**	**No**	**No**	**No**
Czech Republic	Yes	Yes	Yes	
Denmark	**No (under development)**	Yes	**No**	**No (under development)**
Estonia	Yes	Yes	Yes	
Finland	Yes	Yes	Yes	**No (under development)**
France	Yes	Yes	Yes	Yes
Germany	Yes	Yes	Yes	Yes
Greece	Yes	**No**	**No**	
Hungary	Yes	Yes	Yes	**No (under development)**
Ireland	Yes	Yes	**No**	**No (under development)**
Latvia	Yes	**No**	Yes	
Malta	Yes	Yes	Yes	
Poland		Yes	Yes	
Portugal	Yes	Yes	Yes	
Slovakia	Yes	Yes	Yes	**No**
Spain	Yes		Yes	
Sweden	Yes	Yes	Yes	Yes
The Netherlands	Yes	Yes	Yes	Yes
United Kingdom	Yes	Yes	Yes	Yes

[1] *Commission Staff Working Document, Background information supportive to the Communication from the Commission to the European Parliament and the Council concerning the Report on Current Practice with Regard to Provision of Information to Patients on Medicinal Products, in the form of different annexes.* 18 December 2007, Doc. Ref: COM(2007) 862, URL: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2007/2007_12/comm_native_sec_2007_1740_1_en_documentdetravail.pdf, [accessed on 21 Nov 2009].

Several countries provide databases of medicinal products and of treatment options supported by different stakeholder groups like the pharmaceutical industry, healthcare professionals, health insurances, and/or patients' and consumers' organisations, like e.g. the medicines information project in the United Kingdom (UK). This internet portal hosts links to several databases like the electronic medical compendium, which is a register containing the SmPCs and the PLs of all medicinal products available in the UK, like the dictionary of medicines and devices browser which administrates information on reimbursement, like the medicines guide which allows to browse e.g. for treatment options and which is supported by the national institute of health, and like the xPIL-service, which provides special versions of patient information leaflets including e.g. audio formats, screen reader compatible formats and large fonts formats for persons with impaired visions[1].

Beside the information supplied via internet, a few countries traditionally provide comprehensive information in printed form on medicinal products to the public. The Swedish medicines compendium FASS represents an information source for healthcare professionals which has been developed by the Swedish association of the pharmaceutical industry (*Läkemedelindustriföreningen*, LIF) and which is in use for over 40 years[2]. Since 1983, the general public has access to a printed compendium called Patient-FASS, which provides regulatory approved information on medicinal products focussing on the safety-relevant information. In 2001, the Swedish internet portal www.fass.se was developed, which provides the FASS information for healthcare professionals and for patients electronically. In addition the SmPC, the PL and additional information on the active substance is provided including a description of the dosage form and at least in some cases a photo[3]. The Finnish pharmaceutical industry provides a pharmaceutical compendium written in lay language supplied in book form which includes the PLs. This information in contrast is rewritten by the industry, i.e. the information is not approved by the Finnish authority.

Just like the proactive disclosure practiced by the member states' regulatory authorities the reactive disclosure of information held by authorities upon request is not harmonized. Due to a lack of community legislation on freedom of information the reactive disclosure is subject to individual national provisions. Except from Luxembourg, Malta and Cyprus, all EU member states have their own freedom of information laws/provisions in force. With the enactment of the IFG on 1 January 2006, Germany was one of the last EU member state to establish a respective legislation, while other countries already have a long history of freedom of information. The world-wide first freedom of information law was enacted in Sweden in 1766, followed in the EU by France in the nineteen seventies, and Denmark, Greece and Austria in the eighties[4]. While the information on the content, the handling and the outcome of freedom of information requests presented on the websites of the majority of authorities is limited like in Germany, other authorities like e.g. the medicines and healthcare products regulatory agency (MHRA) which is the competent regulatory authority in the UK, publish in contrast quite detailed information on the respective requests. The MHRA classifies the information in its possession into three categories, (i) information that is routinely published, (ii) information that will be disclosed on demand and (iii) information which may only be revealed if a public interest in disclosure applies[5]. For information belonging to the last category a list of documents is provided and the parts of information which will only be disclosed in case of public interest is given as well as the parts that will be disclosed after consultation of the third party concerned. The MHRA

[1] *Medicines Information Project*, Datapharm Communications Ltd., URL: http://www.medicines.org.uk/, [accessed on 21 Nov 2009].
[2] *FASS – the Swedish Medicines Information Engine*, Läkemedelindustiförenigen, URL: http://www.lif.se/cs/E_Handel/Dokument/DF3358A2-5129-4A0C-9682-CE6A486025B6.pdf, [accessed on 21 Nov 2009].
[3] *FASS.se, Källan till kunskap om läkemedel*, URL: http://www.fass.se/LIF/home/index.jsp, [accessed on 21 Nov 2009].
[4] *The online network of freedom of information advocates*, URL: http://www.freedominfo.org/, [accessed on 21 Nov 2009].
[5] *Guidance on the Disclosure of Types of Human and Veterinary Medicines Information Held by the Human and Veterinary Regulatory Authorities*, URL: http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033020.pdf, [accessed on 21 Nov 2009].

