Impact of the new legislative framework within the European Union on non-commercial clinical research and investigator-initiated trials: a cross-European analysis with focus on oncology

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List of Terms and Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AFSSAPS	Agence Française de Sécurité Sociale des Produits de Santé (FR)
AMG	Gesetz über den Verkehr mit Arzneimitteln (DE)
ATU	Autorisation Temporaire d'Utilisation (FR)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (DE)
BMGS	Bundesministerium für Gesundheit und Soziales (DE)
CA	Competent Authority/-ies (of a Member State)
CCMO	Central Committee on Research Involving Human Subjects (NL)
CBER	Center for Biologics Evaluation and Research (US)
CDER	Center for Drug Evaluation and Research (US)
CRO	Clinical Research Organisations
CTA	Clinical Trial Applications
CTD	Common Technical Document
CTD 2001/20	Clinical Trials Directive 2001/20/EC
DoH	Department of Health (UK)
EC	Ethics Committee (term refers to local/research ethics committees)
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ESTRO	European Society for Therapeutic Radiology and Oncology
EU	European Union
FDA	Food and Drug Institution (US)
GCP	Good Clinical Practice
GCP Directive	GCP Directive 2005/28/EC
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product(s)
IMPD	Investigational Medicinal Product Dossier(s)
IND	Investigational New Drug (Application) (US)
IRB	Institutional Review Board
IIT	Investigator Initiated Trial(s)
MA	Marketing Authorisation(s)
MoH	Ministry of Health
MPA	Medical Products Agency (SE)
MS	Member State(s) (of the European Union)
NHS	National Health Service (UK)
NtA	Notice to Applicants
PEI	Paul-Ehrlich Institut, Bundesamt für Sera und Impfstoffe (DE)
PASS	Post Authorisation Surveillance Study/-ies
PMS	Post-Marketing-Surveillance Study/-ies
SAR	Serious Adverse Reaction(s)
SmPC	Summary of Product Characteristics
StrlSchV	Strahlenschutzverordnung (DE)
SUSAR	Suspected Unexpected Serious Adverse Reaction(s)
TOS	Therapy Optimization Study/-ies

Country Codes used:

BE = Belgium	DE = Germany	ES = Spain	FR = France
IT = Italy	NL = Netherlands	SE = Sweden	UK = United Kingdom

EU = European Union US/USA = United States of America

1 INTRODUCTION

1.1 Clinical cancer research

Today, cancer remains a disease ranging nearly world-wide among the leading causes of death. Epidemiologic investigations indicate that the disease in its different forms affects more than 20 million people world-wide. Cancer constitutes a major obstacle for public health with drastic figures in terms of incidence (10 million new cases per year) and mortality (6 millions deaths per year) [1].

For the European Union (EU), recent statistics from the International Agency for Research on Cancer figure out at 2 million new cases per year and 1.2 million deaths annually. With present trends, the death toll will increase to 1.4 million by 2015, due to a 22% increase in people over 65 years and a 50% increase in people over 80 years [2].

Therefore, major health research initiatives are taken to combat cancer, ranging from the appropriation of extra funding and implementation of research programmes on the European level to national action plans and regional endeavours to optimize structures for treatment and care. Clinical cancer research is of tremendous importance to investigate new therapies as well as to prove results from basic and translational research into humans. Approaches as different as the evaluation of completely new treatment forms arising from stem-cell research or genomics, on one hand, as well as classical therapy improvement via optimized multi-modal therapies or patient sub-group adapted drug regimens, on the other hand, illustrate how complex and divergent scenarios and methods for human clinical cancer trials can be in practice. Due to the insufficient therapeutic armament and the low rates of cure for many types of cancer, inventors of new therapeutics as well as clinicians managing daily-routine patients initiate and use clinical trials to constantly improve frontiers and standards of cancer care.

Hence, cancer research represents one of the most dynamic areas of medical research, characterised in particular by a huge number of independent, academic, non-commercial clinical trials carried out in parallel to a growing number of R&D-industry driven clinical development projects. In facts, clinical cancer research represents a remarkable portion of all clinical trials conducted [3]. Figures from the US indicate that more than 25 % of all phase I to III studies are cancer trials. For Europe, figures are difficult to establish as until now no centralised system existed which captured applications for clinical trials [4].

1.2 Current status of European pharmaceutical legislation

Generally accepted rules and principles for the conduct of studies in humans were elaborated by the Internal Conference on Harmonization (ICH) establishing recommendations for 'Good Clinical Practice' (GCP) [5]. The results of this process which were adapted through the last decennium in North America, Europe and Japan are now incorporated into these states' legislative and regulative framework. For the EU, clinical research has seen the kick-down for a harmonised framework in 2001, when the 'Clinical Trials' Directive 2001/20/EC (CTD 2001/20) was issued [6]. Since, its adaptation by the Member States (MS) and further community-wide legislative action are profoundly changing the face of clinical research. Concentrating much more on the industry-sponsored pivotal registration studies and the economic impact on it, the debate has been recently intensified regarding the Directive's impact on independent, academic therapeutic research, which plays an major role to establish the value of new therapies in clinical practice or to generate new therapeutic concepts or standards [7,8].

The present master-thesis aims to analyse the situation and conditions for independent, non-commercial clinical research in the European Union with regard to the new legislation issued since 2001. Therefore, for eight MS the results of the legal adaptation process for the conduct of Investigator-Initiated Trials (IIT) are described and analysed in a comparative way. Despite of pan-European research efforts, medical practice and use of clinical and epidemiologic investigations are still characterised by differing (cultural) habits, regulatory actions and public health environments, resulting into a heterogeneous transposition of the respective directives and guidelines into national MS law.

A thorough revision of the EU pharmaceutical legislation has been completed in 2004 with the publication of the so-called 'Review 2004' (also called '2004 consultation') by the EU Commission. The review contains renewed legislative texts regarding the procedures to obtain marketing authorisations (MA) within the enlarged European Union. In addition, new and updated directives have been issued to regulate the authorisation of traditional herbal medicinal products and to adapt existing legislation regarding GMP and GLP to the current technological 'state-of-the-arte'. Figure 1 summarizes the status of the pharmaceutical legislation at EU level.

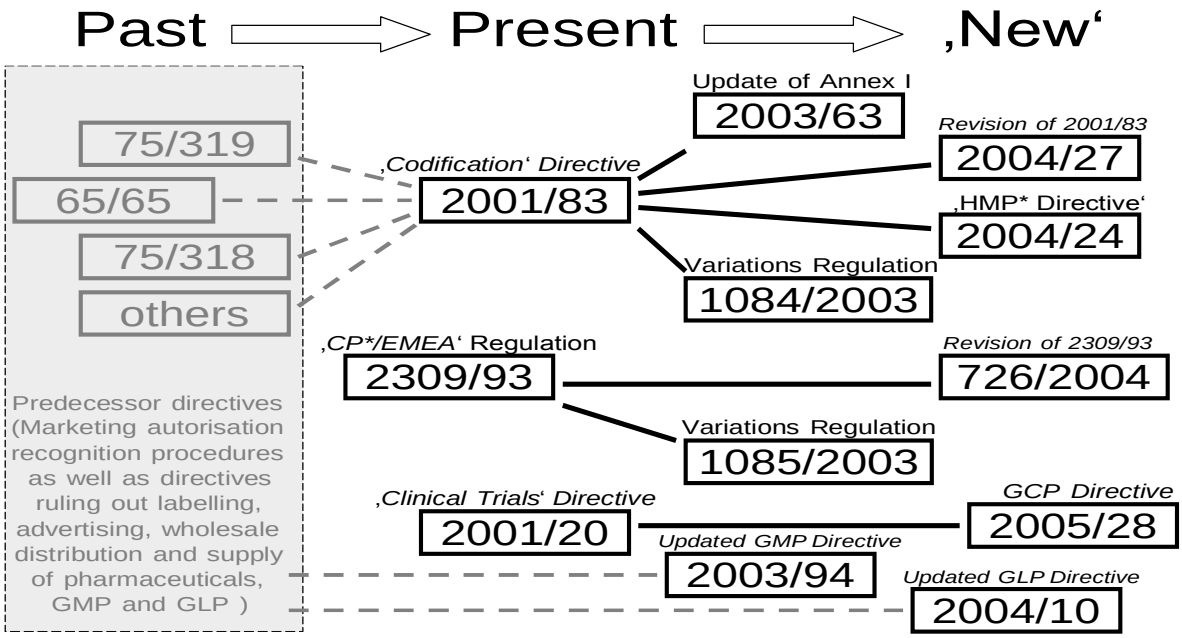

Figure 1: Central elements of the European pharmaceutical legislation: Relevant Directives and Regulations for MA. (Figure from the Drug Inf J (2005) Vol. 39, p. 196. Reprinted with permission of the authors)[i] CP* = Centralised procedure, HMP* = Herbal Medicinal Products

For clinical trials, the 'Clinical Trials' Directive 2001/20/EC [6] and to a much lesser extent the 'Good Manufacturing Practice' (GMP) Directive 2003/94/EC [9] contain the principal information for studies with investigational medicinal products (IMP) in humans[ii]. The CTD 2001/20 came into force as late as 1 May 2004 in order to let MS sufficient time to adapt their legislation to this entirely new piece of legislation dedicated to enhance European harmonisation within this matter.

