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ABSTRACT:

Regulations for clinical trials consist of a multitude of laws, directives, legal ordinance, guidelines and instructions. In this deliverable, regulations and guidelines on an international level are considered; the differences in national laws and guidelines are not discussed. Regulations and guidelines are discussed concerning their role in international clinical trials in general, in trials about personalized medicine in p-medicine trials. The application of these regulations and guidances for the deployment of p-medicine tools is evaluated in detail (clinical trial data management system ObTiMA, use of electronic source data, DoctorEye, Oncosimulator and clinical decision).

KEYWORD LIST: clinical trials, regulatory landscape, drug law, EU Directives, Good Clinical Practice, Declaration of Helsinki, electronic source data,

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¹ R=Report, P=Prototype, D=Demonstrator, O=Other

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1 Executive Summary

Clinical drug trials are investigations with humans intended to discover or verify the effects of one or more medicinal products. General requirements for the conduct of these clinical trials in the EU are provided for in EU Directive 2001/20/EC, which is called the “Clinical Trials Directive”, 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. The Clinical Trials Directive is concretised by Directive 2005/28/EC, the “the GCP Directive”, laying down principles and detailed guidelines for Good Clinical Practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

There are a number of guidelines specifying various aspects of clinical trials, and in particular: (1) the information to be submitted to the competent authorities and to the ethics committees, (2) requirements on safety monitoring and the reporting of adverse reactions, (3) requirements regarding Good Clinical Practice, including the documentation, of the clinical trials (e.g. Trial Master File), (4) specific requirements regarding the products and the clinical trials, (5) inspections of competent authorities and the applicable procedures and (6) requirements relating to the quality, safety and efficacy of products. These guidelines have been published in Volume 10 of “EudraLex - The rules governing medicinal products in the European Union”. The Clinical Trials Directive harmonises the rules in the EU for the approval of clinical trials conducted in a member state. For clinical trials in the US regulations are laid down in a number of Codes of Federal Regulations which are concretised in FDA regulations and guidances.

The European Commission is planning in 2012 to propose a revision of the Clinical Trials Directive 2001/20/EC. This update was supported by public consultation. Here ECRIN (European Clinical Research Infrastructures Network) has provided, together with other organisations and pharma companies, suggestion for improvements.

Because in p-medicine developed software will have direct implications on patient safety, e.g. by providing decision support and decisions on therapies, software must be validated according to GCP (System Validation) and according to medical device laws. Clinical trials on medical devices are regulated by EN ISO 14155:2011 “Clinical investigation of medical devices for human subjects - Good Clinical Practice” and in Europe by EU Directive 2007/47/EG. In addition, guidances on information security, electronic source data and data privacy play an important role for p-medicine software and data processing, for example ISO 27001: Information Security and in Europe EU Directive 95/46/EC, the GCP Inspectors Group’s Reflection paper on expectations for electronic source documents used in clinical trials and GMP Annex 11 and in the US HIPAA (Health Insurance Portability and Accountability Act of 1996).

p-medicine will use biobanks, advanced therapies in cancer research and innovative products and will therefore be subject to the corresponding regulations and guidelines, often still in the state of a draft. Especially this regulatory area, covering requirements for biomarkers, genetic tests and use of tissues, is in development.

The application of these regulations and guidances for several of the software applications developed in p-medicine is evaluated in detail: clinical trial data management systems (CDMS) in trials with medicinal products, with special consideration of ObTiMA clinical trial management system, eSource (electronic source data) data collection, as well as studies with secondary use of data, DoctorEye, Oncosimulator and clinical decision support in clinical trials, and clinical trials involving biobank data.

2 Introduction

2.1 Purpose of this document

Clinical research is necessary to enable the improvement of clinical practice. The highest level of quality of clinical interventional research is based on well-designed randomised clinical trials. Such clinical trials enable control of random error and systematic error but are subject to extensive regulatory requirements to guarantee that European clinical intervention research safeguards participants, maintains high standards, benefits trial participants and promotes European-wide research.

2.2 European wide clinical research

The challenges for high-quality, European wide clinical research, such as research performed within the context of the p-medicine project, makes it necessary to focus on the optimal way to span national boundaries and adjust to national specifics to recruit enough participants and to manage the conduct of international clinical trials efficiently. The challenge for regulatory requirements for international clinical trials is to safeguard participants and at the same time, maintain high quality standards, while not inhibiting collaborative research. The European Directive 2001/20/EC [1], which passed in 2001, is the corner stone of regulations for this type of clinical trials. It aimed to meet existing regulatory challenges by offering a legislative framework for European clinical trials, which was supposed to reduce discrepancies between member states. However, EU member states implemented the Directive into national laws differently using diverse interpretations, thereby preventing a comprehensive harmonisation of regulatory requirements [2, 3]. In addition, the European Directive 2001/20/EC covers only clinical research using medicinal products and therefore research in some other clinical research areas was not affected by harmonization efforts [4, 5, 6]. The European Research Infrastructures Network (ECRIN) has analysed comprehensively for its partner states the implementation of EU Directives and the regulatory situation for all types of clinical research [7]. Several main areas of regulatory homogenization could be identified. Clinical trials on medicinal products require in all ECRIN members an authorization of the application and any additional amendments from competent authorities, a favourable opinion from ethics committees, a dedicated sponsor of the trial, insurance of participants, reporting of SUSARs³ and an Annual Safety Report. The research ethics committees must approve all interventional clinical trials and all ECRIN member countries provide legislation to protect personal data. Variability in the clinical trial legislation exists in different national requirements regarding competent authority, sponsor, insurance and adverse event reporting and regarding interventional clinical research other than clinical trials on medicinal products. Even the definition of interventional and observational studies varies between countries. In some countries an approval by an ethics committee is not required for observational studies. Additional heterogeneity exists for requirements for a waiver of purchase costs of investigational medicinal products for non-commercial trials, the obligation to inform participants about the outcome of a trial and insurance specifics in investigator initiated clinical research [7].

2.3 Support of regulatory and institutional aspects of clinical trials

For the p-medicine project, in task 9.1 UDUS is providing support of regulatory and international aspects of the clinical trials conducted as pilot trials in p-medicine. UDUS will accompany these clinical trials with advice about regulatory and international aspects of trials conduct. For this purpose a report was produced which lists all relevant regulatory documents for international clinical trials. In p-medicine three diseases were selected for the pilot trials: Wilms Tumour, Breast Cancer and Acute Lymphoblastic Leukaemia (ALL). They will address different aspects of the personalized medicine framework of the project. Data

³ Suspected Unexpected Serious Adverse Reactions

collected during these trials are stored in a data warehouse in a secure and anonymised way according to the legal and ethical framework of p-medicine. This document complements the legal and ethical framework of p-medicine and extends it for international European clinical trials conduct. It is the purpose of this document to list all relevant regulatory and guidance documents for the international aspects of European clinical trials to be used as basis for the support of p-medicine pilot trials and for using p-medicine tools in ECRIN trials.

3 Structure of the Deliverable

The deliverable describes the regulatory landscape for international clinical trials with a focus on regulatory requirements for trials in personalised medicine and corresponding international aspects. After an introduction about European wide clinical research and compliance with Good Clinical Practice in clinical trials the regulations relevant for p-medicine clinical trials are displayed. The list of regulations and guidelines is organised according to international, US and European relevance. The list goes from more general ethical documents (e.g. Declaration of Helsinki, ICH Topic E6 Guideline for Good Clinical Practice), to documents specifying concrete clinical trials requirements (EU EU Directive 2005/28/EC, Code of Federal Regulations), to finally documents addressing rather specific requirements for some type of clinical trials (e.g. US Device Regulation, ISO 27001: Information Security, EU directive 95/46/EC, Qualification of novel methodologies for drug development).

In the discussion specific topics with importance to p-medicine are discussed, including the impact of regulations on clinical trials in personalised medicine and the use of advanced therapies and novel medicinal products. Especially the regulatory demands for the development and use of p-medicine tools (ObTiMA clinical trial management system, eSource, software as a medical device, DoctorEye, Oncosimulator and clinical decision support, clinical trials involving biobanks) are presented and discussed. In the appendix, a complete list of EudraLex regulations of volume 1, 4 and 10 is attached.

4 Clinical trials with medicinal products

4.1 Good Clinical Practice compliance

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve research on human subjects [8]. Compliance with GCP provides public assurance that (1) the rights, safety and well-being of trial participants are protected and (2) the clinical trial data collected during the trial is credible. This protection of clinical trial subjects is based on the principles set out in the Declaration of Helsinki [9]. Requirements for the conduct of clinical trials in the European Union (EU), including GCP and good manufacturing practice (GMP) are implemented in (1) Clinical Trial Directive (EU Directive 2001/20/EC) and GCP Directive (EU Directive 2005/28/EC). The European Medicines Agency (EMA) plays an important role in the harmonisation and co-ordination of GCP-related activity at the EU level by coordinating GCP inspections for the centralised procedure, preparing guidance on GCP relevant topics (GCP Inspectors Working Group), coordinating advice on the interpretation of EU GCP requirements and developing of EU-wide guidelines on GCP inspections and related procedures. Information on clinical trial authorisation, safety monitoring, GCP inspections, and GCP and GMP requirements for clinical trials in Europe are presented in Volume 10: clinical trial guidelines of the rules governing medicinal products in the EU [10].

Clinical trials conducted to achieve a marketing authorisation in Europe must be in accordance with the Directive 2001/83/EC Annex I (adapted according to 2003/63/EC). Annex I describes detailed scientific and technical requirements for the presentation and content of the marketing authorisation. This aspect plays a minor role for p-medicine clinical trials. Important for all clinical trials is the ethical standard presented by the Clinical Trials Directive (EU Directive 2001/20/EC). In July 1996, the EU adopted the guideline for good clinical practice, which defines a unified standard for Europe, the United States and Japan. For clinical trials conducted in countries outside the EU the EMA is working on strategies on the acceptance of clinical trials conducted in third countries. In December 2008, EMA published a strategy paper on this problem and in May 2010 a reflection paper on ethical and GCP aspects of clinical trials conducted in third countries was published [11] which highlights the need for cooperation between international regulatory authorities and proposes a series of measures for a framework for the conduct of clinical trials. This reflection paper shows that the number of clinical trials and recruited patients outside Western Europe and North America has been increasing recently. An important topic is the collaboration of EMA with the FDA (Food and Drug Administration). Both agencies launched a joint initiative to collaborate on international GCP inspection activities in July 2009. The main objective of this collaboration is to conduct periodic information exchanges on GCP-related topics and to conduct collaborative GCP inspections.

4.2 International regulations

4.2.1 ICH Topic E6 Guideline for Good Clinical Practice Step 5, CPMP/ICH/135/95 [8]

The EMA has adopted several ICH⁴ guidelines following agreement on a harmonised approach between Europe, Japan and the United States of America (ICH).

This guideline defines Good Clinical Practice (GCP) as an international ethical and scientific quality standard that covers the design, conduct, recording and reporting of trials that involve the participation of human subjects. “Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki [9], and that the clinical trial

⁴ International Conference on Harmonisation

data are credible.” The objective of this guideline is to provide a unified standard for the European Union, Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities. This guideline should be followed not only when generating clinical trial data for submission to regulatory authorities, but also for all other clinical investigations that may have an impact on the safety and well-being of human subjects.

This guideline provides a glossary of all terms relevant to GCP compliant research and defines the principles of GCP: Institutional review board (IRB) / independent Ethics Committee (IEC), responsibilities of sponsor and investigator, need for a clinical trial protocol and protocol amendments, investigational brochure and essential documents for the conduct of a clinical trial.

For the informed consent, the investigator must comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles of the Declaration of Helsinki. Before beginning the trial, the investigator must have the written approval by the IRB / IEC's of the written informed consent form and any other written information to be provided to trial participants. To protect the participants, neither the investigator, nor any trial staff, should coerce or unduly influence a patient to participate in a trial or to continue participating in a trial. In addition the guideline provides a list of information to be provided to subjects during informed consent discussion and in the written informed consent form.

The guideline provides a list of essential documents that must be prepared and collected for a clinical trial. Essential documents are documents that permit the evaluation of the conduct of a trial and the quality of the data produced. These documents can demonstrate the compliance of the investigator, sponsor and monitor with the GCP standard and with all applicable regulatory requirements.

In addition, filing of essential documents at the investigator/institution and sponsor sites can support successful clinical trial management by the investigator, sponsor and monitor. These documents are the subject of audits and inspections by the sponsor or by the regulatory authority as part of the process to confirm the validity of the trial conduct and the integrity of collected data. The minimum list of essential documents to conduct a clinical trial according to GCP is grouped in three sections: (1) before the clinical phase of the trial commences, (2) during the conduct of the trial, and (3) after completion or termination of the trial.

4.2.2 Other relevant international ICH guidelines

ICH Topic E6 is an ICH guideline, but is also one of the “Scientific guidelines” [12] of EMA. The EMA’s Committee for Medicinal Products for Human Use (CHMP) prepares these scientific guidelines in consultation with regulatory authorities in the European Member States. These guidelines provide a practical basis for the harmonisation of processes and the interpretation of the detailed requirements for the demonstration of quality, safety and efficacy by EU Member States. These do not constitute regulations, but rules recorded in these guidelines must be followed. Thus, EMA strongly encourages applicants and marketing-authorisation holders to follow these guidelines. Applicants must justify deviations from these guidelines in their applications at the time of submission. There exist guidelines for the following sections: quality, biologicals, non-clinical, clinical efficacy and safety, multidisciplinary and herbal medicinal product guidelines. Of importance for the conduct of clinical trials are all of these ICH guidelines. These guidelines are harmonised between Europe, Japan and the United States by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH guidelines are provided for: Efficacy, Multidisciplinary, Quality, Safety and Considerations

4.2.3 ICH guidelines for efficacy

This list contains the scientific guidelines on efficacy published by the EMA:

- E 1 Population exposure: The extent of population exposure to assess clinical safety CPMP/ICH/375/95, November 1994, June 1995*
- E 2 A Clinical safety data management: Definitions and standards for expedited reporting CPMP/ICH/377/95, November 1994, June 1995*
- E 2 B (M) Note for guidance on clinical safety data management: Data elements for transmission of individual case safety reports, CPMP/ICH/287/95, November 2000*
- E 2 B (R3) Data elements for transmission of individual case safety report CHMP/ICH/166783/05, October 2011, Deadline for comments March 2012*
- E 2 B (R5) Questions and answers: Data elements for transmission of individual case safety reports CHMP/ICH/3943/03, March 2005, January 2005*
- E 2 C (R1) Clinical safety data management: Periodic safety update reports for marketed drugs CPMP/ICH/288/95, December 1996, June 1997*
- E 2 D Post-approval safety data management, CPMP/ICH/3945/03, November 2003, May 2004*
- E 2 E Pharmacovigilance Planning (PvP) CPMP/ICH/5716/03, Dec 2004, Jun 2005*
- E 2 F Development safety update report HMP/ICH/309348/08, September 2010, September 2011*
- E 3 Structure and content of clinical study reports CPMP/ICH/137/95, December 1995, July 1996*
- E 4 Dose-response information to support drug registration CPMP/ICH/378/95, May 1994, November 1994*
- E 5 (R1) Ethnic factors in the acceptability of foreign clinical data CPMP/ICH/289/95, March 1998, September 1998*
- E 5 (R1) Questions and answers: Ethnic factors in the acceptability of foreign clinical data CPMP/ICH/5746/03, June 2006, June 2006*
- E 6 (R1) Guideline for good clinical practice CPMP/ICH/135/95, July 1996, January 1997*
- E 7 Studies in support of special populations: Geriatrics CPMP/ICH/379/95, September 1993, March 1994*
- E 8 General considerations for clinical trials CPMP/ICH/291/95, September 1997, March 1998*
- E 9 Statistical principles for clinical trials CPMP/ICH/363/96, March 1998, September 1998*
- E 10 Choice of control group in clinical trials CPMP/ICH/364/96, July 2000, January 2001*
- E 11 Clinical investigation of medicinal products in the paediatric population CPMP/ICH/2711/99, July 2000, January 2001*
- E 12 Principles for clinical evaluation of new antihypertensive drugs CHMP/ICH/541/00, June 2000, June 2000*
- E 14 The clinical evaluation of QT / QTs interval prolongation and pro-arrhythmic potential for non-anti-arrhythmic drugs CHMP/ICH/2/04, May 2005, November 2005*
- E 14 Questions and answers: The clinical evaluation of QT / QTs interval prolongation and pro-arrhythmic potential for non-anti-arrhythmic drugs CHMP/ICH/310133/08, June 2008, June 2008*
- E 15 Establish definitions for genomic biomarkers, pharmaco-genomics, pharmaco-genetics, genomic data and sample coding categories CHMP/ICH/437986/06, November 2007, May 2008*
- E 16 Note for guidance on genomic biomarkers related to drug response: context, structure and format of qualification submissions Draft guideline EMEA/CHMP/ICH/380636/2009, September 2010, December 2010.*

Some guidelines are described in more detail:

4.2.3.1 ICH Topic E 10. Choice of Control Group in Clinical Trials. [13]

This guideline describes the general principles involved in choosing a control group for clinical trials to demonstrate the efficacy of a treatment and to discuss related trial design. This guideline does not address the regulatory requirements, but describes what trials using a specific design are able to demonstrate. The general principles described are relevant to any controlled trial but the choice of control group is of particularly critical importance to clinical trials carried out during drug development to demonstrate efficacy and the choice of the control group should be considered in the context of available standard therapies, the adequacy of the evidence to support the chosen design, and ethical considerations. The guideline lists the purpose of the control group and the types of control groups employed to demonstrate efficacy.