treats any request on a case by case basis. The main reasons why documents are considered to be sensitive and may only be disclosed in case of an overriding public interest are (i) the marketing authorisation procedure is ongoing, (ii) trade secrets and/or the third party's know-how are concerned and (iii) personal information is included. Therefore prior disclosure the documents will be redacted accordingly[1]. In addition to this detailed guidance the MHRA publishes on its website all freedom of information requests which have been answered including the authority's replies and the disclosed response documents where appropriate. Response documents that are not available electronically and/or online on the website will be provided on request[2]. Information disclosed by the MHRA upon request include documents prepared by the MHRA like assessment reports as well as documents submitted by third parties to apply for a marketing authorisation, i.e. parts from the quality, safety and efficacy documentation, in particular the expert reports/overall summaries, and periodic safety update reports. It is noteworthy to stress that this deviates substantially from the EMEA approach as outlined in the draft policy on access to the agency's documents and its respective output document[3, 4]. According to this draft EMEA guidance, third party documents are considered to be confidential and may not be disclosed on request.

Regarding the scientific information on medicinal products held by the EU member states' regulatory authorities it is crucial to recognize that due to the harmonised requirements for authorisation and in particular due to the mutual recognition and decentralized procedures large parts of information hold by the authorities are more or less identical. In view of the fact that individual national freedom of information laws rule the public access to official information, the authorities should cooperate closely on this matter to develop a harmonised approach and to avoid that the decision of one authority to protect data is undermined by the disclosure of another authority.

[1] *Guidance on the Disclosure of Types of Human and Veterinary Medicines Information Held by the Human and Veterinary Regulatory Authorities*, URL: http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2033020.pdf, [accessed on 21 Nov 2009].
[2] *Information disclosures under the FOI Act*, URL: http://www.mhra.gov.uk/Aboutus/Freedomofinformationanddataprotection/Freedomofinformation/MHRAinformationdisclosuresundertheFOIAct/index.htm, [accessed on 21 Nov 2009].
[3] *Draft EMEA policy on the practical operation of access to EMEA documents*, 18 December 2008, Doc. Ref: EMEA/110196/2006/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/11019606en.pdf [accessed on 20 Nov. 2009].
[4] *Output of the Draft EMEA policy on the practical operation of access to EMEA documents in the context of the authorisation and supervision of medicinal products for human and veterinary use*. 18 December 2008, Doc. Ref: EMEA/659316/2008/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/65931608en.pdf, [accessed on 20 Nov. 2009].

4. Commercial use of transparency data

Increasing transparency in the drug regulatory environment and in particular non-harmonised and generous national freedom of information acts among the EU member states and third countries give rise to the question to what extend data disclosed for transparency reasons may be used commercially. In the highly competitive pharmaceutical business disclosed data may be of enormous commercial value for third parties, especially with respect to generic marketing authorisation applications. Abridged applications according to article 10 (1) of the community code represent applications for bioequivalent medicinal products relying on preclinical and clinical data of approved reference medicinal products. The pharmaceutical legislation dictates data protection periods according to article 10 of the community code and to article 14 (11) of Regulation (EC) No 726/2004, in which the reliance on previously submitted data is not applicable and respective applications must considered to be invalid (without the informed consent of the originator of the data). The data protection period comprises 8 years in which reliance on these data is not possible followed by an additional 2 year market exclusivity period, in which the usage of a generic licence, i.e. the marketing of the generic medicinal product is prohibited [1]. This exclusivity decade may be further extended due to patents or supplementary protection certificates.

Accordingly, bibliographic applications according to article 10a of the community code require that the applicant demonstrates the well-established medicinal use of the active substance within the community for at least ten years. As explained in the Notice to Applicants bibliographic applications are applications in which results of preclinical tests and clinical trials may be replaced "by detailed reference to published scientific literature […] if it can be demonstrated that the active substance of a medicinal product have been in well-established medicinal use within the community for at least ten years, with recognised efficacy and an acceptable level of safety"[2]. It is important to stress that bibliographic applications according to article 10a have to meet the same requirements regarding the demonstration of quality, safety and efficacy like full applications according to article 8 of the community code as the Notice to Applicants states that "the provisions of Annex I of Directive 2001/83/EC shall apply". In contrast to generic applications, which are abridged application types demonstrating bioequivalence to a medicinal product and which make reference to the preclinical and clinical results of the reference medicinal product, bibliographic applications thus are full application types. As a consequence, it is very difficult to provide sufficient scientific literature to meet the comprehensive prerequisites. Resulting gaps are tried to be closed by the submission of data received due to transparency and freedom of information provisions like assessment reports or data submitted for a reference medicinal product. However, as the competent authorities redact information prior to disclosure especially with respect to details and applied methods, these documents do not allow the assessment of the data. This point is stressed as well in section 5.4 of the Notice to Applicants: "… assessment reports such as the EPAR for community marketing authorisations which are made publicly available by competent authorities for reasons of transparency cannot be considered to supply sufficient information to meet the requirements of Annex I of Directive 2001/83/EC". However, if data disclosed for transparency reasons are used as additional information material the data protection periods have to be taken into account.

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[1] The described data protection periods were introduced into the pharmaceutical legislation in 2004 with Directive 2004/27/EC and Regulation (EC) No 726/2004. For centralised marketing authorisations granted before 20 November 2005 the previous protection rule is sill valid (10 years of data protection). For national authorisations which were granted before 30 October 2005 different national protection periods according to national law of the member states apply (6 or 10 years, repectively).