[i] The cited publication (Hartmann M, Hartmann-Vareilles F. Recent Developments in European Pharmaceutical Law 2004: A Legal Point of View. Drug Inf J (2005) 39: 193-207) summarises the current status of European pharmaceutical law and will be used as a reference for legal aspects throughout this work. Therefore the review is attached as Annex I to this master-thesis.

[ii] In addition to the cited legislative texts, a number of documents with guidance character have been issued by the European Medicines Agency. As these documents mainly focus on aspects of clinical research methodology, they are not discussed in this thesis except in case they are essential for the question or topic analysed.

The issuing of the EU clinical trials directive in 2001 was completed 2004 by a series of guidelines ("soft law") including texts providing detailed guidance on

- the request for authorisation, notification of substantial amendments and declaration of the end of a clinical trial to the Competent Authorities (CA) (ENTR/CT 1) [10],
- the application format and documentation to be submitted in an application for an Ethics Committee opinion (ENTR/CT 2) [11],
- the collection, verification and presentation of adverse reaction reports and
- the Suspected Unexpected Serious Adverse Reaction (SUSAR) database: EudraVigilance – Clinical Trial Module (ENTR/CT 3 & 4) [12,13].

With regard to the requirement of a unique identification number of each new clinical trial entered into the European electronic reporting system (EudraNet), general (ENTR/CT 5) and specific guidance is available from the EU Commission and the European Medicines Agency (EMEA) how to obtain a unique 'EudraCT number' [14,15].

The most recent documents issued related to the CTD 2001/20 are the first 'Notice for Applicants' for the clinical trial process, available since begin of 2005 [16], and an additional Commission Directive, issued on 8 April 2005, laying down principles and detailed guidelines for good clinical practice as regards IMP for human use, as well as the requirements for authorisation of manufacturing or importation of such products [17]. Entitled to enact directives on their own, the European Commission has issued this 'GCP Directive' to accomplish implementing statutes cited in articles 1(3), 13(1) and especially article 15(5) of the CTD 2001/20.

1.3 Commission proposals for further legislative acts affecting clinical trials

Together with the 'Review 2004', additional provisions were announced in order to incorporate further specific areas of health care activities into the harmonisation process. Since, related proposals for regulations and directives have been issued by the European Commission that are currently in process of consultation and institutional review.

Most importantly, the proposal for an EU paediatrics regulation aimed at promoting medicines for children has been subject of thorough public interest since publication of its principles and content end of September 2004. Its provisions are focussing on the enhancement of the inadequate development of medicinal products for paediatric use. This 'Paediatric Regulation' [18] "is built on the public health foundation provided by the EU Clinical Trials Directive". Possible implications of that new proposal for non-commercial studies and IIT will be discussed in chapter 4.9.

New drugs for the treatment of cancer will require from 1 November 2005 on a mandatory assessment by the centralised procedure as laid down in Regulation (EC) No 726/2004 [19], independently if they arise from biotechnological or classical chemical processes. Like for other seriously debilitating and life-threatening diseases, the 'Compassionate Use' of new anti-cancer agents has been much debated. Incorporated into the provisions of Regulation (EC) No 726/2004, 'compassionate use' will be entered now within the EC legislation. It is intended for medicinal products awaiting a future MA but still having no 'mature' product (MA submission) dossier. The proposal from October 2004 for a 'Conditional Marketing Authorisation' for medicinal products [20] is addressed for products with a dossier already 'mature', but posing questions or requiring additional data for an unconditional MA. For medicinal products in early phases of clinical investigation or products not intended to gain MA (e.g. due to missing intellectual

property protection), a guideline on 'Exceptional Circumstances' is under preparation too [21]. The possible impact of these proposals on non-commercial studies will be discussed in chapter 5.

Much more specific, a draft guideline on data fields from EudraCT that may be included in the European database on medicinal products (EuroPharm) has been released too [22].

1.4 Provisions for academic or non-commercial clinical research and Investigator-Initiated Trials within the European Union's legislative framework

The CTD 2001/20 has introduced two new terms for the classification of clinical trials. In addition to ICH-GCP terminology with its well-established distinction between clinical and non-clinical studies, single- and multi-institutional trials and the concept of different study 'phases', clinical trial regulations nowadays must also deal with the differentiation of 'commercial / non-commercial trials' and 'interventional / non-interventional studies'. Table 1 summarizes the characteristics of both new categories.

Non-commercial trial
- Conducted by researchers without participation of pharmaceutical industry - Might be conducted with drugs authorised for prescription on patients with the same characteristics as those covered by the indication specified in the drug's market authorisation (In the latter case: Simplification of drug labelling)
Non-interventional trial
-- Usual manner of prescription in accordance with terms of MA - Decisions 'drug prescription' and 'study participation' clearly separated - No assignment in advance to a particular therapeutic strategy - No additional diagnostic or monitoring procedures - Epidemiological methods for analysis of collected data

Table 1: Definitions for non-commercial and non-interventional trials according to the CTD 2001/20 [6].

Recital No 14 of the CTD 2001/20 points out that non-commercial trials are characterised by the fact that their planning and conduct "does not require particular manufacturing or packaging processes, if these trials are carried out with medicinal products with a MA". Hence non-commercial trials can be conducted (in most cases) with drugs already marketed in the EU - but also with drugs, whose active substance, dosage form, strength or formulation has not yet been subject of an MA. Chapter 6 will briefly analyse the current situation for IIT with IMP not yet marketed in the EU.

Article 14 ('Labelling') states that in the GMP Directive [9] lays down adapted provisions for IMP (with a MA according to the codified EU pharmaceutical law) that are intended for clinical trials in which no particular manufacturing or packaging is required and in which patients as characterised by the Summary of Product Characteristics (SmPC) take part.

Apart from the definitions presented in Table 1 and the above mentioned articles, no specific provisions for IIT are provided in the CTD 2001/20.

A few more specifications on IIT were given in the guidelines published on 30 April 2004.

In guideline ENTR/CT1 [10], the question of non-commercial trials is indirectly addressed in section 4.1.6.2 ('Simplified IMPD'). Most importantly, the sponsor "may submit the current version of the SmPC as the IMPD, if an IMP has a MA in any MS in the EU and is being used in the same form, for the same indications and with the dosing regimen covered by the SmPC". Notably, it is possible to use the SmPC as well "for studies of dosing regimens not covered by the SmPC when the sponsor can show that the information in the SmPC justifies the safety of the proposed new regimen".[iii]

With view to Guidelines ENTR/CT2 to CT5, only ENTR/CT4 [13] mentions non-commercial studies, telling that "in general almost all non-commercial sponsors will fall into the category" of (obligatory) SUSAR reporting to the EudraVigilance Clinical Trial module and to the EudraVigilance Post-Authorisation module.