4.2.3.2 Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) [14]

This guideline was developed to harmonise the way to gather safety information and to take action on them. Agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice standards in safety management. The initiatives already undertaken for marketed medicines through the CIOMS-1 and CIOMS-2 Working Groups on expedited reports and periodic safety update reporting are important precedents and models. However, this guideline addresses special circumstances involving medicinal products under development, especially in the early stages and before any marketing experience is available.

4.2.3.3 ICH Topic E 2 C (R1) Clinical Safety Data Management, periodic safety updates [15]

Harmonisation of periodic safety updates is necessary because the regulatory requirements, particularly regarding frequency of submission and content of periodic safety updates, are not the same in EU, Japan, and USA. In order to avoid duplication of effort and to ensure that important data is submitted with consistency to regulatory authorities, this guideline describes the format and content for comprehensive periodic safety updates of marketed medicinal products. Recently a guideline for the development of safety update reports (E2F) has been issued.

4.2.3.4 ICH Topic E 5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data [16]

This guidance recommends a framework for evaluating the impact of ethnic factors upon a medicine's effect, i.e., its efficacy and safety at a particular dosage and dose regimen. It provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimising duplication of clinical studies and supplying medicines expeditiously to patients for their benefit. This guidance defines ethnic factors as those factors relating to the genetic and physiologic (intrinsic) and the cultural and environmental (extrinsic) characteristics of a population. The objectives are to describe the characteristics of foreign clinical data that will facilitate their extrapolation to different populations and support their acceptance as a basis for registration of a medicine in a new region and to describe regulatory strategies that minimize duplication of clinical data and facilitate acceptance of foreign clinical data.

4.2.3.5 ICH Topic E 8 General Considerations for Clinical Trials [17]

This document describes internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategy for new medicinal products, to facilitate the evaluation and acceptance of foreign clinical trial data by using general approaches and common definitions of relevant terms. It contains an overview of the ICH clinical safety and efficacy documents and a glossary of terms used in the ICH clinical safety and efficacy related documents.

4.2.4 Declaration of Helsinki [9]

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects. It represents the ethical corner stone for clinical research. The statement covers also research on identifiable human material and human data. The basic principle of the declaration declares that “it is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research”. In addition, the Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.” Populations that are underrepresented in medical research should be provided appropriate access to participation in research. In general, the well-being of the individual research subject must take precedence over all other interests in medical research. Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

Medical research is based on ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations, especially those that cannot give consent, are in need of special protection. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects described in the Declaration.

An important aspect is the evaluation of the benefit/risk ratio for the patient before beginning a trial. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them ... Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

The newest version of the Declaration is the 6th revision, decided during the 59th WMA General Assembly in Seoul (Korea), October 2008.

4.3 European regulations

4.3.1 EU Directive 2001/20/EC. Implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use, 4 April 2004. [1]

Directive 2001/20/EC establishes specific rules about the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products. In particular, it regulates the implementation of Good Clinical Practice. Additional protection is given to persons who are incapable of giving legal consent to clinical trials. Member States should lay down rules to the effect that such protected persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent.

The verification of compliance with Good Clinical Practice and the need to inspect data, information and documents to confirm that they have been properly generated, recorded and reported are essential in order to justify the involvement of human subjects in clinical trials.

Important definitions with international relevance listed in this directive are:

Investigational medicinal product

a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

Sponsor

an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

Non-interventional trial

A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

Informed consent

Decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

4.3.2 EU Directive 2005/28/EC. Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, 8 April 2005 [18]

This Directive lays down rules to be applied to investigational medicinal products for human use: the principles of Good Clinical Practice and detailed guidelines in line the principles included in Directive 2001/20/EC, for the design, conduct and reporting of clinical trials on human subjects involving such products; the requirements for authorisation of the manufacture or importation of such products and the detailed guidelines, provided for in Directive 2001/20/EC, on the documentation relating to clinical trials, archiving, qualifications of inspectors and inspection procedures. In detail, member states are advised to establish Ethics Committees on the basis of common detailed guidelines, in order to ensure the protection of trial subjects. It requires that in clinical trials on investigational medicinal products for human use, it is necessary that the safety and the protection of the rights of trial subjects should be ensured. Further specifications are given to the content of the Investigators Brochure, manufacturing and import authorization, the trial master file and archiving of study documents, and inspection procedures.

4.3.3 EMEA Note for guidance on Good Clinical Practices, CPMP/ICH/135/95, July 2002 [10]

CPMP/ICH/135/95 Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are being protected. The principles of the Declaration of Helsinki constitute the basis for this purpose. The objective of this ICH GCP Guideline is to provide a unified standard for the European Union, Japan and the

United States to facilitate the mutual acceptance of clinical data by the regulatory authorities. This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects. It corresponds to ICH E6.

4.4 US regulations

4.4.1 Code of Federal Regulations (CFR)

4.4.1.1 General and permanent rules

The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation. Most important for the FDA are CFR 21, 820, 177, et.al.

4.4.1.2 Code of Federal Regulations - Title 21 - Food and Drugs

Title 21 of the CFR contains the rules of the Food and Drug Administration. Each title of the CFR is revised once each calendar year. The CFR at GPO⁵, both current and historical, can also be searched directly at: <http://www.gpoaccess.gov/cfr/index.html>.

Title 21 contains several sections, the most important are:

Part 11 Electronic records and electronic signature related

Part 50 Protection of human subjects in clinical trials

Part 54 Financial Disclosure by Clinical Investigators

Part 56 Institutional Review Boards that oversee clinical trials

Part 58 Good Laboratory Practices (GLP) for nonclinical studies

The 100 series are regulations pertaining to food

The 200 and 300 series are regulations pertaining to pharmaceuticals (e.g. 202-203 Drug advertising and marketing, 210 cGMPs⁶ for pharmaceuticals, 310 Requirements for new drugs)

The 600 series covers biological products (e.g. vaccines, blood) (e.g. 601 Licensing under section 351 of the Public Health Service Act, 606 cGMPs for human blood and blood products)

The 800 series are for medical devices (e.g. 803 Medical Device Reporting, 814 Premarket Approval of Medical Devices, 820 Quality system regulations, analogous to cGMP, but structured like ISO)

4.4.2 FDA draft regulations and guidances

In addition the FDA provides a number of guidances [19]. Guidance documents represent FDA's current thinking on a topic. Many guidance documents address pharma industry requirements. For example, the regulatory guidance for drug registration and listing Section 510 of the Federal Food, Drug, and Cosmetic Act requires manufacturers, repackers, and relabelers that engage in the manufacture, preparation, propagation, compounding, or processing of human or veterinary drugs and human biological products to register their establishment(s) and submit a listing of every product in commercial distribution with the FDA.

In addition, draft regulations and guidances are documents that have been proposed, but FDA has not made a decision as to whether the proposal will be adopted in whole, in part, or not at all. Draft guidance that may have relevance for international trials are listed:

⁵ GPO: U.S Government Printing Office

⁶ GMP: Good Manufacturing Practice

4.4.2.1 Guidance on Exculpatory Language in Informed Consent, 9/7/2011

This document provides guidance on the regulatory prohibition on the inclusion of exculpatory language in informed consent. The document includes examples of language that OHRP⁷ and FDA consider acceptable as well as examples of language that the agencies would consider exculpatory.

4.4.2.2 Draft Guidance for Industry - Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring, 8/28/2011

FDA is publishing this new draft guidance to assist sponsors of clinical investigations in developing risk-based monitoring strategies and plans for clinical investigations of human drug and biological products, medical devices, and combinations thereof.

4.4.2.3 Draft Guidance for Industry, Clinical Investigators, and Food and Drug Administration Staff - Design Considerations for Pivotal Clinical Investigations for Medical Devices. 8/15/2011

This document is intended to provide guidance to those involved in designing clinical studies intended to support premarket submissions for medical devices and FDA staff who review those submissions

4.4.2.4 Draft Guidance for Industry and Food and Drug Administration Staff - In Vitro Companion Diagnostic Devices, 7/14/2011

This draft guidance is intended to assist sponsors who are planning to develop a therapeutic product that depends on the use of an in vitro companion diagnostic device (or test) for its safe and effective use and sponsors planning to develop an in vitro companion diagnostic device that is intended to be used with a corresponding therapeutic product.

4.4.2.5 Financial Disclosure by Clinical Investigators, Guidance for Clinical Investigators, Industry, and FDA Staff, 5/24/2011

This guidance is intended to assist clinical investigators, industry, and FDA staff in interpreting and complying with the regulations governing financial disclosure by clinical investigators, 21 CFR part 54. This document is a revision of the Guidance for Industry: Financial Disclosure by Clinical Investigators dated March 20, 2001.

4.4.2.6 Proposed Rule - Disqualification of a Clinical Investigator, 04/13/2011

The proposed rule will amend the regulations to expand the scope of clinical investigator disqualification.

4.4.2.7 Electronic Source Documentation in Clinical Investigations, Guidance for Industry (Draft), 1/7/2011

This document provides guidance to sponsors, contract research organizations (CROs), data management centers, and clinical investigators on capturing, using, and archiving electronic data in FDA-regulated clinical investigations. This guidance is intended to ensure the reliability, quality, integrity, and traceability of electronic source data and source records maintained at the site for FDA inspection.

4.4.2.8 Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND, 10/14/2010

This guidance is intended to assist clinical investigators, sponsors, and sponsor-investigators in determining whether human research studies must be conducted under an investigational new drug application (IND), as described in Title 21 of the Code of Federal Regulations, part 312 (21 CFR part 312) (the IND regulations).

⁷ OHRP: Office for Human Research Protections

4.4.2.9 **Proposed rule - Reporting Information Regarding Falsification of Data, 2/19/2010**

The proposed rule will require sponsors to report information indicating that any person has, or may have, engaged in the falsification of data involving studies including, but not limited to, clinical investigations, nonclinical laboratory studies, and clinical studies in animals.

4.4.2.10 **Notice of Availability (1/27/04)**

FDA published a Notice of Availability (1/27/04)-announcing the availability of a draft guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions". FDA is revising its March 2002 guidance for industry of the same title to include guidance for sponsors who will be submitting information required by the Best Pharmaceuticals for Children Act.

4.4.3 **FDA Guidance for Industry: Computerized Systems [20]**

FDA CSUCI: Computerized Systems Used in Clinical Investigations (May 2007) [20]. Although this guidance is concerned with the use of computer systems for clinical trials submitted to the FDA, it provides a standard for all types of computer use in clinical investigations. This document provides guidance about computerized systems that are used to create, modify, maintain, archive, retrieve, or transmit clinical data required to be submitted to the FDA. Because these data form the basis for the FDA's decisions of the safety and effectiveness of new human and animal drugs, biological products, medical devices, and certain food additives, they are of high importance.

This document provides to sponsors, contract research organizations (CROs), data management centers, clinical investigators, and institutional review boards (IRBs), recommendations regarding the use of computerized systems in clinical investigations. Because the source data of clinical trials are necessary for the reconstruction and evaluation of the study to determine the safety of food and color additives and safety and effectiveness of new human and animal drugs, and medical devices, this guidance is intended to assist in ensuring confidence in the reliability, quality, and integrity of electronic source data and source documentation (i.e., electronic records). The guidance supplements the guidance for industry on Part 11, Electronic Records; Electronic Signatures - Scope and Application⁸.

The guidance formulates several general principles. The most important are: (1) each study protocol should identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data; (2) for each study, documentation should identify what software and, if known, what hardware is to be used in computerized systems that create, modify, maintain, archive, retrieve, or transmit data. This documentation should be retained as part of study records; (3) source documents should be retained to enable a reconstruction and evaluation of the trial; (4) when original observations are entered directly into a computerized system, the electronic record is the source document; (5) the design of a computerized system should ensure that all applicable regulatory requirements for recordkeeping and record retention in clinical trials are met with the same degree of confidence as is provided with paper system; (6) clinical investigators should retain either the original or a certified copy of all source documents sent to a sponsor or contract research organization, including query resolution correspondence; et.al.

⁸ 21 CFR Part 11: Electronic Records; Electronic Signatures. Final Rule Electronic Submissions; Establishment of Public Docket; Notice. Federal Register, Vol. 62, No. 54, Thursday, March 20, 1997

5 Clinical trials with medical devices

5.1 International

There exist several norms for ISO compliant software development processes: ISO 13485 (Medical Device Quality Management System), ISO 14971 (Medical Devices, Application of Risk Management to Medical Devices), IEC 62304 (Harmonized Standard for Medical Device Software), CMMI Level II Capability Maturity Model Integration. In addition, FDA CFR 820.30 (Design Controls) demands that each manufacturer of any class III or class II device, and the class I devices listed in paragraph (a)(2) shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met. Because these regulations have little to do with international aspects of clinical trials they will not be discussed in more detail.

5.1.1 EN ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good Clinical Practice" [21]

ISO 14155:2011 addresses Good Clinical Practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. The principles in this document also apply to all other clinical investigations and should be followed as far as possible, depending on the nature of the clinical investigation and the requirements of national regulations. General requirements are specified that protect the rights, safety and well-being of human subjects, ensure the scientific conduct of the clinical investigation and the credibility of the results, define the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices. ISO 14155:2011 does not apply to in vitro diagnostic medical devices.

5.2 Europe

5.2.1 EU Directive 2007/47/EG [22]

This directive is amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market. According to this directive a medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: (1) diagnosis, prevention, monitoring, treatment or alleviation of disease; (2) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, (3) investigation, replacement or modification of the anatomy or of a physiological process; (4) control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

5.3 US Device Regulation

Most of FDA's medical device and radiation-emitting product regulations are in Title 21 CFR Parts 800-1299 [23]. These final regulations codified in the CFR cover various aspects of design, clinical evaluation, manufacturing, packaging, labeling and post market surveillance of medical devices.