[2] *Section 5.4, Chapter 1, Marketing authorisation, Notice to Applicants,* Eudralex, The Rules governing Medicinal Products in the European Community, Volume 2A, URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/vol2a_chap1_2005-11.pdf, [accessed on 21. Nov 2009].

Bibliographic applications have been used in the attempt to disguise generic applications and to undermine data protection rules by submitting protected data disclosed for transparency reasons. These applications typically demonstrate bioequivalence to a reference medicinal product and thus have to be classified as generic applications and not as full applications. Therefore the authorities have to check carefully the legal basis in case of a bibliographic application.

With intent to circumvent the data protection period of a reference medicinal product via a bibliographic application, the applicants refer to publications of clinical trials conducted during the development of the reference medicinal product trying to reschedule the start of the well-established use of the medicinal product to a date long before the original authorisation has been granted and the medicinal product became available in the EU.

This fact raises the following questions:

- May publications of clinical trials during the development of a medicinal product indeed trigger the well-established use of a new medicinal product?
- May documents disclosed for transparency reasons which represent or deal with information under data protection be used commercially?

The idea to undermine the data protection via bibliographic dossiers is not new. In the nineteen nineties the temporary granting of a marketing authorisation for a bibliographic paclitaxel application during the data protection period in the Netherlands called international attention. The EC initiated as a consequence the Directive 1999/83/EC[1], the so-called well-established use directive, dictating conditions for bibliographic applications. With this directive the period needed to demonstrate a well-established-use has been adapted to the data protection period of ten years, as "the period of time required for establishing a "well-established medicinal use" of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the EU". Due to this legislative change, the premature paclitaxel authorisation in the Netherlands was revoked and the ongoing mutual recognition procedure was stopped. Furthermore the EC threatened with an infringement proceeding in case of continuation of the procedure. It is noteworthy to stress that it was one of the explicit aims of the well-established use directive to ensure that "the possibility of submitting 'bibliographical applications' does not discourage innovative companies to publish results of their research as quickly as possible"[2].

The quoted condition was included in the annex of the community code and is therefore still valid. To shorten the ten year period, applicants evidently try to reschedule the beginning of the well-established use within the EU with respect to the conduction and publication of clinical trials. This question is addressed in the EC's Notice to Applicants 2A[3]. The Notice to Applicants clearly states that the "less extensive" use of the substance in clinical trials can not trigger the start of the well-established use decade: "whilst data demonstrating less extensive use (e.g. use in clinical trials, compassionate use, named patient supply) may be submitted, this cannot replace the need to demonstrate extensive use for that 10 year period."

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[1] *Commission Directive 1999/83/EC of 8 September 1999 amending the Annex to Council Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products,* OJ **L243**, 15 September 1999, p. 9-11.

[2] *Recital 4 of Commission Directive 1999/83/EC of 8 September 1999 amending the Annex to Council Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products,* OJ **L243**, 15 September 1999, p. 9-11.

[3] *Section 5.4, Chapter 1, Marketing authorisation, Notice to Applicants,* Eudralex, The Rules governing Medicinal Products in the European Community, Volume 2A, URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/vol2a_chap1_2005-11.pdf, [accessed on 21. Nov 2009].

The characterisation of clinical trials as inadequate to demonstrate extensive use is plausible. This is explained by the experimental character of clinical trials performed to obtain a marketing authorisation. Such clinical trials are planned and conducted under clearly defined conditions to collect data on specific objectives, like e.g. the assessment of efficacy compared to a standard therapy, whereas the demonstration of a well-established medicinal use requires the wide use under everyday conditions.

As an aside it should be mentioned that the threshold which has been established for the qualification of a medicinal product to obtain an orphan drug designation is 5 of 10,000 concerned community citizens. This means that if up to 250,000 EU citizens use a medicinal product, it still may be classified as an orphan drug[1].Therefore the limited exposure of a few thousands of patients in a clinical trial cannot be understood as extensive use.

The fact that the conduction and publication of clinical trials is used to start counting the ten year period in cases of marketing authorisations on a well-established use basis was discussed at the 65th meeting of the Pharmaceutical Committee on 16th March 2009[2]. "The Commission representatives recalled the legal provisions governing well-established medicinal use and the fact that, according to Notice to Applicants, even though trials may be relied on when demonstrating well-established use of an active substance within the community, they are on their own not extensive use." It was underlined that "authorisations under Article 10a of Directive 2001/83/EC should be based on the proper demonstration of the well known and wide use of the substance concerned, and it should be avoided that the use of Article 10a leads to a circumvention of data protection rules in the pharmaceutical acquis."

The second question raised deals with the commercial re-use of data disclosed for transparency reasons. As already mentioned no common EU legislation for the member states exists governing transparency and freedom of information and nearly all of the member states have established individual provisions on this matter. Even though the individual national provisions to increase transparency differ, it is likely that they have been established for comparable reasons. The ultimate aim of transparency in the decision-making process is characterised as the strengthening of "the democratic nature of the institutions and the public's confidence in the administration"[3]. National freedom of information laws exclude from disclosure trade secrets and confidential commercial and financial information as a general rule. This already indicates, that freedom of information laws shall limit intellectual property rights only to such a degree as it is necessary to realise the public information and not to promote the commercial use of intellectual property by competitive third parties.