As a result, it can be stated that the CTD 2001/20 and the related guidelines impact on the classing of non-commercial studies and IIT:

- For the ones who will be - according to the new criteria described – classified as non-commercial, but interventional, only little minor alleviation will be offered with the possibility of a simplified labelling and, in some cases, a simplified IMPD.
- For other ones the option should be proved if they can be handled as non-commercial and non-interventional – avoiding in such a case that the CTD 2001/20 finds application.

With view to that new graduation that affects academic trials by upgrading regulatory hurdles for a majority of these trials, many critics on the CTD 2001/20 were expressed by the European research community.

In order to respond to stakeholders' critics, respective provisions were incorporated into the GCP-Directive from 8 April 2005 [17]. In recital 11, "the specific conditions, under which non-commercial trials are conducted", are recognised again. The directive recommends therefore that "MS foresee specific modalities to be applied to these trials not only when conducted with authorised products and on patients with the same characteristics". Hence "the condition under which non-commercial research is conducted by public researchers (…..), makes the application of certain of the principles of GCP unnecessary or guaranteed by other means". The notion of MS' specific responsibility for non-commercial trials, and also for trials for which no particular manufacturing or packaging is required[iv], is pointed out in the directive's chapter 2 as well.

2 DEFINITIONS AND METHOD OF ANALYSIS

The European 'clinical trials space' still knows a lot of local idiosyncrasies with reference to the classification of clinical trials. In addition to locally grown forms of epidemiological trials or retrospective observations on humans –conditioned by different medical schools- and country-specificities even with regard to prospective study types, further confusion in terminology may arise from the necessity to translate such terms adequately into English. Therefore, a list of definitions is mandatory for a proper distinction and classing of such investigations in humans. The thesis-specific definitions provided in chapter 2.1 are set for the purpose of classification, based on 'common' use of the terms.

[iii] It should be mentioned that the annexed application form for Clinical Trial Applications (CTA) contains in a footnote an official definition of a commercial sponsor: "A commercial sponsor is a person or organization that takes responsibility for a trial which at the time of the application is part of the development programme for a marketing authorisation of a medicinal product"

[iv] Note well: intended to commercial, but non-interventional Phase IV trials!

Second, correct wording regarding judicial terms appears as well to be a sensitive area for a cross-European analysis of legal and regulatory texts. Therefore, the use of a few common denominations is explained in chapter 2.1 too.

Finally, the methodology for analysis and this thesis' structure is depicted in chapter 2.2. It must be emphasized that for this thesis the 30 June 2005 was chosen as 'data-lock' time point. No literature or legislative documents that have been made publicly available after this date were considered for analysis.

2.1 Definitions[v] and explanations for the use of standard terms

Clinical trial(/study/investigation) (according to CTD 2001/20 [6]):

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more IMP(s), and/or to identify any adverse reactions to one or more IMP(s) and/or to study absorption, distribution, metabolism and excretion of one or more IMP(s) with the object of ascertaining its (their) safety and/or efficacy.

Non-commercial (or academic) trial (according to Guideline ENTR CT 1 [10]):

A trial conducted by a sponsor-investigator outside of a product development plan.

Often, but not exclusively, such trials in oncology are conducted by (academic) institutions dedicated to therapeutic research, as cancer research centres or university hospitals.[vi]

Investigator Initiated Trial (IIT):

Any trial that an (independent academic) investigator can initiate and carry out with a drug that has already a first marketing authorisation

For the purpose of this definition (see Annex II of Regulation (EC) No 1085/2003 'Ext. Applications' [23]) - a change of the pharmaceutical form or strength
- a change of the route of administration
- a replacement/modification by/of the active substance

is regarded not to fit in the scope of investigation of an IIT.

On the other hand, any change of drug (administration) schedule, its indication for use, its intended combination with other commercially available drug may be investigated by an IIT. Therefore an IIT can use a marketed medicinal product deviating from its intended, labelled use.

Phase I Study (Human pharmacology) (in line with ICH Guideline E8 [24]):

A clinical study designed to identify the side effects of new medicinal products and the highest dose that can be given safely (to cancer patients)

Phase II Study (Therapeutic exploratory) (in line with ICH Guideline E8 [24]):

A clinical study designed to evaluate the effectiveness of the tested drug for a particular indication or indications in patients with the disease/condition under study and to determine the common short-term side effects and associated risks

Phase III Study (Therapeutic confirmatory) (in line with ICH Guideline E8 [24]):

A clinical study designed to confirm the efficacy or therapeutic value of a medicinal product in the intended patient population statistically sufficiently large to reduce the error probability of the trial to an (generally) accepted level

[v] For definitions taken over from international guidelines, legal or regulatory texts, the sources are cited.

[vi] In the following, the term 'academic' will be omitted for purposes of simplification.

Phase IV Study (Therapeutic use) (in line with ICH Guideline E8 [24]):

Any investigation with products that have a marketing authorisation usually with the objective of ascertaining some new aspect of efficacy or safety

Phase V Study:

A study carried out as part of a clinical development program for a line extension of an already marketed product

The term is used by some authors [25] to distinguish the clinical development (Phase I – III) of line extensions from previously conducted pivotal studies for the first MA.

Post-Marketing-Surveillance Study (PMS):

An observation study intended to collect knowledge about use and especially safety of marketed products

Local idiom: DE: Anwendungsbeobachtung (AWB), Drug Utilisation Study, Estudio Post-autorisatión de tipo observacional (ES)

Related terms (according to ENTR CT 4 [13]): Post-Authorisation Safety Study (PASS)

Therapy Optimization Study (TOS):

Any investigation within or in close proximity to an existing marketing authorization (and primarily conducted by non-commercial sponsors)

The term is (almost) exclusively used in oncology and describes studies intended to optimize the use / practicability / tolerability of drugs and drug combinations. Examples for TOS include sequential drug application schemes or split-course schedules.

Local idiom: DE: Therapieoptimierungsprüfung (TOP), Systematischer Heilversuch [26]

Retrospective & Epidemiologic Observation Studies (according to [27]):

An analysis of a patient collective or a population aimed to obtain information about a specified question without using a pre-defined treatment plan for these patients but analysing data by statistical medicinal methods.

For other terms used for clinical research but not mentioned in this chapter, the definitions given in article 2 of the Clinical Trials Directive should be applied.

Directive & Regulation: Directives and regulations are two legal instruments of different scope of the European Commission (see Annex I). For 'regulations', indicating legislative acts issued by MS (in most cases subordinate legislation texts completing 'laws' in form of implementing statutes), the term is usually replaced by the term 'ordinance(s)'.

Guidelines & Guidance: The term 'Guideline' is restricted in this work to guidance documents issued at a European level (European Commission, EMEA), whereas 'guidance' is primarily used for accomplishing documents published by MS.

2.2 Method of analysis

Due to the complexity of the clinical research process, it is not feasible to describe all changes that were introduced by the European clinical trials framework. The impact of the CTD 2001/20 on pivotal (and) commercial trials has been subject of many meetings, presentations and publications in pharmaceutical, regulatory and legal journals. Hence it is assumed that the reader is in general familiar with the provisions of the CTD 2001/20

and with the subsequently published legislative texts and guidelines from the European Commission.

Assuming that a thorough knowledge of the actual clinical trial process in the EU is extant, the work presented hereby focuses primarily on the specific provisions for non-commercial studies and IIT and its differences compared to commercial (unsimplified) trials. Some legislative aspects (e.g. Informed Consent procedures or GCP-Inspections) do per se not differ, independently what kind of investigation is carried out, and are for that reason not discussed.

With regard to the mandatory transposition of the CTD 2001/20 into MS law, it cannot be expected that readers are familiar with directive's transposition and update of the clinical trial legislation in several or all MS. The last comprehensive review on clinical trial procedures in Europe been published ten years ago [28]. In order to respect the format and to limit the size of this thesis, a brief update of the transposition process is given in Chapter 3. More detailed information about the new regulatory environment for clinical trials in each of the eight MS analysed, are provided in form of reports in tabular form. The reports are attached to the thesis as Annexes II-IX and can be requested from the author.

An overview about the European legislation and Guidelines, taken into account for the present analysis, has been compiled in chapters 1.2 to 1.4. A listing of MS law texts, ordinances and guidance documents that are analysed is provided in chapter 3 too.