The Center for Devices and Radiological Health (CDRH) at the FDA is responsible for regulating firms who manufacture, repackaging, relabel, and/or import medical devices sold in

the United States. In addition, it regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions. According to the regulations, medical devices are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval.

5.4 Code of Federal Regulations (CFR) concerning medical devices

5.4.1 Establishment Registration (21 CFR Part 807)

Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by FDA.

5.4.2 Medical Device Listing (21CFR Part 807)

Manufacturers must list their devices with the FDA. Establishments required to list their devices include manufacturers, contract manufacturers that commercially distribute the device, contract sterilizers that commercially distribute the device, repackagers and relabelers, specification developers, etc.

5.4.3 Premarket Notification 510(k) (21 CFR Part 807 Subpart E)

If the device requires the submission of a Premarket Notification 510(k), one cannot commercially distribute the device until one receives a letter of substantial equivalence from FDA authorizing to do so. A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent.

5.4.4 Premarket Approval (PMA) (21 CFR Part 814)

Products requiring PMAs are Class III devices are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process.

5.4.5 Investigational Device Exemption (IDE) (21CFR Part 812)

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA.

Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with devices of non-significant risk must be approved by the IRB only before the study can begin.

5.4.6 Quality System Regulation (QS)/Good Manufacturing Practices (GMP) (21 CFR Part 820)

The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labelling, storing, installing and servicing of medical devices.

5.4.7 Labelling (21 CFR Part 801)

Labelling includes labels on the device as well as descriptive and informational literature that accompanies the device.

5.4.8 Medical Device Reporting (21 CFR Part 803)

Incidents in which a device may have caused or contributed to a death or serious injury must to be reported to FDA under the Medical Device Reporting program. In addition, certain malfunctions must also be reported.

6 Guidances concerning information security and source data in clinical trials

6.1 International

This area is covered mostly by ISO norms and several guidance documents.

6.1.1 ISO 27001: Information Security [24]

ISO 27001, entitled "Information Security Management - Specification with Guidance for Use", is the replacement for the original document, BS7799-2. It is intended to provide the foundation for third party audit, and is 'harmonized' with other management standards, such as ISO 9001 and ISO 14001. The basic objective of the standard is to help establish and maintain an effective information management system, using a continual improvement approach. It implements OECD (Organization for Economic Cooperation and Development) principles, governing security of information and network systems. Being a formal specification means that it mandates specific requirements. Therefore, organizations that have adopted ISO/IEC 27001 can therefore be audited and receive a certificate of compliance with the standard.

6.2 Europe

6.2.1 GCP Inspectors Group: Reflection paper on expectations for electronic source documents used in clinical trials [25]

This reflection paper on expectations for electronic source documents has become effective on 1 August 2010. It sets out the current thinking of the EU GCP Inspectors Working Group on the use of electronic source documents and data in clinical trials and on the inspection of these. The document is based around the 12 user requirements stated in the CDISC⁹ document on electronic source records¹⁰. The paper describes that source data and source documents form a cornerstone of the approach to record keeping in clinical trials conducted in accordance with GCP. With increasing use of information technology in pharmaceutical development there is a need to have clear guidance on the use of electronic source data and principles that should apply to them. This is necessary in order to ensure that the processes can be used and accepted with confidence when such requirements are met, and that the benefits that these systems offer can be fully utilized.

6.2.2 EudraLex Vol 4, GMP Annex 11 [26]

EudraLex: The Rules Governing Medicinal Products in the European Union. Volume 4 - Good Manufacturing Practice, Medicinal products for human and veterinary use. Annex 11 - Revision 1 issued January 2011 and came into effect on 30 June 2011.

This document has come into operation on 30 June 2011. Annex 11 applies to all forms of computerised systems used as part of GMP regulated activities. A computerised system is a set of software and hardware components which together fulfil certain functionalities. The application should be validated; IT infrastructure should be qualified. Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality. Especially the document describes requirements for the system validation: (1) validation documentation and reports should cover the relevant steps of the life cycle and manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment; (2) validation documentation should include change control records (if applicable) and reports on any

⁹ CDISC: Clinical Data Interchange Standards Consortium, <http://www.cdisc.org/site/index.php>

¹⁰ Electronic Source Data Interchange (eSDI) Group: Leveraging the CDISC Standards to facilitate the use of Electronic Source Data within Clinical Trials. Version 1 (2006).

deviations observed during the validation process. (3) User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. (4) User requirements should be traceable throughout the life-cycle. (5) In addition, the regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.

6.3 Regulations and guidance for paediatric clinical trials

Paediatric clinical study results may be submitted in one of four formats: (1) spreadsheet with trial result information in EMA-determined fields; (2) clinical study report; (3) synopsis in accordance with the ICH E3 guidance in PDF format; (4) complete published with a declaration that the submission complies with the terms of the owner's copyright. All paediatric clinical trial results data for nationally and EMA ("centrally authorized") active substances will become available to the general public through the EMA's website as part of an interim publication before the release of the results database (EudraCT Version 9), which might occur in late 2012 [27].

A paediatric investigation plan (PIP) is a development plan aimed at ensuring that the necessary data are obtained through studies in children, when it is safe to do so, to support the authorisation of a medicine for children. Pharmaceutical companies submit proposals for PIPs to the European Medicines Agency's Paediatric Committee (PDCO). This Committee is responsible for agreeing or refusing the plan. The Paediatric Regulation requires these plans to be submitted to the Agency early, wherever possible.

In general, the normal development of a medicine requires that various studies be performed to ensure its quality, safety and efficacy. The development plan can be modified at a later stage, as knowledge increases. Modifications can also be made if the applicant encounters such difficulties with the implementation of the plan, which render it unworkable or no longer appropriate.

6.3.1 Regulation (EC) No 1901/2006 (12 December 2006) on medicinal products for paediatric use [28]

Considerable problems result from the absence of suitably adapted medicinal products for children, including inadequate dosage information which leads to increased risks of adverse reactions, ineffective treatment through under-dosage, non-availability to the paediatric population of therapeutic advances, lack of suitable formulations and routes of administration and others.

This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.

Any concerns about conducting trials in the paediatric population should be balanced by the ethical concerns about giving medicinal products to a population in which they have not been appropriately tested.

6.3.2 Regulation (EC) No 1902/2006 (20 December 2006) amending Regulation 1901/2006 on medicinal products for paediatric use. [29]

This regulation represents only a short amendment. At the Agency's request, the Commission may impose financial penalties for infringement of the provisions of this

Regulation or the implementing measures adopted pursuant to it in relation to medicinal products authorised through the procedure laid down in Regulation (EC) No 726/2004

6.3.3 European Commission: Communication from the commission regarding the guideline on the data fields contained in the clinical trials database [30]

Taking into consideration that the EudraCT database is only accessible to the competent authorities of the Member States and the European Medicines Agency in order to ensure that the confidentiality of the data is strictly observed and to protect the legitimate interests of sponsors, the information to be made publicly available keeps the balance between this principle and the need to inform the public in the interests of public health and transparency.

6.3.4 European Commission: Communication from the commission— guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) [31]

This guidance sets out the nature of the information to be entered into EudraCT, the information to be made accessible to the public, the paediatric clinical trial results to be submitted and made public and on the responsibilities of the EMEA and related tasks in this context. (for further guidance documents see list Vol 10, annex).

The nature of the required information to be entered into EudraCT is based on its importance to clinical trials contained in an agreed PIP. Two sets of information are required:

- paediatric trial protocol related information: supplied prior to the start of the trial and updated if needed during the trial describing the trial protocol, investigational medicinal products (IMPs), therapeutic indication, trial population, the trial authorisation and the current status of the trial
- paediatric trial results related information: supplied after the completion of the trial and containing a summary of the results and conclusions

7 Data protection

7.1 International

Scientists and healthcare professionals use patient data for research of the causes of diseases and to formulate possible treatments, as well as in studies of the efficacy of medicines and equipment used in patient care. Medical records are still mostly paper-based or held on computer systems that only support limited information transfer. Personal and medical information is also collected for databases such as disease registers, which record and analyse all cases of a particular disease. Population databanks containing large sources of medical data from particular groups of people additionally exist for the purpose of research.

In clinical trials data from patients who consented to participate in a clinical trial, is collected by the investigator in Case Report Forms (CRF). The identity of patients is usually not disclosed in the CRF; their names are replaced by for example an alphanumeric code. The CRF (study database) is shared with the ‘sponsor’ of the study, often a pharmaceutical company, for further review and statistical analysis. In international trials sponsor and investigators are located in different countries and are subject to different national regulations for data protection. The Declaration of Helsinki [9] contains already some requirements for data protection and privacy: it is the duty of physicians who participate in medical research not only to protect the life, health, dignity, integrity of the patient, but also to protect, privacy, and confidentiality of personal information of research subjects. Concerning data protection, it is stated that every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

7.2 EU

In the EU personal data can only be gathered legally under strict conditions, for a legitimate purpose. Furthermore, persons or organisations which collect and manage personal information must protect it from misuse and must respect certain rights of the data owners. Therefore, common EU rules have been established to ensure that personal data have a high standard of protection. On the other hand, to remove potential obstacles to the flow of personal data and to ensure a high level of protection within the EU, national data protection legislation has been harmonised between EU countries. In addition, the Commission also engages in dialogue with non-EU countries to achieve a high level of protection of individuals when exporting personal data to those countries and negotiates international agreements to safeguard the rights of individuals in case their personal data are transferred to third countries.

7.2.1 EU Directive 95/46/EC on the protection of personal data [32]

Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Directive 95/46/EC is the reference text, at European level, on the protection of personal data. It sets up a regulatory framework which tries to find a balance between a high level of protection for the privacy of individuals and the free movement of personal data within the European Union. The Directive sets strict limits on the collection and use of personal data and demands that each Member State set up an independent national body responsible for the protection of these data.

This directive applies to the processing of personal data wholly or partly by automatic means, and to the processing otherwise than by automatic means of personal data which form part of a filing system or are intended to form part of a filing system. It aims to protect fundamental rights and freedom of natural persons and in particular their right to privacy with respect to the processing of personal data. The Directive does not deal with medical

research explicitly. Its implications for the processing of personal data for medical research must be inferred from the information about the general processing of personal data, especially sensitive personal data, and about data processing for research and statistics. For this reason, the directive does not mention medical research specifically unless this can be done without distorting the provisions of the Directive. The Directive defines 'personal data' as: "shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity". With the 'data subject's consent' the data subject signifies his agreement to personal data relating to him being processed.

Article 7 states that personal data may be processed only if: (1) the data subject has unambiguously given his consent; (2) processing is necessary for the performance of a contract to which the data subject is party or in order to take steps at the request of the data subject prior to entering into a contract; (3) processing is necessary for compliance with a legal obligation to which the controller is subject; (4) processing is necessary in order to protect the vital interests of the data subject; (5) processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller or in a third party to whom the data are disclosed; (6) processing is necessary for the purposes of the legitimate interests pursued by the controller or by the third party or parties to whom the data are disclosed, except where such interests are overridden by the interests for fundamental rights and freedoms of the data subject which require protection under Article 1.

7.2.2 EU Directive 2002/58/EC. 12 July 2002. Concerning the processing of personal data and the protection of privacy in the electronic communications sector [33]

The Directive is based on the fact that "the Internet is overturning traditional market structures by providing a common, global infrastructure for the delivery of a wide range of electronic communications services. Publicly available electronic communications services over the Internet open new possibilities for users but also new risks for their personal data and privacy". Therefore, the use of information and communication technologies (ICT), and in particular the Internet and electronic messaging services, call for specific requirements to ensure that users have a right to privacy. This Directive contains provisions that are crucial to ensuring that users can trust the services and technologies they use for communicating electronically. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data requires Member States to ensure the rights and freedoms of natural persons with regard to the processing of personal data, and in particular their right to privacy, in order to ensure the free flow of personal data in the Community. This Directive seeks to respect the fundamental rights and observes the principles recognised in particular by the Charter of fundamental rights of the European Union. In particular, this Directive seeks to ensure full respect for the rights set out in Articles 7 and 8 of that Charter. Confidentiality of communications is guaranteed in accordance with the international instruments relating to human rights, in particular the European Convention for the Protection of Human Rights and Fundamental Freedoms, and the constitutions of the Member States. In the electronic communications sector, Directive 95/46/EC applies in particular to all matters concerning protection of fundamental rights and freedoms, which are not specifically covered by the provisions of this Directive, including the obligations on the controller and the rights of individuals. Directive 95/46/EC applies to non-public communications services.

The provider of an electronic communications service must protect the security of its services by: (1) ensuring personal data is accessed by authorised persons only; (2) protecting personal data from being destroyed, lost or accidentally altered; (3) ensuring the implementation of a security policy on the processing of personal data. In the case of an

infringement of personal data, the service provider has to inform the person concerned, as well as the National Regulatory Authority (NRA).

7.2.3 EU Directive 2006/24/EC. 15 March 2006. On the retention of data generated or processed in connection with the provision of publicly available electronic communications services or of public communications networks and amending [34]

Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data requires Member States to protect the rights and freedoms of natural persons with regard to the processing of personal data, and in particular their right to privacy, in order to ensure the free flow of personal data in the Community. Several Member States have adopted legislation providing for the retention of data by service providers for the prevention, investigation, detection, and prosecution of criminal offences. Those national provisions vary considerably. The legal and technical differences between national provisions concerning the retention of data for the purpose of prevention, investigation, detection and prosecution of criminal offences present obstacles to the internal market for electronic communications, since service providers are faced with different requirements regarding the types of traffic and location data to be retained and the conditions and periods of retention. This Directive relates only to data generated or processed as a consequence of a communication or a communication service and does not relate to data that are the content of the information communicated. Data should be retained in such a way as to avoid their being retained more than once. Data generated or processed when supplying the communications services concerned refers to data which are accessible. In particular, as regards the retention of data relating to Internet e-mail and Internet telephony, the obligation to retain data may apply only in respect of data from the providers' or the network providers' own services.

7.2.4 Regulation EC 45/2001. 18 December 2000. On the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data [35]

Regulation (EC) 45/2001 is based on the insight that regulation is necessary to provide the individual with legally enforceable rights, to specify the data processing obligations of the controllers within the Community institutions and bodies, and to create an independent supervisory authority responsible for monitoring the processing of personal data by the Community institutions and bodies.

Article 286 of the Treaty requires the application to the Community institutions and bodies of the Community acts on the protection of individuals with regard to the processing of personal data and the free movement of such data. A fully-fledged system of protection of personal data not only require the establishment of rights for data subjects and obligations for those who process personal data, but also appropriate sanctions for offenders and monitoring by an independent supervisory body. The persons to be protected are those whose personal data are processed by Community institutions or bodies in any context whatsoever, for example because they are employed by those institutions or bodies. The principles of data protection should apply to any information concerning an identified or identifiable person. To determine whether a person is identifiable, all means likely to be reasonably used either by the controller or by any other person to identify the said person should be taken into account. The principles of protection should not apply to data rendered anonymous in such a way that the data subject is no longer identifiable.

Following requirement is important for defining identifiability: “the principles of data protection should apply to any information concerning an identified or identifiable person”.