As described above, during the data protection period the reliance of a generic marketing authorisation application on clinical and preclinical data of a reference medicinal product is prohibited according to article 10 of the community code and article 14 (11) of Regulation (EC) No 726/2004. Applications that refer to the preclinical and clinical data of the reference medicinal product therefore are invalid and have to be rejected by the competent authorities. As a logical consequence, applications which contain the protected data received by disclosure of another EU or third country authority due to freedom of information provisions make reference to data under protection have to be invalidated and rejected accordingly.

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[1] *Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products,* OJ **L 18**, 22 January 2000, p. 1 - 5.

[2] *Pharmaceutical Committee - human, summary record of the 65th meeting*, 16 March 2009, Doc. Ref: PHARM 572, URL: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2009/2009_09/pharm_572%20_summary_record_16_march_2009_%20final.pdf, [accessed on 21. Nov 2009].

[3] *Declaration 17 of The Treaty on European Union,* OJ **C 191**, 29 July 1992, p. 101.

The re-use of data disclosed for transparency reasons during the data protection period has been discussed in the 65th meeting of the Pharmaceutical Committee, too, and it was concluded that the reliance on such data would lead to a circumvention of data protection rules[2]: "The Commission representatives explained that, during the period of data protection of a medicinal product, the data contained in the pre-clinical and clinical file of that product cannot be relied on by other applicants or the authorities in the procedure to ascertain the safety and efficacy of other products which are shown to be bioequivalent, whether in the framework of Article 10 of Directive 2001/83/EC or under other procedures (Articles 8(3) or 10a). In such circumstances, the reliance by applicants or competent authorities on preclinical and clinical data contained in the dossier of that product within the EU or in third countries, obtained through access to documents or freedom of information legislation, to grant marketing authorisation to another product would lead to a circumvention of the data protection rules of Directive 2001//83/EC (or Regulation (EC) No 726/2004)."

Taken together, the answers to the two questions raised have to be:

- publications of clinical trials cannot trigger the well-established use of a substance, and
- applications which contain data under protection disclosed for transparency reasons make an unacceptable reference and must be rejected.

The disregard of these principles recently caused the initiation of an infringement proceeding against Germany[1]. In this case, bibliographic dossiers have been submitted with intent to circumvent the protection of the results of preclinical tests and clinical trials of a reference medicinal product. The EC criticises that the applications rely on protected data as the competent regulatory authority has accepted data received due to freedom of information provisions during the data protection period. A further point of criticism of the EC is that a clinical trial is not sufficient to trigger the well-established medicinal use of a substance.

[1] *Hollstein, P. Vertragsverletzung wegen Clopidogrel*, apotheke adhoc, 30 July 2009, URL: http://www.apotheke-adhoc.de/Nachrichten/Markt/7160.html, [accessed on 12 Jan 2010].

5. Discussion

The pharmaceutical sector including authorities, pharmaceutical industry and healthcare professionals is faced with new challenges regarding the information of patients and the general public. This concerns on the one hand scientific transparency in particular regarding medicinal products and on the other hand administrative and regulatory transparency dealing with the authorisation of medicines and the decision-making process. Due to new information technologies the society is in general more interested in information on health matters. In the so-called information age the World Wide Web has become a widespread tool to access information on medicines and therapies for the general public which had hardly been attainable in the past. According to a telephone survey of a market research institution performed in March 2002 in the United States of America (USA) for example, 80 % of adult internet users (52 % of the adult US-Americans) search at least sometimes healthcare information in the World Wide Web[1]. With respect to the potential of the internet to increase the patients' knowledge on healthcare and their involvement in therapy decisions, it is crucial to give access to high-quality information on medicinal products to the public. Most commonly patients or consumers look for information on nutrition or diet, on side effects and complications of medicinal products, and on complementary and alternative medicine, or they intend to receive a second opinion on a condition or a treatment[2]. An investigation of the quality, accessibility and readability of health information in the internet published by Berland ***et al***. demonstrated that patients may have difficulties to find complete and accurate information on healthcare issues and to evaluate the information's quality. In addition, they showed that the language of the health information in the internet is found to be hard to understand for lays[3]. This raises the risk that patients or consumers become unsecured, get confused or misinformed on health conditions or medicines. Interestingly in this context is that it has been shown in another survey that nevertheless only about 59 % of patients who seek information in the internet discuss the findings with their healthcare professionals, giving them the opportunity to explain and if necessary to reassure the patients[2]. These studies show that there is an increasing demand for reliable, high-quality information on health-related scientific matters in an understandable language. This need applies as well to the EU citizens and has been recognized by European legislators and regulators. One major step forward in granting public access to scientific and reliable information on medicinal products is the realisation of the EU telematics projects, in particular by the public access to the EudraPharm database and thereby to EudraVigilance, EudraCT and EudraGMP data. In addition the need will be addressed by the planned review of the community code[4]. The proposed directive amending the community code will allow marketing authorisation holders to offer high-quality information on medicinal products available on prescription only while advertisement rend unsolicited dissemination of information remain prohibited. In addition to the granting of access it is essential to ensure that lays searching for medical information really reach the databases. At present it is likely, that the general public primarily uses search engines like "Google" to search for information in the internet leading to large numbers of results (e.g. the Google search for "lipitor" results in about 1.370.000 entries on 04 December 2009). Since lays may have difficulties to evaluate the quality of the information as stated above, the granting of access to high-quality information needs to be accompanied by the increase of public awareness on how to reach it.