To avoid a lengthy country-by-country presentation, chapter 4 analyses key elements of the clinical research process, focussing on the question how far a harmonisation and - in case of alleviations specified for the trials in the EU texts – simplification has been reached for non-commercial trials after the process of transposition of the CTD 2001/20 by MS. Subsequent chapters 5 and 6 deal with specific topics of interest for physicians carrying out biomedical research.

A discussion of the transposition process is presented in chapter 7 in form of a 'feasibility scenario' for a pan-European multi-centre study, illustrating in form of three case studies advantages and problems for non-commercial studies and IIT in the European trials space. In a comparative manner, some interesting concepts and solutions of the US legislation are briefly discussed in Chapter 8.

3 TRANSPOSITION OF THE CLINICAL TRIALS DIRECTIVE 2001/20/EC INTO NATIONAL LAW

In September 2004, five months after its implementation, most MS had implemented the provisions of the CTD 2001/20. As reported during the FIP World Pharmacy Congress, only two MS with a relevant clinical research activity - France and the Netherlands – were still in the process of legal transposition. From MS with small populations, Luxembourg and the accession countries Malta and Cyprus were the ones with no legislation in place or legislation to come into force considerably delayed [29].

At begin of May 2005, one year after the directive's implementation should have been finished, the French and Dutch legislative process was still ongoing. In some other MS, subordinate implementing statutes were still in the process of finalisation. Table 2 summarizes the actual status of implementation of the CTD 2001/20.

With view to the foreseeable difficulties of transposition and interpretation by the MS, the Heads of Agencies group has established a Clinical Trials Facilitating Group, which met for the first time on 4 October 2004 [29,30].

Country	Legal Act	Title of Legal Act or Guidance Document	Date issued	Ref
Germany	Law	'12. AMG-Novelle'	30 Jul 2004	31
	Ordinance	'GCP-Verordnung'	9 Aug 2004	32
	Implementing Statutes	'3. Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen'	4 Jan 2004 (Revised Draft)	33
France	Law	Loi n° 2004-806 rel. à la politique de santé publique	9 Aug 2004	34
	Decree		pending	
UK	Law	'The Medicines for Human Use Regulations 2004'	31 Mar 2004	35
	Guidance	'Description of the medicines for human use regulations act 2004' provided by the MHRA		36
	Guidance	'Final Regulatory Impact Assessment' (FRIA)		37
	Guidance	'EU Directive on GCP in CT' DH & MHRA Briefing note'		38
	Guidance	'Access to information and guidance on the UK CT regulations' provided by the MHRA		39
	Guidance	'Clinical Trials Tool Kit' provided by DH and MRC		40
Belgium	Law	'Loi du 7 May2004'	7 May 2004	41
	Decision	'Arrêté royal du 30 Juin 2004'	30 June 2004	42
	Guidance	'Circulaire N° 447'		43
Sweden	Rule	'LVFS 2003 :6'	26 Jun 2003	44
Netherlands	Law	‚Wet medisch-wetenschappelijk onderzoek met mensen' (WMO)	16 Dec 2003 (pending)	45
	Guidance	'Instruction Manual – Clin. Res. with Med. Prod.'	29 Jun2004	46
Spain	Law	'Real Decreto 223/2004'	6 Feb 2004	47
	Guidance	'Acclaraciones sobre la aplicación de la normativa'		48
Italy	Law	'Decreto Legislativo 24 giugno 2003, N° 211'	24 Jun 2003	49
	Decree	'Decreto 17 dicembre 2004'	17 Dec 2004	50

Table 2: List of legislation and guidance documents of relevant EU MS transposing the CTD 2001/20 into national law.

4 ANALYSIS OF KEY STEPS OF THE CLINICAL TRIAL CONDUCT PROCESS AND OF 'HOT-SPOT'-TOPICS FOR NON-COMMERCIAL CLINICAL RESEARCH AND IIT IN THE MEMBER STATES

A vast majority of non-commercial trials are traditionally conducted with IMP for which already an initial MA has been obtained within the EU or MS. Therefore the analysis of the transposition process in this chapter focuses mainly on provisions for trials with commercially available products, for which a MA dossier is in hands of the EMEA or the CA (RMS/CMS). As pointed out in chapter 2, such studies are defined hereby as 'IIT'.

Figure 2 tries to demonstrate the complex relationship between the (new) classification terms and the well-known terms arising from clinical trial methodology.

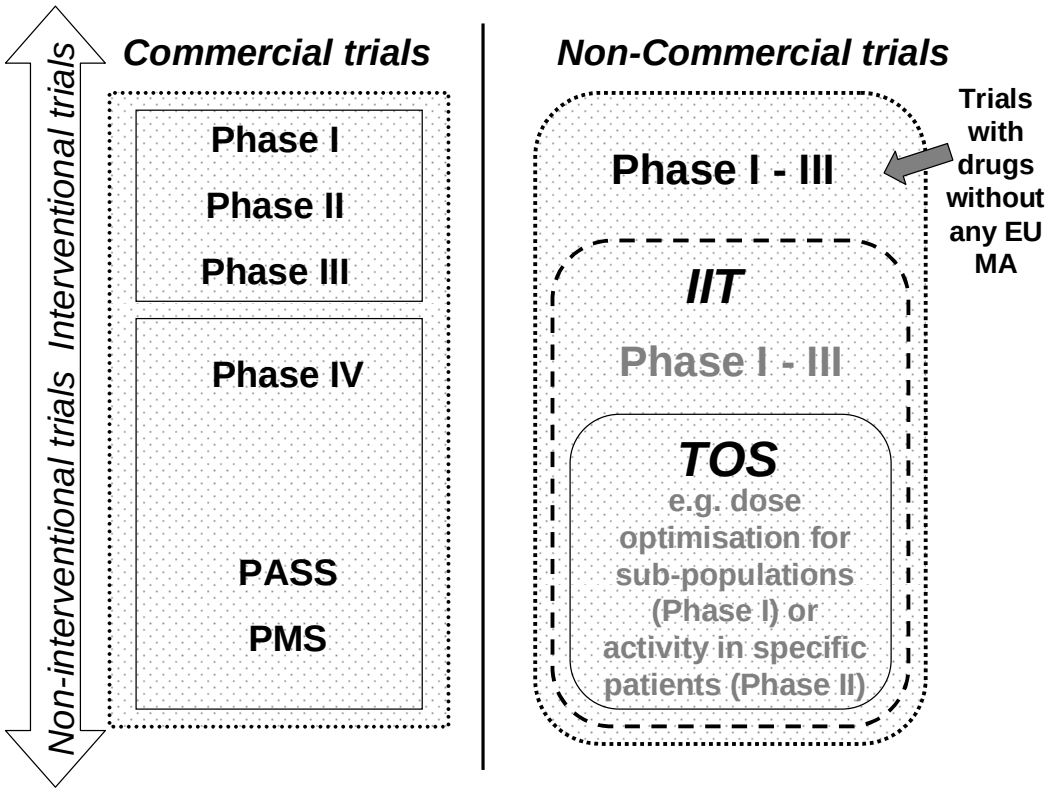

Figure 2: Relationship between trial classification and trial methodology terms.

The terms 'commercial', non-commercial' and 'IIT' use characteristics of sponsorship for classification whereas the terms 'interventional' and 'non-interventional' refer to regulatory issues: the content and the specifications of a SmPC rule out which trials are interventional and which are not. For the methodology terms 'phase I', 'phase II' and 'phase III', a wide-ranging agreement about their definitions can be stated. The term 'phase IV' appears to be more complex because methodological and regulatory intentions are merged. Competent authorities or supranational authorities like the EMEA or the Food and Drug Administration (FDA) can give order to a MA applicant, to carry out to 'post-authorisation studies' in order to resolve remaining uncertainty about characteristics of a product. Such 'post-authorisation' or 'phase IV' trials may range from PMS-studies, examining the 'therapeutic use' of a recently authorized drug, until additional phase III studies, comparing a drug's efficacy e.g. with a comparator. In the past, the FDA has used this tool often in case, MA decisions were accorded by the accelerated approval procedure [51,52]. In the EU, specific obligations for phase IV studies are common too [53]; the EU Commission draft regulation regarding 'Conditional Marketing Authorisations' provides in Art. 4 explicitly similar provisions [20].