7.2.5 EC Directive 97/66/EC. 15 December 1997. Concerning the processing of personal data and the protection of privacy in the telecommunications sector [36]

Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data requires Member States to ensure the rights and freedoms of natural persons with regard to the processing of personal data, and in particular their right to privacy, in order to ensure the free flow of personal data in the Community. Confidentiality of communications is guaranteed in accordance with the international instruments relating to human rights (in particular the European Convention for the Protection of Human Rights and Fundamental Freedoms) and the constitutions of the Member States. Currently in the Community new advanced digital technologies are introduced in public telecommunications networks, which give rise to specific requirements concerning protection of personal data and privacy of the user. The development of the information society is characterized by the introduction of new telecommunications services. This Directive provides for the harmonisation of the provisions of the Member States required to ensure an equivalent level of protection of fundamental rights and freedoms, and in particular the right to privacy, with respect to the processing of personal data in the telecommunications sector and to ensure the free movement of such data and of telecommunications equipment and services in the Community. It also applies to the processing of personal data in connection with the provision of publicly available telecommunications services in public telecommunications networks in the Community, in particular via the Integrated Services Digital Network (ISDN) and public digital mobile networks.

7.3 US

7.3.1 HIPAA (Health Insurance Portability and Accountability Act of 1996) [37]

HIPAA defines health information as "any information, whether oral or recorded in any form or medium" that "is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse"; and "relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual."

Title I of HIPAA regulates the availability and breadth of group health plans and individual health insurance policies. It amended the Employee Retirement Income Security Act, the Public Health Service Act, and the Internal Revenue Code. HIPAA Title II defines numerous offenses relating to health care and sets civil and criminal penalties for them. It also creates several programs to control fraud and abuse within the health care system. The HIPAA Privacy Rule regulates the use and disclosure of Protected Health Information (PHI) held by "covered entities" (generally, health care clearinghouses, employer sponsored health plans, health insurers, and medical service providers). The Department of Health and Human Services extended the HIPAA privacy rule to independent contractors of covered entities who fit within the definition of "business associates". PHI is any information held by a covered entity which concerns health status, provision of health care, or payment for health care that can be linked to an individual. This is interpreted rather broadly and includes any part of an individual's medical record or payment history. Covered entities must disclose PHI to the individual within 30 days upon request and they must disclose PHI when required to do so by law.

The term 'individually identifiable health information' means according to HIPAA any information, including demographic information collected from an individual, that (1) is created or received by a health care provider, health plan, employer, or health care

clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual, the provision of health care to an individual, or the past, present, or future payment for the provision of health care to an individual, and identifies the individual; or with respect to which there is a reasonable basis to believe that the information can be used to identify the individual.

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes [38]. Research is defined in the Privacy Rule as, “a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.” A covered entity may always use or disclose for research purposes health information which has been de-identified (in accordance with 45 CFR 164.502(d), and 164.514(a)-(c) of the Rule) without regard to the provisions below. The following three criteria must be satisfied for an IRB or Privacy Board to approve a waiver of authorization under the Privacy Rule: (1) The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements: an adequate plan to protect the identifiers from improper use and disclosure; an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart; (2) the research could not practicably be conducted without the waiver or alteration; and (3) the research could not practicably be conducted without access to and use of the protected health information.

8 Biobanks

8.1 International

Biobanks are institutions which store human cells and tissues for a diverse range of research projects. This covers the simple storage of collections of biomaterial and biobanks that foster research and allow the international exchange of materials. It is essential for the common purpose of biobanks to define mutual harmonised ethical and legal standards for extraction, storage and exchange of human cells, tissues and accompanying data.

Personal data and genetic data have a special importance in ethics and law. Therefore, the transfer of cells and tissues not only concerns aspects of property, but also aspects of the right to privacy and the right to determine who should have access to special information about the state of a patient's body. For example, the German National Ethics Counsel accepts the use of tissues and cells for biomedical research without the informed consent of the concerned patient, if the tissue is anonymized. Today, research often includes data on genetic dispositions and results of genetic examinations of cells and tissues. This poses the question of standards for the pseudonymisation and anonymisation of data in medical research, but also of privacy and control of personal data. This is of special relevance in international research projects with institutions in other countries (EU and non-EU). The existence of different privacy standards in a clinical trials should be taken seriously, because it may lead to misuse of personal genetic data and represent a potential barrier for international research cooperation. Several different laws and regulations, mostly on the national level like the Biobank Act, Personal Data Act, and Ethical Review Act control the activities at biobanks and the handling of samples. Normally all research using human biological samples requires an ethical approval. On the international level, several guidelines exist.

8.1.1 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention of Human Rights and Biomedicine [39]

Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. Each Party shall take in its internal law the necessary measures to give effect to the provisions of this Convention.

Primacy of the human being: the interests and welfare of the human being shall prevail over the sole interest of society or science. Equitable access to health care: parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality. Professional standards: any intervention in the health field, including research, must be carried out in accordance with relevant professional obligations and standards.

General rule: an intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time.

8.1.2 Steering Committee on Bioethics (CDBI) Draft Explanatory Memorandum to the Draft Recommendation on Research on Biological Materials of Human Origin (Strasbourg, March 15, 2006) [40]

This committee is stressing that research is often trans-disciplinary and international; and has to take into account the current and planned development of collections and banks of biological materials at national levels.

Member states should protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity, right to private life and other rights and fundamental freedoms with regard to any research governed by this recommendation. The recommendations apply to the full range of research activities in the health field involving the removal of biological materials of human origin to be stored for research use. It also applies to the full range of research activities in the health field involving the use of biological materials of human origin that were removed for a purpose other than that mentioned in the previous paragraph; this includes material removed for a previous research project.

Identifiable biological materials are those biological materials which, alone or in combination with associated data, allow the identification of the persons concerned either directly or through the use of a code. In the latter case, the user of the biological materials may either: (1) have access to the code: the materials are hereafter referred to as “coded materials”; or (2) not have access to the code, which is under the control of a third party: the material are hereafter referred to as “linked anonymised materials”. Non-identifiable biological materials, hereafter referred to as “unlinked anonymised materials”, are those biological materials which, alone or in combination with associated data, do not allow, with reasonable efforts, the identification of the persons concerned.

8.1.3 Recommendation Rec (2006) of the Committee of Ministers to member states on research on biological materials of human origin (Strasbourg, 2006) [41]

Object of this recommendation is that member states should protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity, right to private life and other rights and fundamental freedoms with regard to any research governed by this recommendation.

8.1.4 International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS) [42]

This is the third in the series of international ethical guidelines for biomedical research involving human subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) since 1982. Its scope and preparation reflect well the transformation that has occurred in the field of research ethics in the almost quarter century since CIOMS first undertook to make this contribution to medical sciences and the ethics of research.

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee. Provisions should be made to ensure respect for the privacy of subjects and for the confidentiality of records in which subjects are identified. Whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed

8.2 EU

8.2.1 EU Directive 2002/98/EU on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood [43]

This Directive shall apply to the collection and testing of human blood and blood components, whatever their intended purpose, and to their processing, storage, and distribution when intended for transfusion. Where blood and blood components are collected and tested for the sole purpose and exclusive use in autologous transfusion and are clearly identified as such, ... Personnel directly involved in the collection, testing, processing, storage and distribution of blood and blood components need to be appropriately qualified and provided with timely and relevant training, without prejudice to existing Community legislation on the recognition of professional qualifications and on the protection of workers.

8.2.2 Ethical, legal and social implications of genetic testing: Research development and clinical applications (EC: Brussels, 2004) [44]

The report's first two chapters summarise the main points of the state of the art, the views of the various stakeholders, and public perceptions. Chapters 3 to 5 report the current views and the positions of the Group on the specific topics that were discussed – public dialogue, the position of genetic data among all medical information, issues related to gender and ethnicity, 'biobanks' as research tools, and the development of pharmacogenetics. Chapters 6 to 8 address research and development of genetic tests, their clinical implementation and use, and the impact of medical genetic testing on healthcare systems. They underline the challenges, needs and duties of test developers, public health authorities, clinicians and genetic counsellors, and of individuals undergoing genetic testing. Chapter 9 is devoted to the Group's reflections on its own work and its experience of the dialogue. 25 recommendations were developed. These recommendations encompass a 'code of conduct' applicable to any actor in the field but, where possible, seek more specifically to be considered an "action plan for genetic testing" to be implemented by policy-makers. They are organised into three main chapters: general framework, implementation of genetic testing in healthcare systems, and genetic testing as a research tool.

8.2.3 EU Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, 31 March 2004 [41]

This Directive applies to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications. Where such manufactured products are covered by other directives, this Directive shall apply only to donation, procurement and testing. This Directive shall not apply to: (1) tissues and cells used as an autologous graft within the same surgical procedure; (2) blood and blood components as defined by Directive 2002/98/EC; (3) organs or parts of organs if it is their function to be used for the same purpose as the entire organ in the human body.

8.2.4 EU Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing,

preservation, storage and distribution of human tissues and cells, 24 October 2006 [46]

This Directive shall apply to the coding, processing, preservation, storage and distribution of: (1) human tissues and cells intended for human applications; and (2) manufactured products derived from human tissues and cells intended for human applications, where those products are not covered by other directives. The important term "traceability" is defined by "the ability to locate and identify the tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the tissue/cells, and the ability to identify the recipient(s) at the medical facility/facilities applying the tissue/cells to the recipient(s); traceability also covers the ability to locate and identify all relevant data relating to products and materials coming into contact with those tissues/cells".

8.3 US

Three sections of US federal law primarily govern human subject research and associated patient data. Federal regulatory law referred to as the Common Rule requires that researchers obtain informed consent from donors for collecting, storing and using their tissue for research purposes. An exception applies if an IRB determines that (1) the research involves no more than minimal risk to the subjects; (2) the waiver will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The FDA has a separate system designed to protect the rights of human subjects for FDA-regulated clinical investigations. The HIPAA Privacy Rule governs research use of protected health information (PHI) such as names, social security numbers, and medical record information that is associated with tissue samples. A researcher bound by the Privacy Rule cannot disclose an individual's PHI without obtaining an authorization unless the researcher has de-identified the data by removing most of the personal information or uses a limited data set without any direct identifiers.

8.3.1 OHRP¹¹ Guidance on Research Involving Coded Private Information or Biological Specimens [47]

This document applies to research involving coded private information or human biological specimens (hereafter referred to as "specimens") that is conducted or supported by HHS¹². This document provides guidance as to when research involving coded private information or specimens is or is not research involving human subjects, as defined under HHS regulations for the protection of human research subjects (45 CFR part 46) and reaffirms OHRP policy that, under certain limited conditions, research involving only coded private information or specimens is not human subjects research. It clarifies the distinction between (1) research involving coded private information or specimens that does not involve human subjects and (2) human subject research that is exempt from the requirements of the HHS regulations.

The term "coded" means that: (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

¹¹ Office for Human Research Protections

¹² U.S. Department of Health and Human Services

9 Regulation and guidances for clinical trials for advanced therapies and innovative medical products

Personalised medicine as conducted in p-medicine trials can belong to the development of innovative medical products or the evaluation of advanced therapies. To this area belongs for example the co-development of diagnostics and drugs. These co-developed diagnostics guide the investigator to these patients that will be more likely to benefit from the drug. In this context the FDA is developing guidance documents that cover strategies for clinical trial design and regulatory considerations for co-developing a novel companion diagnostic and therapy simultaneously. This includes also the use of biomarkers for patient selection and screening for clinical trials.

9.1 EU

9.1.1 Detailed guidelines on good clinical practice specific to advanced therapy medicinal products, ENTR/F/2/SF/dn D(2009) 35810, Brussels, 03/12/2009 [48]

These guidelines address specific issues related to Good Clinical Practice for clinical trials involving advanced therapy medicinal products. These guideline supplements the principles set out in the Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use in general. It demands for advanced therapy medicinal products, that apart from the sponsor, investigator and manufacturer/importer, other actors have to be considered, including tissue/blood establishments, procurement organisations, animal facilities and donors. It is important to put the role of these parties, and the applicable legislation, in the context of the roles and responsibilities for clinical trials.

Subjects should be followed-up during and, if necessary, after the end of the clinical trial both for their own care and to allow data collection as needed. Where an advanced therapy medicinal product contains human cells or tissues, the sponsor of the trial, the manufacturer and the investigator/institution where the product is used should ensure that there is a traceability system in place complementary to, and compatible with, the requirements laid down in the Directives. The traceability procedures and the documentation process should be described in the clinical trial protocol and amended as needed. As regards the keeping of records, the rules as set out in Directive 2001/20/EC and 2005/28/EC apply. The traceability records should be kept for a minimum of 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorization or by the agreement with the sponsor.

9.1.2 EU Directive 2009/120/EC. 14 September 2009. On the Community code relating to medicinal products for human use as regards advanced therapy medicinal products [49]

This directive is concerned with advanced therapy products that are submitted for market authorisation and therefore may be not important for p-medicine. Due to scientific and technical progress in the field of advanced therapies, as reflected in Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, it is appropriate to adapt Annex I. The definitions and detailed scientific and technical requirements for gene therapy medicinal products and somatic cell therapy medicinal products should be updated. Moreover, detailed scientific and technical requirements should be established for tissue engineered products, as well as for advanced therapy medicinal product containing devices and combined advanced therapy medicinal products. Marketing authorisation applications for advanced therapy medicinal products shall

follow specific format requirements (Modules 1, 2, 3, 4 and 5) described in Part I of the Annex.

It is important that due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application. The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used in vivo, the level of integration of nucleic acids sequences or genes into the genome, and others.

9.1.3 Qualification of novel methodologies for drug development: Guidance to applicants. EMEA/CHMP/SAWP/72894/2008 Corr1 [50]

The EMA has established a qualification process for drug development. This process is a new, voluntary, scientific pathway leading to either a CHMP¹³ opinion or a scientific advice on innovative methods or drug development tools: 1. CHMP Qualification Opinion on the acceptability of a specific use of the proposed method (e.g. use of a novel methodology or an imaging method) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data; 2. CHMP Qualification Advice on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted.

Scope of this guidance is a qualification process that addresses innovative drug development methods and tools. It will focus on the use of novel methodologies developed by consortia, networks, public/private partnerships, learned societies and pharmaceutical industry for a specific intended use in pharmaceuticals R&D.

9.1.4 Reflection paper on the use of genomics in cardiovascular clinical intervention trials. EMEA/CHMP/PGxWP/278789/2006 [51]

The paper reviews scientific matters concerning the use of genomic data in assessing therapeutic efficacy and tolerance of drugs in cardiovascular clinical intervention trials, focusing on genetic association with clinical endpoints. Taking into consideration genetic issues in the design of such trials is perceived as potentially very important for improving their outcome and may be important not only for cardiovascular trials, but also for other areas.

9.1.5 General principles: Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement [52]

This document explains how the FDA and the EMEA will process requests for Joint FDA/EMEA voluntary genomic data submission (VGDS) briefing meetings. The FDA and the EMEA issued Guidance for Industry: Pharmacogenomic Data Submissions and Guideline on Pharmacogenetics Briefing Meetings, respectively. Both documents encourage the voluntary submission of genomic data by the sponsors to the Agencies.

¹³ COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

9.1.6 Final ICH Concept Paper for Topic E16: Pharmacogenomic (PG) Biomarker Qualification: Format and Data Standards [53]

This concept paper supports a proposal for a new harmonized ICH guideline on important aspects for the qualification of PG biomarkers. In particular, this new guideline will provide recommendations on the collection of data to support the qualification of PG biomarkers, including (1) how to define the qualification context and the claims for intended use, (2) standard methods for data collection, and (3) formats for submission of data to regulatory authorities.

9.1.7 Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development [54]

A genomic biomarker (PGBM) is a measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions. The scope of this paper is the co-development of a new PGBM and the relevant assay(s) in the context of either a drug development or for qualification purposes. It includes assessing drug-response (toxicity, PK/PD, dose-response, efficacy or adverse reactions), condition/disease and PGBM used for optimizing clinical trials design. The Qualification procedure for biomarkers development shall be considered in order to obtain scientific advice on Biomarker assays co-development. All processes related to sample and data handling and assay methodology are to be done in compliance with GLP and GCP standards and current guidelines as applicable.