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[1] *Taylor H. Cyberchondriacs update. The Harris Poll #21.* 1 May 2002 URL: http://www.harrisinteractive.com/harris_poll/index.asp?PID=299, [accessed on 21 Nov 2009].

[2] *Diaz JA, et al., Patients' Use of the Internet for Medical Information.* JGIM **17,** 2002, p. 180-185.

[3] *Berland GK, et al., Health information on the Internet: accessibility, quality, and readability in English and Spanish.* JAMA **285**, 2000, p. 2612-2621.

[4] *Proposal for a Directive of the European Parliament and of the Council amending, as regards information to the general public on medicinal products subject to medical prescription, Directive 2001/83/EC on the Community code relating to medicinal products for human use,* Doc. Ref: 2008/0256, URL: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0663:FIN:EN:PDF, [assessed on 18 Nov. 2009].

Increasing administrative and scientific transparency may furthermore serve to improve the public perception of drug regulation and pharmaceutical companies and to enhance the knowledge and the understanding of the decision-making process. The EMEA states that the "ultimate aim" of its transparency policy "is to further strengthen trust and confidence in the agency's operation"[1]. In line with this intention the HMA describe in their strategy paper a general "lack of understanding of the regulatory system" of stakeholders especially regarding the tasks and the boundaries of the responsibilities of the regulatory authorities[2]. The lack of trust and confidence may partially result from safety issues of approved medicinal products in the recent years that lead to subsequent warnings or even withdrawals and revocations. The serious cardiovascular events of rofecoxibe and finally the withdrawal of the marketing authorisation may serve as an example in this context. Beneath the severe criticism the manufacturer received for the failure to address early concerns with appropriate trials, it was called into question if the pharmacovigilance systems of the competent authorities (especially the Food and Drug Administration (FDA), which is the competent regulatory authority of the USA) were capable to detect safety alerts in time and if appropriate measures were dictated[3]. Furthermore, it has to be stressed that the reputation of pharmaceutical companies fell dramatically in the last decade. In 1997 79 % of the participants of a telephone survey performed by a market research institution stated that pharmaceutical companies do a good job compared to only 44 % of the participants in 2004[4]. This public distrust is likely to be intensified by sensational media that focus on risks and safety concerns of medicinal products giving the impression that marketing authorisations for new medicinal products are granted, that have not yet been investigated fully. In this context, often the fact is stressed that the agency and other competent authorities are financed at least partially by fees paid by applicants, i.e. pharmaceutical companies. With respect to this fact, public and especially independent experts' access to scientific information on medicinal products is crucial. In particular the opening of EudraVigilance is pivotal, as the access to all individual case safety reports may give external experts the opportunity to perform independent data analysis with respect to specific questions. Involvement of stakeholders like patients', consumers' and healthcare professionals' in scientific discussions of the EMEA committees as well as in regulatory issues like the development of new guidelines and policies are likely to be appropriate measures to enhance understanding and to strengthen the confidence in the agency's work. In addition, the declaration of integrity of the members of the scientific committees at the EMEA according to article 63 of Regulation (EC) No. 726/2004 is of enormous importance in this context.

Pharmaceutical industry faces a further point of criticism regarding the publication of clinical trial results. Several studies have shown that clinical trials with a positive outcome are more likely to be published and are published earlier than trials with a negative outcome, which may cause a biased evidence basis leading to a biased risk-benefit assessment[5, 6]. This problem is addressed by the implementation of article 57.2 of Regulation (EC) No. 726/2004 and of the transparency related

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[1] *The EMEA Transparency Policy, Draft for Public Consultation.* 19 June 2009, Doc. Ref: EMEA/232037/2009 – rev, URL: http://www.emea.europa.eu/pdfs/human/transparency/23203709en.pdf, [accessed on 20 Nov. 2009].

[2] *The Heads of Medicines Agencies Strategy Paper - Developing the Heads of Medicines Agencies Strategy for the European Medicines Regulatory Network – A Discussion Document,* http://www.hma.eu/63.html, [accessed on 01 Nov 2009].

[3] *Maxwell SR, et al. COX-2 selective inhibitors: important lessons learned.* Lancet **365,** 2005, p. 449-451.

[4] *The Harris Poll, 5* May 2006, URL: http://www.harrisinteractive.com/NEWS/allnewsbydate.asp?NewsID=1051 [accessed on 10 Nov 2009].

[5] *Turner, EH; et al., Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy,* NEJM **358,** January 2008, p. 252-260.

[6] *Whittington CJ, et al., Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data.* Lancet **363**, 2004, p. 1341-1345.

provisions of the Paediatric Regulation[1]. It is planned that information on clinical trials – in particular on results – prospectively originating from the EudraCT database shall be transferred and be published in the EudraPharm database granting access to the general public.

However, all stakeholders including patients and the general public have to be aware that medicines are not without risk. Rare effects of a medicinal product may not be known or realised at the time of approval, as therefore clinical experience in large numbers of patients over appropriate periods of time is needed, which will be collected after launch. Transparency and clear communication may help stakeholders to get more realistic expectations, realising that medicinal products may cause harm and marketing authorisations result from benefit-risk assessments.