In the following, special consideration is given to definitions of these terms, in case they are used in the legislation of a specific MS.

4.1 Scope of legislations and definitions

Historically, MS have established their clinical trial legislations from different starting points. In some MS, rules were worked out primarily to handle the circulation and specificity of pharmaceutical products still under development or intended for bio-medical use. In other MS, legislation was developed from the patient protection viewpoint, hence providing unifying rules for all kind of bio-medical research: trials with any kind of IMP, irradiation trials, improved surgical/therapeutic techniques or new medical devices.

A striking feature of the transposition process is the fact that the CTD 2001/20 as well as the 'GCP Directive' 2005/28/EC – both limited to trials with IMP – are incorporated into different legislative concepts in each MS, resulting in a kind of new horizontal disharmony for clinical trials conducted into the MS. Figure 3 outlines the current situation.

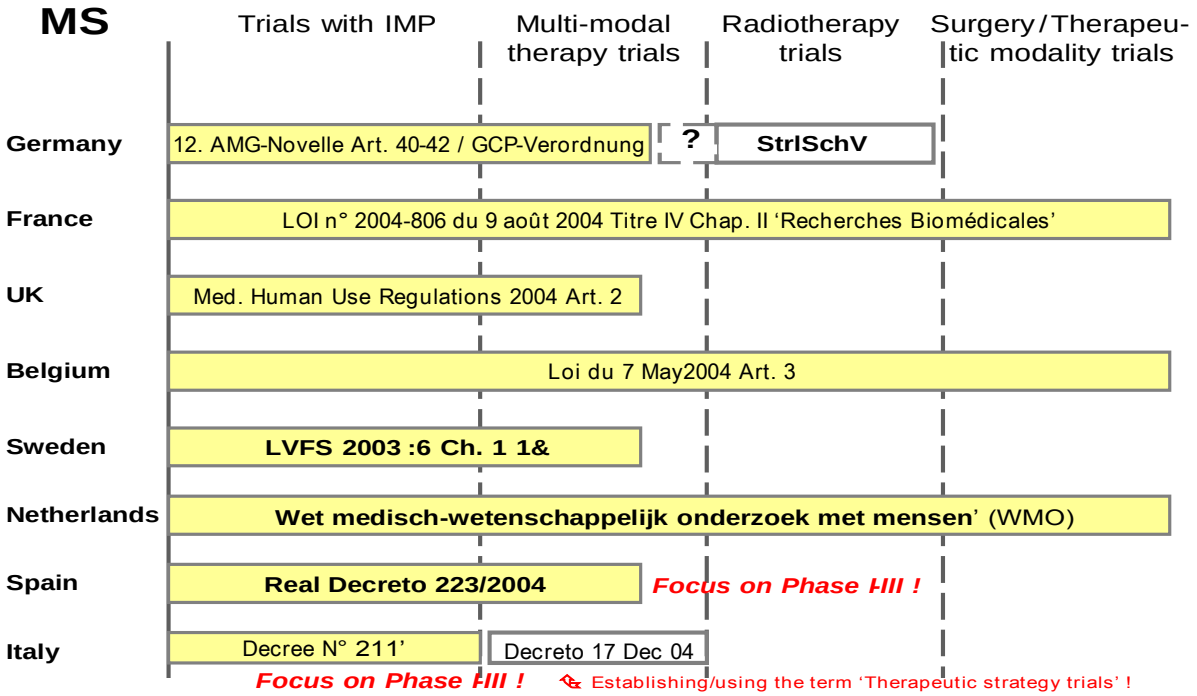

Figure 3: Scope of national legislations revised in order to cope with the requirements of the CTD 2001/20. Shadowed boxes indicate legislations affected by the transposition process [see Annexes II-IX].

The Belgian, Dutch and French exceptions represent the most striking features. Interestingly, these MS have different concepts of review for 'biomedical research' (FR) and 'experimentations on humans' / 'medical research on human subjects' (BE/NL). In Belgium, all experimentations, incorporating e.g. ones with biologic or embryonic material, have to be approved by an EC, whereas only 'clinical (drug) trials' are subject of submission to the CA. The Netherlands have established a flexible review system[vii]. In France, all biomedical research projects[viii] must be reviewed and authorised by both bodies.

[vii] In the Netherlands, 'low-to-medium-risk' medicinal research (e.g. trials outside novel therapy forms, trials with subjects able to give Informed Consent, phase III-IV trials and non-interventional trials) are subject of ethical review by a local EC (the central EC becomes CA!), whereas in high-risk trials ethical review is performed by the central committee (CCMO) with the Ministry of Health becoming the CA.

[viii] Including trials with (Recherche Biomédicale portant sur les médicaments) or without pharmaceutical products, trials with cosmetics, studies in behavioural sciences and investigations/sampling of biological material (tissue).

In Spain and Italy, only studies of phases I – III are intended to become regulated by the national medicinal products legislations. For Italy, this fact might be explained historically: since the issuing of a Ministerial Decree dated 4 Dec 1990 (Article 2), which was aimed at limiting post-marketing studies to those that were regarded as scientifically ethical and which was intended to exclude marketing promotion studies, only a very limited number of phase IV studies were conducted thereafter [28].

Italy like Belgium define non-commercial trials in their legislation. In Italy, a new decree from December 2004 [50] defines the non-commercial sponsor status as following: "a duly authorised institution, retaining ownership of data, and different from the health product patent's owner". Belgium law defines non-commercial research as follows: the sponsor is i) a university or co-ordinated hospital, a research organisation, authorized hospital unit or other authorized organisation; ii) different from the medicinal product's patent holder; iii) the intellectual property owner of the research's conception, its realisation and its scientific data [see Annex V]. Apart from both definitions, MS laws actually do not provide systematic definitions of non-commercial research. France uses instead the term 'institutional trials' outside of legal texts, an amendment to the revised 'Huriet Law' (the so-called 'Fagniez-amendment') is in preparation but mainly intended to lay down provisions for non-interventional trials.

Although only two of the eight MS have defined non-commercial trials, non-interventional trials are mentioned/defined in almost all legislations revised so far (Table 3).

Country	Legal Act		Terminology used	Notification	Ref
Germany	Law	§ 67	Anwendungsbeobachtung	(EC)*/CA	31,54
France	Law	L1121-1	No term established – Paraphrasing is used	EC	34
UK	Law	Part 1(1)	Non-interventional trial	-	35
Belgium	Law	Art. 2	Essai non-interventionnel	-	41
Sweden	Rule	3§	Non-interventional trial	-	44
Netherlands	Manual	Ch. 1.6	Observational study	CGR**	55
Spain	Law	Art.2	Estudio post-autorisatión de tipo observacional	EC/CA	47,56
Italy	Law	Art. 2	Sperimentazione non interventistica	-	50

Table 3: MS terminology in place for non-interventional studies. Legal obligations for non-interventional studies with medicinal products differ between MS. (*consultative, ** CGR = Stichting Code Geneesmiddelenreclame, a committee controlling pharmaceutical practice in the Netherlands)

In most of the revised legislations, non-interventional studies require neither a CA nor an EC approval. In France, ethical review is required nevertheless. A differing situation can be seen in Germany, where 'Anwendungsbeobachtungen'[ix] have to be submitted for notification to the national as well as regional authorities. The recommendations, issued by the BfArM, allow at the same time for 'cohort studies with groups for comparison', and demand for protocol set-up [54]. Similar provisions exist in Spain ([56], see Annex VIII), where phase IV trials are regulated apart from phase I-III trials[x]. Depending on the kind of phase IV trial, Spanish law lays down differing notification requirements.

An extended review of country-specific modalities in the clinical trial process after implementation of the CTD 2001/20 has been provided by the February 2005 meeting of

[ix] Defined to be per se non-interventional in the respective guidance document.

[x] Since 1990, dossier submission for phase I-III studies for clinical trials with IMP and CA approval were required in Spain for any trials from phase I-III – for phase IV trials graduated procedures were established.

the European Clinical Research Infrastructures Network (ECRIN) [57]. The comparative analysis on clinical research infrastructures and its legal environment inside six MS (Germany, France, Italy, Spain, Sweden and Denmark) summarizes the transposition process and its implications end of 2004 [58,59,60,61,62].