9.1.8 Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection [55]

Development of genomic biomarkers (GBM) and diagnostic tests may involve the additional development of tests (so-called “companion diagnostics”) or specific kits to detect the presence or absence of the GBM. Issues relating to these topics are outside the scope of this reflection paper but a short discussion is included. Scope of this paper is to highlight key principles that should be considered by stakeholders with focus on use of GBM in relation to patient selection and associated issues with trial methodology. The principles are considered applicable to the development and validation of a GBM through the life cycle of a medicinal product, i.e., pre-authorisation and post-marketing stages. The main discussion will be related to drug development and use of the GBMS that predict drug response but many principles are applicable to GBMs that relate to prognosis as well.

9.2 US

9.2.1 Genomics and Personalized Medicine Act of 2006 [56]

This bill was submitted to congress but never became law. It defines personalized medicine as the application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a patient's predisposition to a particular disease or condition. The Secretary shall expand and accelerate research and programs to collect genetic and genomic data that will advance the field of genomics and personalized medicine, with prioritized focus on: (A) studies of diseases and health conditions with substantial public health impact; (B) population-based studies of genotype prevalence, gene-disease association, gene-drug response association, and gene-environment interactions; (C) systematic review and synthesis of the results of population-based studies using methods of human genome epidemiology; (D) translation of genomic information into molecular genetic screening tools, diagnostics, and therapeutics, through well-conducted clinical trials and studies; etc.

9.2.2 Genomics and Personalized Medicine Act of 2010 [57]

This bill was submitted to congress, but did not become law. It should secure the promise of personalized medicine for all Americans by expanding and accelerating genomics research and initiatives to improve the accuracy of disease diagnosis, increase the safety of drugs, and identify novel treatments, and for other purposes. It requires the Secretary of Health and Human Services (HHS) to establish the Office of Personalized Healthcare, the purpose of which shall be to coordinate HHS activities related to genomics and personalized medicine with those of other agencies and entities to ensure that personalized medicine meets the highest standards of safety, efficacy, and clinical validity and utility. Sets forth provisions related to the collection of genetic and genomic data, including providing for a national biobank. It directs the Secretary to: (1) improve genomics and personalized medicine training; (2) establish a committee to examine barriers to personalized medicine product development; and (3) review billing, coverage, and reimbursement methodologies for personalized medicine products and services; etc.

10 Pharmacovigilance legislation

10.1 EU

The new pharmacovigilance legislation (Regulation (EU) No 1235/2010 [58] and Directive 2010/84/EU [59]) was adopted by the European Parliament and European Council in December 2010. The legislation has significant implications for applicants and holders of European Union marketing authorisations. The legislation is effective from July 2012.

Marketing-authorisation applicants and holders will be impacted by the legislation in a number of key areas. The legislation aims to:

- make roles and responsibilities clear;
- minimise duplication of effort;
- free up resources by rationalising and simplifying adverse drug reaction (ADR) reporting and periodic safety update report (PSUR) reporting;
- establish a clear legal framework for post-authorisation monitoring.

Additional monitoring:

- PSURs will have a single assessment for the same active substance or a combination of active substances.
- Routine PSUR reporting is no longer necessary for products with low risk or for old or established products unless concerns arise.
- PSUR reporting will be electronic following the establishment of an EU repository. PSURs will be sent directly to the European Medicines Agency.
- There will be a strengthened legal basis for requesting post-authorisation safety and efficacy studies (PASS/PAES) from the pharmaceutical industry.
- Risk-management systems will be required for all newly authorised medicines.

10.2 Regulation (EU) No 1235/2010 [58]

Regulation (EC) No 726/2004 creates a Union-wide marketing authorisation procedure for certain categories of medicinal products (the ‘centralised procedure’), lays down rules for the pharmacovigilance of those products and establishes the European Medicines Agency. Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products for human use placed on the market, as the full safety profile of medicinal products for human use can be known only after they have been placed on the. In order to allow all competent authorities to receive, access and share pharmacovigilance information for medicinal products for human use authorised in the Union, the Eudravigilance database should be maintained and strengthened as the single point of receipt of such information. In order to increase transparency as regards pharmacovigilance issues, a European medicines web-portal should be created and maintained by the Agency.

10.3 Directive 2010/84/EU [59]

In the light of the experience acquired and following an assessment by the Commission of the Union system of pharmacovigilance, it has become clear that it is necessary to take measures in order to improve the operation of Union law on the pharmacovigilance of medicinal products. While the fundamental objective of the regulation of medicinal products is to safeguard public health, this aim should nevertheless be achieved by means that do not impede the free movement of safe medicinal products within the Union. It has emerged from the assessment of the Union system of pharmacovigilance that divergent actions by Member States in relation to safety issues pertaining to medicinal products are creating obstacles to the free movement of medicinal products. In order to prevent or eliminate those obstacles the existing pharmacovigilance provisions at Union level should be strengthened and

rationalised. It is necessary from a public health perspective to complement the data available at the time of authorisation with additional data about the safety and, in certain cases, the efficacy of authorised medicinal products.

10.4 Concept paper submitted on activities related to pharmacovigilance [60]

In September 2011, the European Commission published a concept paper [60] on implementing measures for the performance of activities related to pharmacovigilance for public consultation until 7 November 2011. The paper provides technical details that the European Medicines Agency, medicines regulatory authorities in European Union (EU) Member States and marketing-authorisation holders will need to apply when implementing the new legislation, including:

- pharmacovigilance system master files;
- the quality system for the performance of pharmacovigilance activities;
- the use of internationally agreed terminology, formats and standards;
- monitoring data in the EudraVigilance database;
- the electronic transmission of suspected adverse reactions;
- electronic periodic safety update reports and risk-management plans;
- post-authorisation safety studies.

10.5 ICH Guidelines for Safety

Safety guidance at ICH is under the Efficacy heading. It is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics / genomics techniques to produce better targeted medicines. The tripartite harmonised ICH Guideline was finalised under Step 4 in October 1994. This document gives standard definitions and terminology for key aspects of clinical safety reporting. It also gives guidance on mechanisms for handling expedited (rapid) reporting of adverse drug reactions in the investigational phase of drug development.

10.5.1 ICH Harmonised Tripartite Guideline on clinical safety data management: Definitions and standards for expedited reporting. [61]

10.5.2 ICH Harmonised Tripartite Guideline on clinical safety data management: Data elements for transmission [62]

10.5.3 Clinical Safety Data Management: Data elements for transmission [63]

In June 2011, the E2B (R3) Expert Working Group finalised the Step 2 ICH Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs), Data Elements and Message Specification which includes the key parts of the updated E2B(R3) Guideline. This document now enters the consultation period, Step 3 of the ICH Process.

10.5.4 ICH Harmonised Tripartite Guideline Pharmacovigilance Planning [64]

The tripartite harmonised ICH Guideline was finalised under Step 4 in November 2004. This Guideline is intended to aid in planning pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug (in this Guideline, the term "drug" denotes chemical entities, biotechnology-derived products, and vaccines). The main focus of this Guideline is on a Safety Specification and Pharmacovigilance Plan that might be submitted at the time of licence application. The main focus of this guideline is on a Safety

Specification and Pharmacovigilance Plan that might be submitted at the time of licence application. The guideline can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the Safety Specification and Pharmacovigilance Plan into the Common Technical Document (CTD).

10.5.5 Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports [65]

Databases should be routinely screened to detect and eliminate duplicate cases. This guideline proposes methods for detecting, confirming and managing duplicate cases suitable for organisations receiving pharmacovigilance data in various different formats.

10.6 VOLUME 9A of The Rules Governing Medicinal Products in the European Union [66]

Pharmacovigilance information in accordance with internationally agreed formats. In addition, the European Commission is also required to publish a reference to an internationally agreed medical terminology. This Volume 9A has therefore been prepared by the European Commission in close consultation with the Agency, Member States and interested parties and is specifically related to human pharmacovigilance. It brings together general guidance on the requirements, procedures, roles and activities in this field, for both Marketing Authorisation Holders and Competent Authorities of medicinal products for human use; it incorporates international agreements reached within the framework of the International Conference on Harmonisation (ICH).

Volume 9A is presented in four parts:

- Part I deals with Guidelines for Marketing Authorisation Holders
- Part II deals with Guidelines for Competent Authorities and the Agency
- Part III provides the Guidelines for the electronic exchange of pharmacovigilance in the EU
- Part IV provides Guidelines on pharmacovigilance communication

10.7 Implementation plan for the note for guidance Eudravigilance human - Processing of safety messages and Individual Case Safety Reports [67]

Scope of the Note for Guidance EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (Doc. Ref. EMEA/H/20665/04/Final, Revision 1). The scope of the revised Note for Guidance is to improve the quality and consistency of ICSRs reported electronically to EudraVigilance. This has been achieved by strengthening of the validation process of ICH E2B(R2) data elements and by making mandatory the population of certain ICH E2B(R2) data elements in the ICSRs. The improvement of the data quality is of major importance.

10.8 Detailed guidance on the collection, verification and presentation of adverse reaction reports [68]

The sponsor is responsible for the ongoing safety evaluation of the investigational medicinal product(s). The sponsor is responsible for the prompt notification to all concerned investigator(s), the Ethics Committee and competent authority of each concerned Member State of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

The sponsor is responsible for arranging systems and written standard operating procedures to ensure that the necessary quality standards are observed in every step of the case documentation, data collection, validation, evaluation, archiving and reporting.

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases. Individual adverse events should be evaluated by the investigator and where indicated by the guidance in section 5, they should be reported to the sponsor for evaluation. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

10.9 Regulations concerning aspects of Data Management Systems

10.9.1 Clinical trial Data Management Systems (CDMS) in trials with medicinal products

All CDMS and other software solutions used in clinical trials and processing patient data have to be GCP compliant. In addition, CDMS use has to comply with regulations like the ones for data protection. The regulatory framework related to Clinical Trial Data Management Systems (CDMS) is based on European regulations, Directives (that are transposed into national law), guidance for industry and other documents, such as EMA reflection papers. International guidelines, such as ICH E6 on Good Clinical Practice and also relevant USA regulations and guidance have also to be taken into consideration. Currently, no recognised industry standard for CDMS requirements is available. Nevertheless, specific requirements for CDMS are formulated in ICH E6 (R1), EU 2001/20/EC, EU 2005/268/EC, EU 95/46/EC, Eudralex, Vol. 10 and Vol. 4, Annex11, reflection paper of GCP Inspectors WG, FDA CRF (11), FDA Guidance Part 11, FDA CSUCI. These documents contain detailed requirements concerning audit trail, validation, data, storage, change and configuration management, electronic signature, archiving, etc., that needs to be taken into consideration, if CDMS are used in clinical trials with medicinal products. A detailed list of these requirements is available in Transform: Deliverable 3.2, Part A: Regulatory requirements, 31 March 2011.

Eudralex, Vol. 4, Annex 11 and ICH E6 require a system validation of CDMS before routine use in clinical trials. For computer system validation purposes a number of additional guidelines are in use for specific aspects of data management, like the PIC/S Guide [69] which defines requirements from the inspectors' point of view and the GAMP® guide [70] defining best practices for system validation. On the other hand, ISO standards cover only the general level of IT infrastructure aspects (e.g. ISO 27001, security management system) [24].

The ECRIN¹⁴ standard, which is aimed at academic clinical trial units, provides specific requirements with respect to validation [71]. A recent survey by ECRIN [72] has shown that data management in clinical trials performed by academic trial units still faces many difficulties (e.g. heterogeneity of software products, deficits in quality management, limited human and financial resources and complexity to run a local computer centre). Unfortunately, no specific, practical and open standard for both the GCP-compliant data management and the underlying IT-infrastructure is available. This provided the motivation for the "Working Group on Data Centres" of ECRIN has developed a standard specifying the requirements for high quality GCP-compliant data management in multinational clinical trials. The ECRIN standard lists 115 IT requirements, (15 sections), 107 DM requirements (12 sections) and 13 other requirements (2 sections). Sections IT01 to IT05 deal with the basic IT infrastructure, while IT06 and IT07 cover validation and local software development. IT08 to IT015 are concerned with aspects of IT systems that directly support clinical trial management processes. Sections DM01 to DM03 cover the implementation of a specific clinical data management application, for a specific trial, whilst DM04 to DM12 address data management of trials across the unit. There exist also several specific requirements: IN01 is dedicated to international aspects of clinical trials (e.g. translation of case report forms) and ST01 to the competence of a trials unit's staff (e.g. training). For each section requirements are organised as a list of individual requirements and a category: minimal requirement or best practice. The minimal requirements are mandatory to achieve full GCP compliance for the corresponding data centre. The ECRIN standard is used for the certification of ECRIN data centres. Best practice standards are not essential but have been included in the standard to provide a guide for data centres who want to improve their data management practices. Certification as an ECRIN data centre demonstrates not only compliance with regulations and standards, including GCP, but also compliance with recommendations of ECRIN data management,

¹⁴ European Clinical Research Infrastructures Networks

expertise of staff, and competence in managing data for international, multicentre clinical trials.

10.9.2 Regulations concerning the secondary use of data

Studies, which are based on analysis of existing data (secondary use) are non-interventional and therefore do not fall under the drug or medical device law. Here, rules and regulations on data protection and confidentiality and ethical rules have to be taken into consideration (e.g. EU Directive 95/46/EC). The Directive prohibits further processing of data that would be incompatible with the purpose the data was collected for. Consequently, the purpose for which genetic data and human tissue samples are collected and processed has to be specified clearly in the research project. Sensitive data, including data genetic data and any medical patient data, can be processed if the data subject has given explicit consent¹⁵ to the processing of those data. As a consequence, with respect to clinical trials and scientific research conducted within p-medicine, the processing of health data implies that the data subject has given his consent. This has to be covered by the informed consent procedure within clinical trials. Since clinico-genomic data are collected and used not only for specific research questions in one clinical trial, but also for future research projects, a specific model of consent referring to a purpose of intermediate scope (tiered consent) has been developed in the context of the previous ACGT¹⁶-project. This model should be updated and extended within the p-medicine project.

Of particular help in this process could be the report on regulatory requirements, confidentiality and data privacy issues developed within the EU-funded project TRANSFoRm (Translational Research and Patient Safety in Europe) [73]. The underlying concept of TRANSFoRm is to develop a ‘rapid learning healthcare system’ driven by advanced computational infrastructure that can improve both patient safety and the conduct and volume of clinical research in Europe. Providing interoperability between different clinical information systems, across national boundaries, and integration of clinical care systems and research systems lies at the heart of the eHealth Action Plan 2004 [74]. In TRANSFoRm this is a two-way street, just as clinical data are needed for research (for participant identification and evaluation of outcomes) research data is needed to support and improve clinical care. In both domains fragmentation of records and proprietary systems that do not adhere to standards are as much of a challenge as the legal and ethical issues that complicate or make access to clinical data for researchers impossible. The fact is that the single richest source of routine healthcare data lies within the records of Europe’s General Practitioners and any project that aims to comprehensively support the integration of clinical and research data has to begin with primary care data [75].