Beneath the plenty advantages of increasing transparency, it is essential to establish boundaries. According to the regulation on public access to documents, public interests, personal data and commercially interests including intellectual property need to be protected[2]. At present there is no common legislation among the EU member states ruling transparency, freedom of information or protection of commercial confidential information and therefore a harmonised legal definition of the term commercially confidential is missing. As a consequence member states have established individual provisions, determining which kinds of information may be disclosed or need to be protected. The example of the current practice of the competent UK authority MHRA demonstrates substantial discrepancies to the suggested practice of the EMEA[3]. While the MHRA discloses on demand documents prepared by applicants or holders of a marketing authorisation like e.g. the expert reports or overall summaries, the EMEA clearly declares that these documents are considered to be confidential and may not be disclosed in principle. A common understanding within the European medicines regulatory system on which information may be disclosed and which information need to be protected is crucial, since if one member states discloses more information than other ones, the efforts of the more restrictive authorities to redact the documents and to protect sensitive information will be undermined.

General provisions exist in form of the agreement on trade-related aspects of intellectual property rights (TRIPS agreement) between members of the World Trade Organisation[4]. Article 39 (3) of the agreement states that data required for a marketing authorisation shall be protected against "unfair commercial use" by the members, when their "origination … involves a considerable effort". Furthermore, the members shall protect these data against disclosure, unless (i) there is an overriding public interest in disclosure or (ii) the data are protected against unfair commercial use.

With respect to EMEA documents, the agency has established principles for the deletion of commercially confidential information prior to disclosure which are in line with the TRIPS agreement[5]. According to this document commercially confidential information comprises on the one hand confidential intellectual property including e.g. formulas and on the other hand commercial confidences

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[1] *Art. 41, Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 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,* OJ **L 378,** 27 December 2006, p.1-19.

[2] *Art. 4, Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents.* OJ **L145,** p. 43-48.

[3] *Output of the Draft EMEA policy on the practical operation of access to EMEA documents in the context of the authorisation and supervision of medicinal products for human and veterinary use*. Doc. Ref: EMEA/659316/2008/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/65931608en.pdf, [accessed on 20 Nov. 2009].

[4] *TRIPS agreement, Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization*, 15 April 1994, URL: http://www.wto.org/english/docs_e/legal_e/27-trips.pdf, [assessed on 21 Nov. 2009].

[5] *Principles to be Applied for the Deletion of Commercially Confidential Information for the Disclosure of EMEA Documents*, 15 April 2007, Doc. Ref.: EMEA/45422/2006, URL: http://www.emea.europa.eu/pdfs/human/euleg/4542206en.pdf, [accessed on 20 Nov. 2009].

like e.g. development plans. The annex of the document provides detailed guidance on the deletion of commercially confidential information in assessment reports. In principle, detailed information is considered to be confidential whereas general information may be disclosed. While preclinical and clinical information in general is considered not to be commercially confidential, large parts of the pharmaceutical quality documentation represent confidential information that need to be protected like e.g. the whole pharmaceutical development part, details on synthesis and manufacturing, degradation products and impurities, validation, quality testing and the quantitative composition of the medicinal product. Despite exceptional details, neither the information on the outcome of inspections nor the outcome of the scientific discussion in the respective committee is regarded as confidential.

Restrictions are as well essential regarding disclosure of information by authorities on demand. The draft EMEA policy on access to EMEA documents and the respective output file foresees that documents submitted by applicants are considered to be confidential and may not be disclosed on demand by the agency[1, 2]. Nevertheless, the lack of a harmonized legislation on access to information among the member states and the implementation of individual freedom of information acts cause different practices regarding the reactive disclosure of documents on demand, like e.g. implemented by the MHRA. The situation is even more complex since information on competitor dossiers may be disclosed by third-country authorities. In this context, the FDA plays a pivotal role. According to the Code of Federal Regulations the FDA discloses all information that is not concerned by exemption 4 of the Freedom of Information Act, which protects "trade secrets and commercial and financial information"[3]. In particular the following information generally may not be disclosed: (i) information on manufacturing and quality control, (ii) financial information, e.g. on production and sales distribution and (iii) information on quantitative and semiquantitative formulas. Immediately after approval of a new drug application summarised safety and efficacy data evaluated during assessment of the application, i.e. the summary basis of approval, may be disclosed on request. In addition, adverse events reports and post-marketing study protocols are available on request[4].

In addition to a harmonised approach on the proactive and reactive disclosure of information, restrictions regarding the usage of disclosed information are essential. In this context the European legislation provides the directive on the re-use of public sector information. While Directive 2003/98/EC lays down rules to facilitate the re-use of documents held by authorities of the member states, it is without prejudice to existing rules in the member states regarding the right to access documents and concerns only documents held by authorities for which the disclosure is allowed according to national legislation[5].

Restrictions regarding the usage of disclosed information result from the TRIPS agreement, since data originated with considerable efforts required for a marketing authorisation application of a pharmaceutical product shall be protected against unfair commercial use by a competitor[6]. According

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[1] *Draft EMEA policy on the practical operation of access to EMEA documents*, 18 December 2008, Doc. Ref: EMEA/110196/2006/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/11019606en.pdf, [accessed on 20 Nov. 2009].