Another conceptual definition is used by Dutch authorities, differentiating between interventional and observational studies and between 'therapeutic' (phase III-IV) and 'non-therapeutic' trials (phase I-II). The classing is sometimes meaningful to decide, if ethical review is performed by a local (METC) or central ethics committee (CCMO).

4.2 Sponsorship in non-commercial trials: responsibilities, liabilities and research funding

Sponsorship and funding issues have been revealed to constitute the greatest challenge for non-commercial trials under the revised legislations. Many commentaries have outlined the difficulties to define and set-up 'public sponsors', reflecting the necessity for investigators in public and/or academic institutions, to take over the enlarged burden of sponsor responsibilities in association with their principal (institution) or financing charity [63,64,65,66]. The much differing context and background of public health systems and health care institutions in the MS renders the adaptation of existing sponsor constructs to the requirements of the CTD 2001/20 in some countries extremely difficult. The sponsorship issue was also a cornerstone of debate within a discussion, organised by the European Forum for Good Clinical Practice (EFGCP) in May 2005 in Brussels. The forum 'Examining the Value and Impact of the EU Clinical Trial Directive' pointed out the necessity to set-up 'public sponsors' for national like trans-national studies[xi]. The recently published Q&A document from the EU Commission [16] has underlined the legitimacy of co-sponsoring agreements to form organisations for clinical trials in such a way that "the collective agreement fulfils all the required roles and responsibilities of a sponsor". The concept of co-sponsoring, initially elaborated in earlier legislation from UK due the long-standing Anglo-Saxon tradition of charities and trusts funding and undertaking own research, might be copied now more widely in the EU[xii]. In contrast, a public or third-party co-sponsoring is still difficult in Spain, where actually a tendency towards industrial co-sponsoring in IIT is observed in favour to share the sponsorship responsibilities. The Spanish legislation does clarify the situation of 'observational studies' but does not mention 'non-commercial clinical trials' as an own specimen of CT - the trend towards industrial co-sponsoring might therefore reflect this legal specificity [see Annex VIII].

The difficulties to set-up sponsorship arrangements under the new EU-legislation are caused by raised legal responsibilities and subsequent liability issues. The sponsor takes over ultimate responsibility for the initiation, management and/or financing of a clinical trial [6], even if by co-sponsoring agreements the charge can be divided (e.g. financing) and even if an organization can be entitled by writing to act as a sponsor. For public (or institutional) sponsors or sponsor-investigators this definition indicates a cascade of legal questions which must be resolved (Figure 4). The term 'and/or financing' in the EU sponsor definition has initially raised concerns, if funding of a trial, e.g. by industry, already implicates an involvement into sponsor obligations. The Commission's

[xi] A résumé of this important conference, questioning the current EU-wide status of clinical research one year after the implementation date of CTD 2001/20, is enclosed as Annex X to this document.

[xii] The actual UK regulation points out that "the (new) regulations do not change the underlying allocation of responsibilities and potential liabilities in collaborative academic trials". In order to better reply to the new European framework, UK legislation has now denominated a "chief-investigator" for such trials [Annex IV]. Nevertheless, UK charities in general are not willing to take over sponsorship for trials managed outside the organisation [Annex X].

Notice to Applicants (NtA) from January 2004 clarifies the question in that way that "support from the industry by providing IMP free or at reduced costs or by providing financial or material or scientific support should not be taken to imply that industry is participating into the trial … and should not disqualify the trial from being regarded as a non-commercial trial" [16].

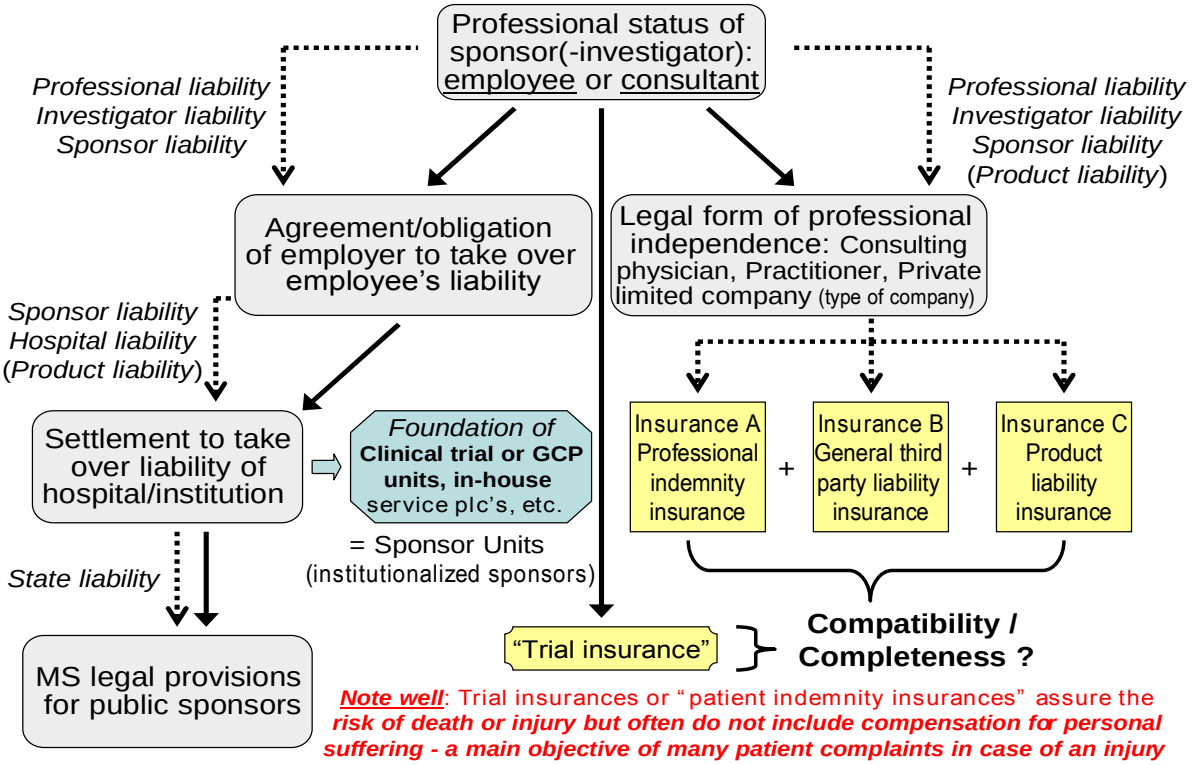

Figure 4: Sponsor responsibilities and the upstream take-over of liabilities for non-commercial sponsors and sponsor-investigators in public institutions. The set-up of 'institutionalized sponsors' in some MS serves as a model to collimate responsibilities in specific structures in form of private limited companies.

The resolution of the liability issues differs considerably from one MS to each other, depending on general public health care provisions and ownership models for public health institutions. Several countries had elaborated comprehensive legal frameworks for public biomedical research before the transposition of the CTD 2001/20, in which state liabilities guaranteed in general a coverage towards indemnities or recourse for those initiating and carrying out such research.

A look to the French and German ways to resolve the question of public sponsors is of interest to highlight the different approaches. In France with its dominant role of public hospitals[xiii], non-commercial biomedical research is carried out in form of 'institutional trials' within the regulative framework [see Annex III]. Therefore the civil responsibility is guaranteed by the institution in which the biomedical research project is carried out[xiv], covering cases of "strict liability" caused by investigator negligence or (hospital-intern) general third-party injury. Nevertheless, a trial insurance to cover patients for any

[xiii] In large towns, hospitals are grouped under one administrative roof [e.g. AP-HP "Assistance Publique – Hôpitaux de Paris » or AP-HL ("Assistance Publique – Hôpitaux de Lyon »)], in other areas hospitals are administered depending on their focus and role by the county, or by regional or national powers.