The TRANSFoRm regulatory requirements focus on the use of private and medical / health data for research purposes and is therefore of interest for p-medicine. Because the implementation of Directive 95/46/EC has been very divergent in the European member states with regard to the use of health data for research, international cross-border research has been discouraged. Some regulatory and security frameworks exist already in Europe from other projects. They are, however, dedicated mostly to specific countries (e.g. US), specific diseases (e.g. cancer), specific situations (e.g. only research context with informed consent by the patient) or to specific data sources (e.g. only use of secondary data). Given the divergences between the member states and the problems of consent for the use of data for research, those projects often aim at only using fully anonymous data or explicit consent in all cases. Such a restrictive approach renders a framework easy to use, but not very

¹⁵ Explicit consent is also known direct consent and means that the patient can clearly choose to agree or disagree with the collection, use, or disclosure of personal information

¹⁶ Advancing Clinico Genomic Trials. ACGT is a European Union co-funded project aiming at developing open-source, semantic and grid-based technologies in support of post genomic clinical trials in cancer research.

nuanced. Sometimes more refined data will be needed for research or it will be necessary to contact the patient. To address these challenges, the TRANSFoRm approach intends to find a balance between individual privacy interests on the one hand and research with health care data for the public good on the other hand. At the same time TRANSFoRm supports strongly the use of privacy enhancing technologies (PET) to resolve that tension as much as possible. Technology is not considered as neutral; instead it should be seen as operating in the background of ethical and regulatory principles. As a first step TRANSFoRm formulated a set of principles which are form normative starting points. Based on these principles, a framework for international research within TRANSFoRm was created. TRANSFoRm deals with heterogeneous data from different data sources (e.g. primary, secondary), related to different context (medical care, research), located in databases in different countries (UK, Sweden, The Netherlands) and associated with different degrees of risk of identification (personal identifiable, pseudonymous, anonymous). Different data sources can exist in the data source zone are, for example primary not aggregated data in electronic health care records, databases which have been derived from such records and have been structured in a certain way, clinical trial databases, databases which combine data from various types of sources (like GP EHR, hospital information system records). The TRANSFoRm framework uses the compiled definitions, requirements and principles to develop a model to describe the dataflow for different research projects (TRANSFoRm use cases). As preparatory work, semantic clarification of the terminology was needed and definitions were compiled, that are based on the EU Data Protection Directive, and additional documents. A structured representation of the framework was developed based on elements of structured analysis and data flow diagrams. The full range of different data sources is divided by zones with the idea to represent graphically different context areas (medical, research...). Zones are areas of data sources that are comparable and similar with respect to purpose, rules and regulations for use. The idea is to have personal identifiable data, pseudonymised data and anonymous data in different zones. The zones are structured according to the risk of confidentiality and data privacy issues, representing areas with low, medium and high risk of identification. In the framework three major zones are distinguished: care zone (e.g. Electronic Health Record), non-care zone (e.g. registers, research databases, cohort studies) and research zone. Within zones subzones are defined, which contain data that are comparable and can be used for the same or a very similar purpose and with similar applicable rules and regulations for their use (e.g. GPs EHRs within one country). Data transfer between zones/subzones is described by data flow diagrams, illustrating the data flow from one data source in one zone to another data source in another zone. To make this data flow possible, specific functions (processes) are applied using Privacy Enhancing Techniques (PET) in order to ensure privacy protection for the patient (e.g. anonymisation, pseudonymisation, coding and data aggregation). In order to join data from different data sources so-called data linkers are used. Linking of data may be performed by one-way coding or by two-way coding. A standardised notation is used for the graphical representation of the framework making the model easily adaptable to the requirements and data flows in different projects and trials.

A major obstacle for research is that databases in different countries operate under different rules and regulations concerning confidentiality and data privacy. Even in one country, differences between different types of data bases exist. Therefore, in addition to the main zones (care zone, non-care zone and research zone); subzones within the main zones were defined. These subzones contain data that are comparable and can be used for the same or a very similar purpose and with similar applicable rules and regulations. Examples of subzones are: EHR within one country is one subzone (similar types of data and similar applicable rules and regulations) and EHR from another country are a different subzone (often somewhat different data and certainly different applicable rules and regulations). Some research databases may be subsumed under one subzone and other may not.

It is a principle of the TRANSFoRm framework that in principle, explicit consent from the patient should be obtained whenever direct or indirect identifiable data are used by a third

party. However consent to treatment or participation in a trial has a different meaning than consent that someone data can be used in observational research or health research in general. Hence Directive 95/46/EC leaves room for exceptions on the consent principle for statistics and health research in the data protection regulations of the member states. But a explicit consent can have disadvantages like an undue burden for health care providers who have to ask for consent, bias in the data of those who will be included, often to the detriment of the less privileged groups. Using coded anonymous data is one way to solve the tension, but is not always feasible. A lighter form of PET should be used next to perhaps a lighter consent modality like opt-out in conjunction with research exemptions insofar as the member state allows for this exemption.

10.9.3 eSource (electronic source data) in clinical data collection

Of increasing importance is the use of electronic source data (eSource data) in clinical trials. eSource data are source data initially captured into a permanent electronic record. This covers, among others, electronic case report forms (eCRF), laboratory test results, ECGs, X-rays and patient diaries. The current regulatory framework is still focused on paper-based documents and processes. Recently, this issue has been addressed by an EMA reflection paper [76] and draft FDA guidance on eSource documentation [77]. The CDISC eSDI Working Group has identified 12 user requirements that an eSource system must fulfil [78]. The eSDI document describes the use of electronic technology in the context of existing regulations for the collection of eSource data (including eDiaries, EHR, EDC) in clinical trials for regulatory submission by leveraging the power of the CDISC standards, in particular by using the Operational Data Model (ODM)¹⁷ Transform: Deliverable 3.2, Part A: Regulatory requirements, 31 March 2011 provides explanatory information and a mapping to ICH GCP for these 12 requirements. If eSource is used in p-medicine trials special attention has to be given to these guidelines and standards.

10.9.4 Co-ordination of Notified Bodies Medical Devices (NB-MED). Recommendation NB-MED/2.2/Rec4. Software and Medical Devices. 2001 [79]

Requirements for the use of software in Medical Devices and software as Medical Device is defined.

10.10 Regulatory and research related issues concerning personalised medical trials in p-medicine

Clinical trials conducted in the area of personalised medicine and here especially the p-medicine trials; uncover the deficiencies in the regulatory landscape of clinical cancer research. The drug development process is anachronistic. The shift from the use of non-specific cytotoxic chemotherapeutic agents in cancer therapy to more specific molecularly targeted agents has necessitated a re-evaluation of the entire cancer drug development process. There is a need for additional methods to evaluate potential new drugs and to optimise development strategies. This is particularly true in the field of oncology where the increased understanding of genetic and molecular mechanisms involved in malignant cellular transformation has led to major changes in therapeutic approaches.

Current strategies for drug development are based on the concept that investigational agent has a dose-toxicity relationship and the efficacy is related to toxicity [80]. While these assumptions are valid for traditional cytotoxic drugs, these are not valid for molecularly target agents [80]. For this kind of agents, the end point in a clinical trial becomes a biological instead than a toxicity end-point [81].

¹⁷ ODM is a CDISC standard designed to facilitate the archiving and interchange of the metadata and data for clinical research. <http://www.cdisc.org/odm>

The drug development begun in the '60s and it's not suitable for new, molecularly target agents. This problem was recognized in 2004 by Regulatory Agencies such as FDA (Food and Drug Administration) and EMA (European Medicines Agency) have issued new guidelines for Phase 0 trials. Phase 0 trials are investigational new trials which take place before the traditional Phase I trial and administer sub-pharmacological doses to the participants. The participant in these trials is not a patient but a healthy subject. As defined by EMA and FDA guidelines, Phase 0 trials are early “first in human” clinical studies, that focus on extensive agent characterization and target-assay development in a limited number of subjects (normally about 10-15), who will be exposed to a limited number of doses of the study agent (less than two weeks). There is no therapeutic intent and the treatment is not beneficial for the participants.

Phase 0 trials are not suitable for all kinds of drugs, but only for those drugs that are relatively non-toxic in preclinical models and for which pharmacokinetic and pharmacodynamic assays can be developed [82]. Though, phase 0 clinical trials have no therapeutic or diagnostic purpose, they should allow researchers to establish whether a novel compound has appropriate pharmacokinetic and pharmacodynamic profiles in humans. In traditionally designed phase I cancer trials, a starting dose is selected designed to be safe based on animal toxicology studies. Patients are treated in cohorts, doses are escalated to a maximum tolerated dose (MTD), defined by toxicity criteria. The size of increment between successive dose levels is progressively decreased as toxicity is observed [83]. In contrast, in phase 0 trials, the end point is the biological effect and not the effect of the MTD with its typical associated severe side effects [84].

In this context, patient issues must be discussed. According to King [85], there are three possible kinds of benefit deriving from participation in clinical research and in phase 0 trials:

- direct benefit to subjects, defined as “benefit arising from receiving the intervention being studied”;
- indirect benefit, defined as “benefit arising from being a subject, even if one does not receive the experimental intervention” (e.g. a free physical exam and testing, free medical care, personal gratification of altruism);
- aspirational benefit, defined as “benefit to society and to future patients, which arises from the results of the study” [85].

Restricting the field of interest to oncology, data collected from the National Cancer Institute (NCI) point out that only 5% of eligible cancer patients participate in clinical trials. Because of this limited enrolment, it's necessary to increase participation in clinical research. But how? The practice of monetary compensation for participants in clinical trials has been the target of many criticisms. Another way is represented by the concept of “libertarian paternalism (LP)”. This is an approach which was recently developed by Sunstein and Thaler [86] and can be defined as a weak and non-intrusive type of paternalism [86]. In other words, the autonomous choices are not blocked or fenced off in LP, but only steered towards a certain direction. Such a move can be classified as a “nudge”, defined by the Mac Millian dictionary as “to encourage someone in a gentle way to do something”.

Owing to the low doses administered, the limited number of humans treated and the reduced risk of toxicity, the phase 0 strategy would require fewer preclinical in vitro and in vivo studies than phase I clinical trial and a reduced amount of the experimental drug. Potentially, phase 0 clinical trials could eliminate drugs before they reach phase I testing, reducing costs and time and improving the efficiency of drug development [87].

Despite the opportunity of performing phase 0 trials in oncology, only few studies have been published employing this trial type. Actually open questions still remain:

- whether the phase 0 study will improve the efficacy of subsequent trials;
- whether patients will take part in a trial that is no benefit to them

- whether phase 0 trials are needed to demonstrate pharmacodynamic effects of the drugs or whether this could be implemented in traditional phase I trials

Barriers and regulations play an important role for this clinical trial approach. There is disparity between Japan, United States and Europe on the way that anticancer drugs have been treated and also the speed in which they have been examined by regulatory authorities. 38 percent of the drugs turned down by EMA have been previously authorised by the FDA. There are also concerns about the scientific advice procedures within the EMA and the lack of open discussion with patients. In cancer it has an initiative entitled “Reinventing the regulation of cancer drugs” and it has a cancer programme which involves cancer patients in the process and allows them to participate in meetings with FDA and drug companies. With respect to cancer drugs, the EMA is risk-adverse rather than taking a risk-management approach.

Decisions taken by the world’s leading regulatory agencies, such as FDA and EMA, are often considered as a reference by other health authorities in the world (Australian government..., Saudi Food and Drug Authority, Directorate general of health services...).

The FDA and EMA have agreed on projects regarding different topics with the aim to harmonize decision making processes (EMA biblio). The goals are to increase efficiency and consistency in regulatory process, avoiding replication of similar procedures, waste of time and of financial and human resources, to learn from each other’s experiences.

The aim of Trotta’s study [88] was to compare the evaluation and approval of new products with anti-cancer indication by the EMA and FDA and to identify possible clinical implications associated with any differences in the wording. Differences reported in this trial regarded co-therapy or prior treatment; schedule, treatment line, patient population.

Overall, 42 anticancer drugs were approved by EMA between 1995 and 2008, corresponding to a total of 100 indications for the treatment of several tumors or malignancies. The primary analysis revealed that in 52 of 100 indications, there were non-differences between the EMA and FDA. Therefore, 47 therapeutic indications showed a difference between the two agencies. The majority of indications (69%) were first approved by the FDA, although a trend shows that there is a continuous increase of first approvals by the EMA.

The fact that an indication is approved by one agency but receives a negative opinion by another agency represents a crucial issue from a public health perspective. Differences in access to treatments may have several consequences. First, in the countries where the indication is not approved, a growing pressure on regulatory bodies, both from patients and health care professionals, can be expected. Second, the off label is fuelled where the indication is not approved. When the indications are approved by both agencies, a problem occurs when corresponding indications differ in wording and/or meaning. This means that the same indication is more restricted by one of the two agencies. In Trotta’s analysis, such differences exist in approximately 60% of indications.

Oncology products include both drug products and biological products. Marketing approval of drugs in the United States requires substantial evidence of clinical benefit (or efficacy) from adequate and well-controlled investigations (21 CFR). Efficacy should be demonstrated by the prolongation of life, improvement in the quality of life. If a company does not confirm clinical benefit by conducting post-approval clinical trials, the regulations allow the drug to be removed from the market (21 CFR)

Progression free survival (PFS) and time to progression (TTP) are frequent primary end points in clinical trials in advanced cancer and are the most difficult endpoints for the FDA to interpret when considering a drug for either regular or accelerated approval. PFS or TTP is accepted by the FDA as a basis for regular approval of a drug.

The purpose of the accelerated approval regulation is to make drugs more rapidly available to cancer patients. The FDA has taken two policy initiatives to optimize the accelerated approval process and maximize the benefits of earlier availability of drugs to cancer patients.

First, the accelerated approval regulations require that drugs that are granted accelerated approval be better than “available therapy”.

Second, post-approval trials to confirm clinical benefit for accelerated approvals need not be conducted in the same population as the trial that was considered for the accelerated approval and may be conducted in patients with a less advanced stage of the same cancer type.

The FDA considers “better than available therapy” to mean better efficacy. Although a drug with equal efficacy and less toxicity could possibly qualify as better than available therapy, the difference in toxicity must be substantial. Post approval clinical trials performed with due diligence are required by the FDA to confirm clinical benefit and allow conversion of an accelerated approval to regular approval. Of the 47 new indications that received accelerated approval, 26 had clinical benefit confirmed in post approval clinical trials and were converted to regular approval; 21 have not been converted to regular approval because clinical benefits has not been confirmed.

Personalized medicine has been defined as “health care that tailors interventions to individual variation in risk” [89]. Most designs of randomized trials to evaluate personalized medicine identify a high-risk group using a biomarker or a panel of biomarkers that are specified before the start of the trial [90]. The following three trial designs are often considered:

- the biomarker stratified design in which the patients are stratified as positive or negative for a biomarker and then randomized;
- the enrichment design in which only participants positive for a biomarker are randomized;
- the biomarker strategy design in which participants tested are randomly assigned to a control arm or an experimental arm in which the biomarker is used to select treatment [91].

A common denominator in these designs is having previously identified biomarker or a panel of biomarkers. In the absence of a previously identified biomarker, investigators might consider implementing the adaptive signature design [92] to evaluate personalized medicine. In the adaptive signature design, investigators randomly split the participants in a randomized trial into a test set or a training set, with each set involving some participants randomized to the control arm and some randomized to the experimental arm. In Baker’s study, the authors, to evaluate personalized medicine, propose a new design for a randomized trial that makes efficient use of high-throughput data (such as gene expression microarrays) and clinical data collected at baseline from all participants. In this type of design, involving experimental and control arms, investigators first estimate the risk of mortality in the control arm. Then, they use data from both randomization arms to estimate the effect of treatment among all participants and among participants in the highest pre-specified category of risk [93]. This proposed design identifies biomarkers that define a high-risk subset and evaluates the treatment effect in this subset as well as the treatment effect among all participants. The identified biomarkers are prognostic, which means that they predict outcome in a control arm. The authors evaluate also these biomarkers as predictive to predict the effect of treatment among those patients with specified biomarkers. This type of design may be less likely than the adaptive signature design to identify those participants most likely to benefit from treatment.