[2] *Output of the Draft EMEA policy on the practical operation of access to EMEA documents in the context of the authorisation and supervision of medicinal products for human and veterinary use*. Doc. Ref: EMEA/659316/2008/Final, URL: http://www.emea.europa.eu/pdfs/general/direct/65931608en.pdf, [accessed on 20 Nov. 2009].

[3] *5 USC 552, Public information; agency rules, opinions, orders, records, and proceedings, b, item 4,* Unites States Code, Title 5, Part I, chapter 5, subchapter II, § 552.

[4] *21 CFR 314.430, Availability for public disclosure of data and information in an application or abbreviated application,* Code of Federal Regulations, Title 21, Volume 5.

[5] *Art. 3, Directive 2003/98/EC of the European Parliament and of the council of 17 November 2003 on the re-use of public sector information*, OJ **L 345**, 31 December 2003, p. 90-96.

[6] *Art. 39, (3), TRIPS agreement, Annex 1C of the Marrakesh Agreement Establishing the World Trade Organization,* 15 April 1994, URL: http://www.wto.org/english/docs_e/legal_e/27-trips.pdf, [assessed on 21 Nov. 2009].

to the community code[1] and Regulation (EC) No. 726/2004[2] as amended the clinical and preclinical data of a marketing authorisation application are protected for 8 years following the grant of the authorisation. After this period a generic applicant is not required to provide the results of preclinical tests and clinical trials, but may refer to the documentation of the originator. For additional two years, the marketing of the generic medicinal product is prohibited. Establishing transparency to the general public within the European medicines regulatory system must not touch these data protection rules. This applies to generic applications according to article 10 of the community code as well as to bibliographic applications according to article 10a, which allows replacing of the preclinical tests and clinical trials by scientific publications in exceptional cases as detailed in chapter 4.

However, during the data protection and marketing exclusivity period a bibliographic application according to article 10a is not applicable, since the well-established medicinal use within the EU for a period of ten years is required. In contrast, one could argue, that the publication of a large clinical trial in the EU prior to authorisation could serve as trigger for the demonstration of well-established use. For the reasons illuminated in chapter 4, this argument is not applicable. First of all, the well-established use directive[3] was adopted to prevent a subsequent application within ten years following the granting of the reference registration. In addition, the use of a medicinal product in an even large clinical trial neither can be understood as "extensive" nor as already "well-established" due to the experimental character of clinical trials. The pharmaceutical committee shares the opinion that the counting of the ten years period may not be rescheduled to a date prior to the marketing authorisation and it exacts that such a circumvention of data protection rules must be avoided. It argues that the well-established use has to be understood as "the proper demonstration of the well known and wide use of the substance concerned" and may not be demonstrated only by reference to published clinical trials[4].

Restrictions regarding the commercial use of data received by third parties due to transparency reasons are evidently necessary, in particular when the disclosed data are still protected according to the data protection rules of the community code and Regulation (EC) No 726/2004, respectively. Restrictions have to apply on the one hand to the data themselves and on the other hand to information that summarise or analyse the protected data like e.g. assessment reports of authorities.

However, according to the Notice to Applicants published or reactive disclosed assessment reports of a regulatory authority may be added to a bibliographic application as supportive documentation but they "cannot be considered to contain sufficient information" [5] to demonstrate safety and/or efficacy of a medicinal product. Therefore a bibliographic application whose clinical or preclinical documentation is based only on an assessment report of a regulatory authority does not meet the requirements of a marketing authorisation application outlined in article 8(3) and in annex I of the community code. However it should be self-evident, that for the reliance on an assessment report the same data protection periods apply as for the data themselves.

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[1] *Art. 10(1), Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use,* OJ **L 311**, 28 November 2001, p. 67–128.

[2] *Art. 6(1), Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency,* OJ **L 136**, 30 April 2004, p. 1–33.

[3] *Commission Directive 1999/83/EC of 8 September 1999 amending the Annex to Council Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products,* OJ **L243**, 15 September 1999, p. 9-11.

[4] *Pharmaceutical Committee - human, summary record of the 65th meeting,* 16 March 2009, Doc. Ref: PHARM 572, URL: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2009/2009_09/pharm_572%20_summary_record_16_march_2009_%20final.pdf, [accessed on 21. Nov 2009].

[5] *Section 5.4, Chapter 1, Marketing authorisation, Notice to Applicants,* Eudralex, The Rules governing Medicinal Products in the European Community, Volume 2A, URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/vol2a_chap1_2005-11.pdf, [accessed on 21. Nov 2009].

In any case the usage of protected data for generic applications must be excluded. The aim of transparency as characterised in the present thesis is the strengthening of public trust in institutions and in decision-making processes of official bodies. Transparency may limit intellectual property rights only to such a degree as it is necessary to realise the public information and shall not promote the commercial use of intellectual property by competitive third parties. During the data protection period the reference of a subsequent application to an originator dossier to rely on the preclinical and/or clinical documentation of a reference medicinal product is not possible, neither for applications according to article 10 (generic application), nor for applications according to articles 8(3) (full or hybrid applications) or 10a (bibliographic application), as discussed above. The same restrictions have to apply if the protected data are disclosed and submitted by an applicant due to a freedom of information request in an other member state or in a third country. This is underlined by the pharmaceutical committee which concludes that the reliance on data received due to transparency and freedom of information provisions would “lead to a circumvention of data protection rules”.