[xiv] In commercial trials, the sponsor has to provide a declaration ("Attestation d'Assurance Responsibilité Civile – Promoteur de Recherché Biomédicale") about a liability insurance guaranteeing for the research project's risk (patients' injury), and that of the investigator and the investigator's collaborators [Art. R.1121-2 -6 CSP].

protocol-related injury is requested too. In Germany, the situation is much more opaque and intrinsic due to the co-existence of community-owned hospitals and, to an increasing amount, institutions in private ownership. Research as well as health care are partly duties of the Länder, who are actually reviewing their liability provisions in order to match with the new requirements. Public-limited companies ("Sponsor GmbHs") and private hospital units are set-up, to address the issue and to resolve reimbursement questions in a manageable and transparent manner[xv]. The establishment of 'Co-ordinating centres for clinical studies' (KKS) inside university hospitals, proposed and founded by an initiative of the German Ministry of Research [67] in addition to independent 'Sponsor GmbHs', is seen as an attempt to build-up in-house-CRO-competence.

Strongly related to the key issue of sponsorship is the topic of investigator/sponsor liability and trial insurance. Traditionally, insurance and liability questions are national issues due to their linkage to social security provisions and EU MS' ongoing responsibility therein [see Annex I]. Insurance and liability questions have been recently identified as major hurdles for future non-commercial trials due to sharply rising insurance premiums doubling yearly since 2003, the notice of termination of existing annual group contracts by insurance companies and the withdrawal of insurers from the clinical trials market [Annex X]. A workshop held in May 2005 by the 'Vienna Initiative to Save European Academic Research' (VISEAR) was dedicated to highlight the current situation impacted by the transposition of the CTD 2001/20 [68].

Sponsor-investigators in non-commercial trials have in general to arrange for i) indemnities for subjects in clinical trials in case of injury or death, ii) the investigator's liability and iii) the sponsor liability. Adequate indemnity for trial subjects plus liability is required by the Art. 6 of the CTD 2001/20 which asks the EC to check that the provisions are met before an opinion can be issued. Apart from EU requirements, CA in France and Netherlands ask applicants, to provide them with the respective documents too. Differing liability classing is factual when comparing actual MS practice: in case of negligent (minor) protocol deviations ('no fault based insurance case') the principle of "strict liability" of the policy holder finds application in most EU MS, whereas in Germany and the Netherlands the patient insurance is regarded to potentially cover such kind of indemnification. In case of an obvious investigator fault, patients can refer for indemnity to investigator and sponsor policies. In Spain, the burden of proof for such negligence lies with patients. In case of a patient's death or injury whilst treatment was carried out in full accordance with protocol provisions, patients are EU-wide covered by the trial insurance, but differences remain in place regarding the amounts (individual or total per trial) specified by each MS and regarding the fact if and how far compensations for personal suffering can be demanded by trial participants.

From the insurer's point of view, cancer trials are confronting special problems due to the high rate of treatment and disease specific serious adverse events. At the EFGCP and VISEAR conferences, agreements with insurers to cover restrictively only SUSAR have been proposed as a solution to limit the cost explosion. Such an agreement should be based on a common understanding that cancer and/or treatment associated serious adverse events are disease concomitant symptoms not actuating an insurance liability.

In the UK, regulators draw much attention to the question of liability for public sponsors, mainly concerning trials carried out in facilities of the National Health Service (NHS). A joint statement of 'Universities UK' and the Department of Health (DoH) [69] clarifies the research liabilities taken over by the NHS. From the UK point of view, the CTD 2001/20

[xv] The situation of trial related costs has caused many concerns after Germany's Social High-Court decision from July 2004 (BSG-Urteil 22.07.2004) stating that any trial-related costs in drug trials are to be paid in total by the trial sponsor. The legislative body (Bundesministerium für Gesundheit und Soziales - BMGS) has therefore revised German law (14. AMG-Novelle, Art. 4 & 5 –Änderungen des Krankenhausentgeltgesetzes und der Bundespflegesatzverordnung), to modify the legal basis and to allow that the financial obligation of sponsors will be reduced in the future to the trial's relevant overhead costs [92].

does not require the provision of a "specific" compensation scheme for non-negligent harm (negligent harm = investigator liability) [38]. Hence, if an injury occurs in publicly founded trials, provisions are foreseen in form of an 'ex gratia payment' to trial participants. In line with the existing practice in the UK, commercial sponsors should nevertheless provide a no-fault compensation in case of personal injury resulting from clinical research[xvi]. For non-commercial trials, product-related liabilities are seen to remain related to the product manufacturer's liability[xvii]. Similar approaches, requiring by law specific patient indemnity provisions for commercial trials and offering state liabilities for publicly sponsored trials, are seen in Sweden and the Netherlands.

Due to the increased obligations of sponsors for the set-up, conduct and reporting of clinical trials, costs are supposed to increase considerably for studies under the new legal framework in the EU - especially in countries in which public sponsorship issues had been revised thoroughly. First estimates indicate a two- to three-fold rise for non-commercial studies [Annex X]. Concerns are expressed that this situation creates a stronger dependence of academic sponsors towards industrial 'co-sponsors'. In any case, fund-raising becomes the determining aspect of sponsor-investigator activity. To light up the situation in the EU, a survey about available non-commercial funding[xviii] in the EU MS has been recently conducted by the European Cancer Research Managers Forum (ECRM)[70]. The survey concludes that i) independent charities strongly support cancer research in Europe, ii) funding is (proportionally) insufficient for preventive and clinical research, iii) the per-capita and percentage spend in the EU remains four to five times below the cancer research spend expended in the United States. Among the leading funding bodies were public agencies from Germany, France and the UK (Table 4).

Rank	Country	Spend*	Rank	Leading organisations+	Spend*
1	UK	€ 388 m	1	BMBF (Germany)	€ 180 m
2	Germany	€ 353 m	2	Cancer Research UK	€ 174 m
3	France	€ 240 m	3	CNRS (France)	€ 100 m
4	Italy	€ 76 m	4	Medical Research Council (UK)	€ 97 m
5	Netherlands	€ 60 m	5	Deutsche Krebshilfe (Germany)	€ 60 m
6	Sweden	€ 57 m	6	Dutch Cancer Society (Netherlands)	€ 57 m
7	Belgium	€31 m	7	Deutsche Forschungsgemeinschaft	€ 50 m
8	Denmark	€ 22 m	8	INSERM (France)	€ 48 m
9	Norway	€ 22 m	9	DKFZ (Germany)	€ 46 m
10	Spain	€ 18 m	10	Department of Health (UK)	€ 40 m
11	Finland	€ 16 m	11	Cancerfonden (Sweden)	€ 34 m
12	Ireland	€ 13 m	12	AIRC (Italy)	€ 31 m

Table 4: Cancer research funding figures (Top-12) for Europe according to the ECRM survey [70] (* in million Euros, + Governmental (in italics) and non-governmental organisations)

[xvi] The ABPI's clinical trial compensation guidelines recommend such assurance for their members. For both, commercial and no-commercial trials, ethics committees are asked by the Universities UK and DoH joint statement to "continue to consider the need for it case by case".

[xvii] A specific NHS Litigation Authority's risk pooling scheme is in place to cover NHS bodies' product liability, e.g. in case of an injury caused by a drug interaction due to an (experimental) combination of drugs or in case of use outside of a drug's authorised indication.

[xviii] Including governmental and public funding as well as funding from charitable (not-for-profit) organisations.

4.3 The ethical review process

In the past, ethical review systems in MS were much differing due to a varying history and medical perception of ethical review in each MS. Depending on this complex background, single- or double-stringed EC systems have developed in MS. In some MS, the system's development has been driven primarily by legislation, in other ones by local initiatives, creating a decentralised network of local ethics committees. Belgium with its approximately 200 EC represents the latter approach and an example of a single-stringed system without neither hierarchy nor repeal instance, whereas the Dutch system with the CCMO and its strong central power reflects the idea of a double-stringed system.

The deliberation of one national vote in multi-centre-studies has been perceived as an outstanding achievement of the Clinical Trials Directive [71]. Independently from the Directive's requirement, some MS had already in the past done some efforts towards a consultation procedure for unified ethical review as in the UK through Multi-centre Research Ethics Committees (MREC) or by the '8. AMG-Novelle' 1998 in Germany, allowing the start of a multi-centre trial, once the EC of the co-ordinating investigator (Leiter der klinischen Prüfung (LKP)) had issued a positive vote.