Investigator-initiated academic clinical research has contributed substantially to modern oncology [94]. Academic investigators have played critical roles in discovering targeted biotherapies [95] and driving innovation in design and execution of company-sponsored pivotal trials. Academic investigators participate in company-sponsored pivotal trials for developing databases for tumour profiling and patient selection, for recruiting and monitoring subjects, for collecting safety and efficacy data, for testing novel applications of existing drugs. Cancer treatment transition from a disease specific orientation to a targeted

individualised approach requires new thinking from both regulators and companies to ensure that investment in new drugs continues to make sense financially. Academia's interest in translational science, in many cases, dovetails with industry's desire to bring new products to market [96].

Pharmaceutical companies may provide support to academic investigators, while the academic researcher assumes the responsibility for designing the study, writing the protocol, monitoring the study, selecting study personnel. A survey of 28 pharmaceutical and biotechnology companies revealed that 88% have defined processes for accepting proposal from academic investigators [97], but companies must be able to justify the financial support for research both internally and to regulatory bodies to ensure that the investment is legitimate and not covert promotion. In the field of personalized medicine, a new model should be proposed whereby expert organisations provide a forum for academia and industry to plan studies within a regulatory framework to support authorisation and reimbursement for new molecularly targeted agents and biomarkers. One of the roles of the industry should be communicate with academic investigators about data required to support product licensure or a new drug indication. Main roles of Academia should be to conduct basic and translational studies, to identify and develop biologically relevant, validated biomarkers and to provide feedback to pharmaceutical companies on trials design.

11 Discussion and Conclusion

11.1 Introduction

In recent years, the increasingly global nature of clinical research, and here especially the conduct of clinical trials with human participants, has aggravated certain ethical issues, especially when researchers from one country wish to conduct research in another country or want to exchange biomaterial or patient data. As the pace of international collaborative biomedical research has increased and with the demand of enhanced collaboration for trials in personalised medicine, long-standing questions about the ethics of designing, conducting, data processing, database access, follow-up in international clinical trials have re-emerged. On the other hand the international aspects of clinical trial regulations let still much room for interpretation, and for example the EU directive is interpreted differently in different European countries. Nonetheless, a large number of guidance documents support the planning and conduct of international clinical trials and reinforce the regulations. Several aspects of the regulatory framework are discussed in more detail.

In this deliverable a large number of regulatory documents relevant for the international aspects of clinical trials were listed. They will apply to different degrees to clinical trials conducted within p-medicine. In general, adherence to the principles of GCP, including human subject protection is universally recognized as the critical requirement for the conduct of research involving human subjects. Many countries have adopted the GCP principles as laws and regulations. Several guidance documents address important aspects of GCP compliant trial conduct [8, 13, 14, 15].

The Clinical Trials Directive harmonises the rules in the EU for the approval of a clinical trial. As regards national competent authorities, the details are set out in the 'Commission Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial. All these guidelines are published in EudraLex Volume 10. A European database (EudraCT) contains all on-going or completed clinical trials falling within the scope of Directive 2001/20/EC. This database gives the competent authorities of the member states and EMA the necessary information to communicate on clinical trials and to maintain oversight of clinical trials and IMP development. This will provide for additional protection of clinical trial subjects and patients receiving IMPs. Paediatric clinical trials that form part of a Paediatric Investigation Plan (PIP) but are conducted in third countries will also be included in the near future (paediatric clinical trials with sites in the EU/EEA are already included). EU legislation provides that certain information contained in EudraCT is to be made accessible to the public. This public accessibility concerns clinical trials with paediatric as well as non-paediatric participants and contains some protocol-related information and result-related information. It covers both negative and positive results.

To implement the legislation further, the Commission has issued a set of guidelines, which are accessible via chapter V of EudraLex, Volume 10. Regulations for clinical trials in Europe are listed comprehensively in EudraLex (see annex). EudraLex Volume 4 deals with Good manufacturing practice (GMP) Guidelines, including Directive 2003/94/EC, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. EudraLex Volume 1 deals with the pharmaceutical legislation medicinal products for human use, including Directives 2001/83/EC, Directive 2001/83/EC, 2011/62/EU, 2010/84/EU and many others. EudraLex Volume 10 deals with clinical trials guidelines, including Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial, Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical and many others.

Dependent on the interventions investigated in the clinical trials within p-medicine (e.g. medicinal product, medical device), the applicable rules and regulations have to be followed (e.g. medical drug law, medical device law). It is the duty of the trial sponsor to assure compliance with all relevant legal and ethical issues. This is the usual business of a sponsor and will not be tackled in this document. Instead, in this document the relevance of rules and regulations for the use of p-medicine tools and services in clinical trials will be discussed.

11.2 Regulatory issues about tools used in p-medicine

So far it is planned to use the following p-medicine tools and services in the pilot trials. This, however, may need adaption during the course of the p-medicine project.

Wilms trial	Breast cancer trials	ALL trials
ObTiMA	Oncosimulator	Oncosimulator
DoctorEye		Tools to access biobanks
Oncosimulator		Data warehouse
Tools to access biobanks		Portal function
Tools to manage SAEs/SUSARs		Patient empowerment tool
Tools to manage DICOM transfer		

Table 1: p-medicine tools and services used in pilot clinical trials

Within WP5 (Legal and ethical framework) a report will be given on legal and ethical issues for p-medicine tools used for international clinical trials (Deliverable 5.5, month 18). In this document an overview on regulatory and international aspects of the clinical trials will be given to be used as input for Deliverable D5.5.

11.2.1 ObTiMA clinical trial management system

It is planned to use ObTiMA within p-medicine in prospective clinical trials with medicinal products. Therefore, the requirements described above must be fulfilled by ObTiMA with consequences for architecture and design of the software. Furthermore, certification of ObTiMA for the use in GCP conform clinical trials is planned within p-medicine (Task 9.3). ObTiMA as an ontology based trial management application will be developed, evaluated and validated within Task 8.3, which has to be performed according to the regulations and guidelines discussed in this section.

11.2.2 DoctorEye, Oncosimulator and clinical decision support

The relevance of the EU Medical Device Directive on the tools developed within p-medicine should be specified for DoctorEye (within p-medicine DoctorEye will be used in GCP compliant clinical trials (see WT 9.3)), the Oncosimulator, clinical decision support tools and any other tools used specifically for diagnostic and/or therapeutic purposes. It has to be worked out whether these tools are used for validation on retrospective data or prospective with relevance for the diagnosis and treatment of the patient. In the latter case, rules and regulations on medical devices have to be applied.

11.2.3 Clinical trials involving biobanks

Recently, human biological material (body fluids, cells, tissues, intracellular substances or RNA/DNA) and the associated data have become an important resource for academic

medical research. This dependency on biomaterial has been increased in personalised medicine. But especially in research involving biobanking the fragmentation of the regulatory systems is seen as a serious obstacle to research. Though several European guidelines exists [36, 37, 38, 40] national and local differences are governing the access to biomaterial in Europe. Most European countries do not have a general legal framework applicable to biobanks for scientific research, but rather recommendations for informed consent and data protection. Therefore, a need for international standardization to support increased cross border flow of biological materials of human origin and data has been recognised [98]

Biological material is always associated with personal data that describe the donor (age, gender etc) and the disease (e.g. cancer), as well as data that allow researchers to draw conclusions about disease progression, response to treatment and adverse effects. Personal information on biobank donors collected in a register or in another form falls under the regulations of the different national Personal Data Protection Acts as well as other legislation regarding personal information and health-related data in the healthcare area. Though there is a European Directive on data protection, the laws and practices governing the storage and use of personal data for research vary considerably between European countries. There is a consensus around a general principle: patients have a right to keep their medical details confidential, and that biobanks may therefore only store anonymised data. The problem is that anonymisation can be interpreted in different ways. Some countries assign a code to each donor that is used to identify their data and their biological samples, and the link between the donor and the code is then destroyed. But many countries use a two-way coding of their biobank data. With two-way coding a third party keeps the link, thus enabling researchers to request further information about a donor.

Differences also exist in the Informed Consent requirements. A comparative review [99] of international laws, guidelines and regulations on biobanking based research and consent requirements, showed a number of different types of Informed Consent that were demanded by different national laws, like specific informed consent, partially restricted consent, broad consent, etc. Though, most European regulations agree that the consent should be given free and that the requirement for consent should be waived only in exceptional cases and authorized by an ethics committee, the required type and amount of information that should be given to a donor varies from “broad to restricted”. For the secondary uses of biosamples and their data the various forms of informed consent recommended differ at international, European and national levels [99]. For example, there is a tendency that in France [100] a specific informed consent may be required, in Germany [101] a broad consent, and in Italy [102] a partially restricted consent¹⁸ [99].

There is a full WP in p-medicine dealing with access to biobanks (WP10). In Deliverable No. 10.1, an overview on current legal and ethical rules and guidelines for biobanks has been given. WP5 defines the legal and ethical framework for p-medicine, including a report on legal and ethical issues regarding access to biobanks (D5.3). This report will be provided at month 24. In this document only a short overview is given on the regulatory aspects of biobanks with a focus on clinical trials. Details concerning the regulatory aspects of biobanks are given in the named deliverables.

The clinical trial EU Directives 2001/20/EC (1) and EU Directive 2005/28/EC (18) do not specifically refer to research on biobanks. There are, however, specific rules on the collection and use of human tissue (e.g. EU Directive 2002/98/EC, EU Directive 2004/23/EC (41)). EU Directive 2002/98/EC is setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, EU Directive 2004/23/EC(41) standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. EU Directive 2002/98/EC covers the collection and testing of human blood and blood components, irrespective of their final destination, thus also including clinical trials (Del. 10.1). According to

¹⁸ Multi-layered and restricted consent, protects donor autonomy at the expense of research interests

this Directive any unauthorised changes to donation registries or processing records or the unauthorised disclosure of information should be prevented. Data, to which third parties have access, have been rendered anonymous so that the donor is no longer identifiable. EU Directive 2004/23/EC applies to human tissues and cells intended for human applications and manufactured products derived from human tissues and cells intended for human applications. Human biobanks that contain human body material that is intended for research processes (including clinical trials) are not covered by the scope of this Directive. If no specific regulations on the collection and use of human tissue for clinical research apply, rules and regulations for clinical trials (e.g. trials on medicinal products, medical devices) and the general rules of EU Directive 95/46/EC (Data Protection Directive, (29)) have to be followed. EU Directive 95/46/EC is only applicable to personal data, which also covers pseudonymous data (29). This is relevant because clinical trial databases usually contain pseudonymous data. According to this Directive, sensitive data may be processed, if the data subject has given explicit consent, which should be the case in prospective clinical trials. The data controller/processor has to implement technical and organizational measures to adequately protect personal data, unfortunately, the Directive does not regulate which technology has to be used (e.g. privacy enhancing techniques) and what is state of the art (Del. 10.1). By the “Art. 29 Data Protection Working Party” several general and also specific documents on genetic data have been issued, which may also be of relevance for clinical trials involving biobanks.

Apart from these and associated EU-regulations (and their respective national implementations), various international guidelines have been developed as to activities concerning human body tissues and genetic data. Such guidelines have been provided by the United Nations (including UNESCO), the Council of Europe, OECD and international scientific organisations. These guidelines, which do not specifically refer to biobanks for research and clinical trials, are usually not legally binding but provide useful principles and recommendations for biobanks to be taken into consideration.

11.2.4 Regulatory aspects of personalised medicine and advanced therapies in clinical trials

The clinical trials in p-medicine will apply advanced methodology¹⁹ for personalised medicine. In general there are several problems for investigators to conduct clinical trials in personalised medicine [103]: (1) unclear regulatory considerations (from the EMA and FDA) are a challenge to the personalised medicine drug development; (2) in many cases it is difficult to associate diseases with molecular markers; and (3) suitable biomarkers do not exist for characterising / stratifying patient populations.

In principle, for advanced therapies, the same basic principles for assessment apply as for any other biotechnological medicinal product. Nevertheless, the extent of data for quality, safety, and efficacy can be highly specific. Until recently, advanced therapies were not uniformly regulated across Europe, e.g., tissue engineered products were regulated either as medicinal products or medical devices. The draft guideline on Good Clinical Practice for clinical trials with advanced therapies describes specific additional requirements, e.g., ensuring traceability. The Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA) has been established to meet the scientific and regulatory challenges with advanced therapies.

To address advanced therapy problems, EMA supports personalised medicine by the development of several regulatory guidance (e.g. publishing of reflection papers), the development of a dedicated biomarker qualification procedure, and by offering regulatory support to projects in the Innovative Medicines Initiative (IMI) and Critical Path (eg Joint EMA/FDA VXDS on BM nephrotoxicity) [104].

¹⁹ For example, Advanced therapy investigational medicinal products are medicinal products involving cell or gene therapy or tissue engineering.

EMA has developed a number of guidance mainly addressing biomarkers (see chapter 9). In January 2009, EMA issued a formal qualification process outlined in the guidance document EMEA/CHMP/SAWP/72894/2008 [50]. This procedure provides framework and to engage with EMA to support biomarker. Also the FDA has modified its approach to facilitating biomarkers for drug development. Its introduction of the biomarker qualification process, Voluntary Exploratory Data Submission, provides the opportunity to discuss biomarker development with FDA from an early stage on. Advice on study design and data on samples can be obtained through formal processes. In addition EMA and FDA are developing guidance for clinical trial design and regulatory considerations for co-developing a novel companion diagnostic and therapy simultaneously. This includes the strategic use of biomarkers for patient selection and screening in clinical trials. Proper clinical trials design should allow for an ethical patient selection strategy [54, 55].

In the US even a personalised medicine law has been submitted to Congress. In 2006 the “Genomics and Personalized Medicine Act of 2006” tried to improve access to and appropriate utilization of valid, reliable and accurate molecular genetic tests by all populations. In 2010 the fourth version of a personalized medicine bill was reintroduced into the U.S. House of Representatives. This bill also failed, but it is likely to be reintroduced during the next congressional session [56, 57]. One important part will be the establishment of a national biobank for the US. One can suppose that eventually a personalised medicine act will pass into law [99].

11.3 Software and medical device law

According to EU Directive 2007/47/EC “medical device” means any instrument, apparatus, appliance, **software**, material or other article, whether used alone or in combination, together with any accessories including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes. Furthermore, software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, is a medical device. Software for general purposes when used in a healthcare setting is not a medical device (EU DIRECTIVE 2007/47/EC, (22)). As a consequence, software has to be treated as medical device if [105]:

- If used for diagnosis, monitoring or treatment,
- If the purpose is to control or influence the functioning of a medical device within the meaning of the European Directives
- if it is used for the analysis of patient data generated by a medical device, with a view towards diagnosis and monitoring
- if it is designed to be used for, or by, patients in the diagnosis or treatment of a physical disease or mental health condition.

Software that is not covered by the Directives is that used for administrative purposes such as in the handling of patient files and data, or for educational purposes such as training physicians in how to use a medical device [105]. Documents to support classification under the Community regulatory framework is available (EU Commission, Manual on Borderline and Classification, Version 1.11). As an example PACS (Picture Archiving and Communication Systems) may not fall within the definition of a medical device if only intended for archiving and storage of data (without manipulation). PACS intended to be used for viewing, archiving and transmitting images are generally classified as Class I medical devices. PACS with post-processing of images for diagnosis (image processing functions, complex quantitative functions) or with image enhancing have to be classified under Class IIa or IIb.

Taking account of the growing importance of software in the field of medical devices, be it as stand-alone or as software incorporated in a device, validation of software in accordance with the state of the art should be an essential requirement (EU Directive 2007/47/EC, (22)). Software must be validated according to the state of the art taking into account the principles

of development lifecycle, risk management, validation and verification [105]. The EU Directives provide a body of rules with an annex containing essential requirements and CE certification procedures with a reference to international standards. Examples of applicable standards are EN 60601 (medical electrical equipment) and EN 62304 (software life cycle processes). Software that is a medical device but is not CE-marked can only be used inside an approved clinical trial setting after being validated.