In other words, if data are protected, the reliance on obviously identical data obtained on demand by another EU or third country authority due to freedom of information legislations undermines the data protection rules. In the light of the TRIPS agreement which shall prevent “unfair commercial use” by competitors, it is crucial, that such a misuse of transparency provisions must be prevented.

6. Summary

In the last years transparency of drug regulating authorities has become a matter of public interest. The different aspects of transparency, which are analysed in the present thesis, can be classified on the one hand as administrative or scientific transparency describing the kind of information, and on the other hand as proactive or reactive transparency, describing the way of disclosure.

Administrative transparency of regulatory authorities deals in particular with the supply of information on the daily business. The aim is mainly to strengthen the public trust in the authorities' work and to increase the understanding of the regulatory processes. It is implemented e.g. by the publication of documents like meeting minutes, agendas, information on organisational matters as well as of the composition of committees accompanied by personal details like the qualification and declaration of financial interests. Scientific transparency deals mainly with information on medicinal products and with access to high-quality information for stakeholders and the general public. Scientific transparency within the European medicines regulatory system is implemented according to the community code (Directive 2001/83/EC) and Regulation (EC) No 726/2004 by public access to assessment reports and to product information texts like the summary of product characteristics and the package leaflet. In addition, the establishment of the EudraPharm database which shall become a central register for European medicines, providing general information as well as information on pharmacovigilance issues and clinical trials represents a further major source for scientific transparency. The access to this information which is mainly granted proactively by publication on the competent authorities' websites or in databases is ruled in particular by the community code and Regulation (EC) No 726/2004.

In contrast, the reactive transparency deals with the public access to information held by authorities on demand. This comprises documents written by members of the authorities as well as third parties like e.g. the pharmaceutical documentation of a marketing authorisation. Whereas the access to information held by EU institutions is subject to Regulation (EC) 1049/2001 and to several implementing guidelines, no harmonised legislation addresses the disclosure of information held by authorities of the member states. Therefore the access to this information on demand is implemented individually based on national freedom of information legislations. As a consequence of the missing community legislation, no common definition of the term "commercially confidential" exists among the member states. For that reason the EU authorities protect or disclose different parts of information.

Increasing transparency and in particular non-harmonised national freedom of information acts give rise to the question to what extend data disclosed for transparency reasons may be used commercially. In the present thesis the use of disclosed information to obtain a premature generic marketing authorisation via a bibliographic application is analysed. Focus is given in that context on the arising problems with the demonstration of a well-established medicinal use and with data protection rules. In summary, transparency in regulatory processes and decisions is undisputable essential, but appropriate measures must be taken to prevent misuse of disclosed information and violation of existing data protection rules.

7. References

21 CFR 314.430, Availability for public disclosure of data and information in an application or abbreviated application, Code of Federal Regulations, Title 21, Volume 5.

5 USC 552, Public information; agency rules, opinions, orders, records, and proceedings, b, item 4, Unites States Code, Title 5, Part I, chapter 5, subchapter II, § 552.

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Annex

The AMIS queries described in chapter 3.4.1 were performed on 21 September 2009 with the following parameters:

a) First set of queries to display the total number of authorisations granted in the requested period excluding parallel distribution and centralized authorisations as well as the number of authorisations for each competent authority:

BGVV abbreviates for *Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin*. This institute was formerly the competent higher authority for the registration of medicinal products for veterinary use.

	BfArM;BGVV;PEI	in	**Zustaendigkeit**
NICHT	**S**	in	**Parallelimport-Code**
NICHT	**9**	in	**EU-Zulassungscode**

Filter:
Zulassungszeitraum von **20050906** bis **20090906**
(no further restrictions)

Number of authorisations granted in the requested period for each authority:

	BfArM	in	**Zustaendigkeit**
NICHT	**S**	in	**Parallelimport-Code**
NICHT	**9**	in	**EU-Zulassungscode**

Filter:
Zulassungszeitraum von **20050906** bis **20090906**
(no further restrictions)

	PEI	in	**Zustaendigkeit**
NICHT	**S**	in	**Parallelimport-Code**
NICHT	**9**		

Filter:
Zulassungszeitraum von **20050906** bis **20090906**
(no further restrictions)

	BGVV	in	**Zustaendigkeit**
NICHT	**S**	in	**Parallelimport-Code**
NICHT	**9**		

Filter:
Zulassungszeitraum von **20050906** bis **20090906**
(no further restrictions)

b) Second set of queries to display the number of authorisations granted in this period for which the public assessment report and/or the product information texts (SmPC and PL) are available:

The following filters were subsequently added to each of the four queries:

Mit Fach-/Gebrauchsinformationen:	**ja**
Öffentliche Bewertungsberichte/PAR:	**keine Einschränkungen**

Mit Fach-/Gebrauchsinformationen:	**keine Einschränkungen**
Öffentliche Bewertungsberichte/PAR:	**ja**

Mit Fach-/Gebrauchsinformationen:	**ja**
Öffentliche Bewertungsberichte/PAR:	**ja**

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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Unterschrift