Decision on whether particular software must be CE marked under the Medical Devices Directives: The manufacturer must decide whether particular software needs to be “CE” marked, and should be able to justify that decision. Depending on the use intended by the manufacturer and the manner in which the product is placed on the market, the software can be [79]:

- a medical device or an accessory to a medical device, which must be CE marked
- a component and integral part of a medical device, which cannot be CE marked in its own right, but which is covered by the conformity assessment of the
- medical device of which it forms a part or
- none of the above and therefore not covered by the Medical Devices Directives.

Software is regarded as a medical device when one or more of the following circumstances apply [79]:

- software is for a purpose explicitly mentioned in a Medical Device Directive.
- software is intended to control or influence the functioning of a medical device
- software is intended for the analysis of patient data generated by a medical device with a view to diagnosis and monitoring
- software is intended for use for / by patients to diagnose or treat a physical or mental condition or disease

The last point is the most important. Even though, p-medicine does not aim at developing commercial software, tools and services should be commercially exploitable. This means that based on the results of the p-medicine project, commercial software companies should be able to develop and provide software fulfilling all regulatory requirements, including the medical device law. For the p-medicine project it is, however, important to specify, which software tools falls under the medical device law and which tool is used in which clinical trial specified under WP9.

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13 Abbreviations and acronyms

<i>ALL</i>	Acute Lymphoblastic Leukaemia
<i>CDBI</i>	Steering Committee on Bioethics
<i>CDISC</i>	Clinical Data Interchange Consortium
<i>CDRH</i>	Center for Devices and Radiological Health
<i>CFR</i>	Code of Federal Regulations
<i>CIOMS</i>	Council for International Organizations of Medical Sciences
<i>CPMP</i>	Committee for Proprietary Medicinal Products
<i>CRF</i>	Case Report Form
<i>CRO</i>	Clinical Research Organisation
<i>GCP</i>	Good Clinical Practice
<i>ECRIN</i>	European Clinical Research Infrastructures Network
<i>EMA</i>	European Medicines Agency
<i>GCP</i>	Good Clinical Practice
<i>GLP</i>	Good Laboratory Practice
<i>GMP</i>	Good Manufacturing Practice
<i>ICH</i>	International Conference on harmonisation
<i>ISO</i>	International Organization for Standardization
<i>IRB</i>	Institutional Review Board
<i>OECD</i>	Organisation for Economic Cooperation and Development
<i>OHRP</i>	Office for Human Research Protections
<i>QT</i>	QT interval
<i>SUSAR</i>	Suspected Unexpected Serious Adverse Reaction

14 Annex

14.1 EudraLex - Volume 10 Clinical trials guidelines

Volume 10 of the publications "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

<http://ec.europa.eu/health/documents/eudralex/vol-10/>

Chapter I: Application and Application Form

Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (revision 3 of March 2010)

Annex 1 revised Pdf version, Word version msw8 (revision 4 of November 2009) - EudraCT Version 8.0 uses the Revision 4 dated November 2009 of the Clinical Trials Application Form

Substantial Amendment Notification Form (revision 3 of June 2010)

Declaration of the End of Trial Form : PDF version - Word version (revision 3 of June 2010)

Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (revision 1 of February 2006)

Detailed guidance on the European clinical trials database (EUDRACT Database) (revision of April 2004)

Chapter II: Monitoring and Pharmacovigilance

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (revision 2 of April 2006)

Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance - Clinical Trial Module) (revision 1 of April 2004)

Questions & Answers specific to adverse reaction reporting in clinical trials (December 2009)

ICH guideline E2F - Note for guidance on development safety update reports (September 2010)

Chapter III: Quality of the Investigational Medicinal Product

Good manufacturing practices for manufacture of investigational medicinal products (February 2010)

Community basic format for manufacturing authorisation / Community basic format for manufacturers / importers

Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials

Guidance on Investigational Medicinal Products (IMPs) and 'non investigational medicinal products' (NIMPs) (rev. 1, March 2011)

Chapter IV: Inspections

Guidance for the preparation of GCP inspections (June 2008)

Recommendation on inspection procedures for the verification of good clinical practice compliance (July 2006)

Guidance for the conduct of GCP inspections (June 2008)

Annex I to Guidance for the conduct of GCP inspections - investigator site (June 2008)

Annex II to Guidance for the conduct of GCP inspection - clinical laboratories (June 2008)

Annex III to Guidance for the conduct of GCP inspections - computer systems (June 2008)

Annex IV to Guidance for the conduct of GCP inspections - Sponsor and CRO (June 2008)

Annex V to Guidance for the conduct of GCP inspections - Phase I Units (November 2008)

Annex VI to Guidance for the conduct of GCP inspections - Record keeping and archiving of documents (March 2010)

Annex VII to Guidance for the conduct of GCP inspections - Bioanalytical part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials (November 2008)

Guidance for coordination of GCP inspections and co-operation between GCP inspectors, the reference and concerned Member States and CMD(h) , in the context of the evaluation of the GCP compliance of marketing authorization applications for mutual recognition and decentralized procedures (June 2009)

Guidance for exchange of GCP Inspection Reports according to Article 15(2) of Directive 2001/20/EC (revision 1, May 2009)

Guidance for the communication on GCP inspections and findings (June 2008)

Procedure for standardisation of GCP inspection entries in EudraCT (November 2008)

Guidance for the preparation of Good Clinical Practice inspection reports (June 2008)

Recommendations on the qualifications of inspectors verifying compliance in clinical trials with the provisions of Good Clinical Practice (July 2006)

Chapter V: Additional Information

Guidelines on good clinical practice (ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95) (1996)

Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (December 2009)

Recommendation on the content of the trial master file and archiving (July 2006)

"Questions & Answers" Document - Version 8 (March 2011)

Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008)

Guideline 2008/C168/02 on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products (July 2008)

List of fields contained in the 'EudraCT' clinical trials database to be made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004 and its implementing guideline 2008/C168/02 (February 2009)

Guideline 2009/C28/01 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 (EMA), in accordance with Article 41 of Regulation (EC) No 1901/2006 (February 2009)

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 (February 2009)

EudraCT - List of additional fields contained in EudraCT (reasons for negative opinions of the Ethics Committee) - (November 2010)

Chapter VI: Legislation

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.

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (Official Journal L 262, 14/10/2003 p. 22 - 26).

14.2 EudraLex - Volume 1 - Pharmaceutical Legislation Medicinal Products for Human Use

Some of the rule apply to fees or marketing authorization procedures relevant only for pharma industry

Directives

2001/83/EC 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 (Consolidated version : 05/10/2009).

2010/84/EU Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. (Official Journal L 348, 31/12/2010, p. 74 - 99).

Corrigendum (Official Journal L 21, 25/1/2011 p. 8).

2009/53/EC Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 amending Directive 2001/82/EC and Directive 2001/83/EC, as regards variations to the terms of marketing authorisations for medicinal products. (Official Journal L 168, 30/6/2009, p. 33 - 34).

2002/98/EC Amended by Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (Official Journal L 33, 8/2/2003 p. 30 - 40).

Corrigendum (Official Journal L 230, 24/8/2006 p. 12 PL).

2003/63/EC Amended by Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Official Journal L 159, 27/6/2003 p. 46 - 94).

Corrigendum (Official Journal L 302, 20/11/2003 p. 40 DE).

2004/24/EC Amended by Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal L 136, 30/4/2004, p. 85 - 90).

2004/27/EC Amended by 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 (Official Journal L 136, 30/4/2004 p. 34 - 57).

2008/29/EC Amended by Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the implementing powers conferred on the Commission (Official Journal L 81, 20/3/2008, p. 51 - 52).

2009/120/EC Amended by Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products (Official Journal L 242 15/9/2009, p. 3 - 12).

2001/20/EC 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 (Official Journal L 121, 1/5/2001 p. 34 - 44).

Corrigendum (Official Journal L 300, 5/11/2002 p. 58 - 58 NL).

2003/94/EC Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (Official Journal L 262, 14/10/2003 p. 22 - 26).

2005/28/EC Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Official Journal L 91, 9/4/2005 p. 13 - 19).

89/105/EEC Council Directive 89/105/EEC, of 21 December 1988, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems (Official Journal L 40, 11/2/1989 p. 8 - 11; Finnish special edition: Chapter 15 Volume 9 p. 45; Swedish special edition: Chapter 15 Volume 9 p. 45).

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2008/29/EC Amended by Directive 2008/29/EC of the European Parliament and of the Council of 11 March 2008 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the implementing powers conferred on the Commission (Official Journal L 81, 20/3/2008, p. 51 - 52).

2009/219/EC Amended by Regulation (EC) No 219/2009 of the European Parliament and of the Council of 11 March 2009 adapting a number of instruments subject to the procedure referred to in Article 251 of the Treaty to Council Decision 1999/468/EC with regard to the regulatory procedure with scrutiny Adaptation to the regulatory procedure with scrutiny - Part Two (Official Journal L 87, 23/3/2009, p. 109 - 154, especially p. 116 - 118, Annex 2.9, where Regulation (EC) No 726/2004 is adapted).

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Corrigendum (Official Journal L 75, 4/4/1995 p. 29).

EC/2743/98 Council Regulation (EC) No 2743/98 of 14 December 1998 amending Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products (Official Journal L 345, 19/12/1998 p 3 - 8).

EC/494/2003 Commission Regulation (EC) No 494/2003 of 18 March 2003 amending Council Regulation (EC) No 297/95 on the fees payable to the European Agency for the Evaluation of Medicinal Products (Official Journal L 73, 19/3/2003 p. 6 - 7)

EC/1905/2005 Council Regulation (EC) No 1905/2005, of 14 November 2005, amending Regulation (EC) No 297/95 on fees payable to the European Medicines Agency (Official Journal L 340, 13/11/2005 p. 1 - 9)

Consolidated version Consolidated version of the Council Regulation (EC) No 297/95 on fees payable to the European Agency for the Evaluation of Medicinal Products (20.11.2005)

EC/312/2008 Commission Regulation (EC) No 312/2008 of 3 April 2008 amending Council Regulation (EC) No 297/95 as regards the adjustment of the fees of the European Medicines Agency to the inflation rate

EC/249/2009 Commission Regulation (EC) No 249/2009 of 23 March 2009 amending Council Regulation (EC) No 297/95 as regards the adjustment of the fees of the European Medicines Agency to the inflation rate (Official Journal L 79, 25/3/2009 p. 34 - 36).

EC/540/95 Commission Regulation (EC) No 540/95, of 10 March 1995, laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorized in accordance with the provisions of Council Regulation (EEC) No 2309/93 (Official Journal L 55, 11/3/1995 p. 5 - 6).

EC/1662/95 Commission Regulation (EC) No 1662/95, of 7 July 1995, laying down certain detailed arrangements for implementing the Community decision-making procedures in respect of marketing authorizations for products for human or veterinary use (Official Journal L 158, 8/7/1995 p. 4 - 5).

Corrigendum (Official Journal L 249, 17/10/1995 p. 47 PT).

EC/2141/96 Commission Regulation (EC) No 2141/96, of 7 November 1996, concerning the examination of an application for the transfer of a marketing authorization for a medicinal product falling within the scope of Council Regulation (EEC) No 2309/93 (Official Journal L 286, 8/11/1996 p.6 - 8).

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

EC/847/2000 Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (Official Journal L 103, 28/4/2000 p.5 - 8).

EC/1084/2003 Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State (Official Journal L 159, 27/6/2003 p.1 - 23).

EC/1085/2003 Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93 (Official Journal L 159, 27/6/2003 p.24 - 45).

EC/2049/2005 Commission Regulation (EC) No 2049/2005, of 15 December 2005, laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises (Official Journal L 329, 16/12/2005 p.4 - 7).

EC/507/2006 Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council (Official Journal L 92, 30/3/2006 p.6 - 9).

EC/1901/2006 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.

EC/1902/2006 Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use.

2008/C 243/01 Communication from the Commission - Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (Official Journal C 243, 24/9/2008 p.1 - 12).

EC/658/2007 Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council (Official Journal L 155, 15/6/2007 p.10 - 19).

EC/1394/2007 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Note: shall apply from 30 December 2008)(Official Journal L 324, 10/12/2007 p. 121 - 137).

EC/1234/2008 Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (Official Journal L 334, 12/12/2008 p. 7 - 24).

EC/668/2009. Commission Regulation (EC) No 668/2009 of 24 July 2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises (Official Journal L 194, 25/7/2009 p. 7 - 10).

EU/1235/2010 Commission Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 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, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. (Official Journal L 348, 31/12/2010 p. 1 - 16).

75/320/EEC Council Decision 75/320/EEC, of 20 May 1975, setting up a Pharmaceutical Committee (Official Journal L 147, 9/6/1975 p. 23; Spanish special edition: Chapter 13 Volume 4 p. 102; Portuguese special edition: Chapter 13 Volume 4 p. 102; Finnish special edition: Chapter 13 Volume 4 p. 108 Swedish special edition: Chapter 13 Volume 4 p. 108).

Corrigendum (Official journal L 229, 15/8/1986 p. 63 DA; Official journal L 220, 20/8/1975 p. 22 DE).

78/25/EEC Council Directive 78/25/EEC, of 12 December 1977, on the approximation of the laws of the Member States relating to the colouring matters which may be added to medicinal products (Official Journal L 11, 14/1/1978 p. 18 - 20; Finnish special edition: Chapter 13 Volume 8 p. 39; Greek special edition: Chapter 13 Volume 7 p. 34; Swedish special edition: Chapter 13 Volume 8 p. 39; Spanish special edition: Chapter 13 Volume 8 p. 86; Portuguese special edition Chapter 13 Volume 8 p. 86).

Corrigendum (Official Journal L 229, 15/8/1986 p. 63 DA).

90/219/EEC Council Directive 90/219/EEC, of 23 April 1990, on the contained use of genetically modified micro-organisms (Official Journal L 117, 8/5/1990 p. 1 - 14; Finnish special edition: Chapter 15 Volume 9 p. 198; Swedish special edition: Chapter 15 Volume 9 p. 198).

Corrigendum (Official Journal L 7, 10/1/1991 p. 38 IT).

98/81/EC Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms (Official Journal L 330, 5/12/1998 p. 13 - 31).

Corrigendum (Official Journal L 93, 8/4/1999 p. 27 DA DE EL EN ES IT NL SV).

Corrigendum (Official Journal L 216, 21/8/2007 p. 26 PL).

2001/18/EC Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (Official Journal L 106, 17/4/2001 p. 1 - 39).

Corrigendum (Official Journal L 3, 7/1/1999 p. 23 EN).

EEC/1768/92 Council Regulation No (EEC) 1768/92, of 18 June 1992, concerning the creation of a supplementary protection certificate for medicinal products (Official Journal L 182, 2/7/1992 p. 1 - 5; FI and SV special editions: Chapter 13 Volume 23 p. 78; Swedish special edition: Chapter 13 Volume 23 p. 78; CS, ET, HU, LT, LV, MT, PL, SK and SL special editions Chapter 13 Volume 11 p. 200 - 204).

6/5/1982 Commission Communication on parallel imports of proprietary medicinal products for which marketing authorizations have already been granted (Official Journal C 115, 6/5/1982, p. 5).

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93/39/EEC, 93/40/EEC and 93/41/EEC, adopted on 14 June 1993. (Official Journal C 82, 19/3/1994 p. 4).

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2004/C 24/06 Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 2 ó October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal products (CVMP) (Official Journal C 24, 2006 p. 6 - 18).

2006/C 133/05 Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC (Official Journal C 133, 8/6/2006 p. 5 - 7).

2008/C 243/09 Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (Official Journal C 243/1, 2008).