Experiences with amended legislations and several reviews of the current situation after the implementation of the CTD 2001/20 show that the goal of a single opinion per MS and unified timelines for review has only partly been reached [72, Annex X]. The current status in some countries like Spain or Germany is best described in terms of a 'single signature for multiple opinions'. Inappropriate review times (e.g. 4-5 months in Spain), discrete dates communicated when submissions are accepted, and differences in legislation who communicates with the EC (sponsors versus investigators) are noted among the discrepancies that are still EU-wide present in today's ethical review process.

The duplicate system of approval by both, EC and CA, has strengthened the necessity of recognition and communication between both bodies under the new legislation. In Belgium, a unique split of responsibilities among them is observed. The parallel system, in which the CA focuses its review on quality and safety (with respect to CTD modules 3 and 4) and the EC on the clinical evaluation and the protocol, still allows sponsors and investigators to start with the trial if no objections from the CA were received within the delay specified. In order to adapt the Belgian system to EU requirements and due to its high density of EC (actually ~ 200), the evaluation of protocols can only be performed by EC evaluating more than 20 protocols/year from January 2006 on[xix].

As ethical review follows – independently from the question of who undertakes research - fundamental, non-tangible values, ensuring the protection of human beings that are subject to research, the sponsorship issue does impact only modestly on ethical requirements. Instead, more attention should be paid to open questions regarding to differences in the ethical review of non-interventional trials. The issue was discussed on the 'Conference on Research Ethics Committees in Europe', held in January 2005 under the auspices of EU Commission's Directorate General Research. Until now, rules of regional chambers of physicians differ in some member states (e.g. Germany): for some of them 'research on human beings' includes epidemiological studies and for others not. Apart from European mainstream is the French situation, in which also psychologists and epidemiologists, who do research in human beings, have to present their research proposals to a competent EC[xx] [71].

[xix] Belgian law provides an exemption for non-commercial trials regarding the fees payable to the EC and CA.

[xx] In addition, since the 'Loi Huriet-Sérusclat' came into force 1988, an ongoing discussion took place in France about the status of phase IV studies and the ethical procedures in research with human biological material. The status of phase IV studies, especially of non-interventional studies, will be addressed by the 'Fagniez' amendment (currently in preparation). Another specificity of the old French law, the differentiation of medical

A topic of ongoing discussion is the changed legal/professional statute of EC and respectively their limits of liability. The question is of minor importance in countries in which EC are installed and supervised by public order. In countries in which EC are established by medical institutions itself (in close analogy to the US-system of 'Institutional Review Boards'), the transposition of the CTD 2001/20 required legal clarifications of their statute and provisions for appeal procedures. For such 'semi-private' EC, additional liability insurances were either required or guarantees of state liability[xxi].

As a conclusion, in the EU major differences in the scope of ethical review are still present as well as differing legal provisions for EC's duties ranging from a pure opinion-issuing to comprehensive functions like the provision of methodological and scientific advice. For non-commercial multi-centre trials, the unachieved harmonisation at MS-level as well as at regional level still requires attention from multi-centre study co-ordinators.

Interestingly, new Italian legislation asks EC to verify the relevance of non-commercial trial protocols in terms of 'public interest' and 'patient benefit' in order to give such protocols access to specific alleviations laid down for non-profit research [50].

4.4 Investigational medicinal product dossiers and dossier approval by competent national authorities

The preparation and submission of an IMPD for an interventional clinical trial with an investigational medicinal product (IMP) and the dossier revision and trial approval by the CA in each MS constitutes one of the major innovations of the CTD 2001/20. Before, an explicit authorisation of new drug trials in humans was only mandatory in some MS: Spain ("Productos en Investigacion"), Sweden and the UK[xxii] [28].

Due to the detailed guidance laid down in the Commission's ENTR/CT 1 guideline [10], the MS have transposed the requirements on CA and IMPD in a quite harmonised way. No relevant deviations in practice (e.g. implicit versus explicit authorisation depending on the status of the medicinal products[xxiii] or regarding procedural timelines) are observed today, although differences in application/submission formats, additional forms and information requested and discrete provisions when to submit dossiers can be found among the MS.

Hence, non-commercial like commercial sponsors should be aware about some particularities in the present system. The Netherlands have voted for a system in which – depending of the nature and issue of a protocol – the Ministry of Health or the central ethics committee (CCMO) become CA: In cases in which a protocol is allowed to get reviewed by a local EC[xxiv], the CCMO examines the dossier. Anyway, in the Dutch system

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research 'with' or 'without direct individual benefit' for the participant has been excluded when the revision process took place that transposed the Clinical Trials Directive into French law.

[xxi] 'Semi-private' means EC set-up by universities or hospitals or Physicians' State Chambers. In Germany, some Länder took over full liability for EC, whereas in other ones the EC are asked to cover their liability by insurance – in such cases the Land takes over only the residual risk. Two Länder (Bremen and Berlin) opted for public EC, in the latter one as a consequence of the lawsuit of the State Chamber of Physicians in Berlin against the Land.

[xxii] By the 'Medicines Act' from 1968, UK has introduced quite early a framework and notifications for clinical trials. The Clinical Trials Certificate (CTC), its exemption - the Clinical Trials Exemption (CTX) and the Doctors and Dentists Exemption (DDT) – were ahead of the notification systems in place in other EU MS. Anyway, it must be noted that in the past more than 90 % of all clinical trials in the UK were run with a CTX or DDX.

[xxiii] In Spain, all IMP classified as 'productos en investigacion' (PEI) still require explicit authorization.

[xxiv] Which is the case in nearly all interventional studies with conventional therapies and patients able to consent.

the CA gives just an additional input in terms of 'grounds for non-acceptance' in case the European database indicates safety concerns for a product.

Italy as well has created graduated CA responsibilities: i) for well-known and established medicinal products the regional health unit ("Direcione Sanitaria") is entitled to conduct the review, whereas ii) the Higher Health Institute ("Istituto Superiore di Sanita") is competent for trials with new chemical/biological entities or iii) the Ministry of Health in case of experimental therapeutic forms like gene, xenocellular or somatic cell therapy.

As a majority of IIT are run with commercially available drugs, issues concerning alleviations of the investigational medicinal product dossier ('simplified IMPD') and the question of a reduction of fees payable to CA are interesting many sponsors. Regarding the simplified IMPD, all reviewed MS refer to the graduation scheme laid down in the Commission's guideline ENTR/CT1 (Table 1 in [10]). Anyway, caution is required to use the different ways of '(a)bridging' to existing dossiers or data: (i) Use of letters of authorisation to cross-refer to data submitted previously, (ii) cross-referencing to an IB for clinical and pre-clinical data and (iii) filing of a SmPC.

If a product in oncology is planned to be investigated in another indication (e.g. related organ or histology, or at an earlier stage of disease) such IMP is used outside conditions of the SmPC according to the European definition: non-clinical and clinical data are required. The German GCP-decree [32] allows alternatively the filing of the SmPC also in case, the substance is used 'in close proximity' of the labelled indication.

A practical problem with cross-references to an IB occurs, if a new version of an IB becomes available during the approval process. CA recommend in such a situation to wait until the CA's decision is issued and submit a note of amendment afterwards.

As a consequence of the transposition process and the trial registration via the EudraCT-system, industrial sponsors are obliged to centralise the set-up of sponsored IIT as integral parts of clinical development programs in order to obtain valuable data about the safety and efficacy of a drug in additional settings and patient populations. As the co-ordination of such activities becomes mandatory, often 'head-' or 'lead trials' are commenced in order to establish a dossier for 'referencing' e.g. into separate indications. Further studies by non-commercial sponsors can then be run, using such a dossier and an authorisation for simplification during the submission process. This might result in a stronger dependence of non-commercial sponsors from pharmaceutical companies, as the agreement to cross-refer may depend on factors like the attainable patient population or the national regulatory framework for non-commercial trials in MS.

Several MS have – in order to favour conditions for non-commercial trials – set forth fee reductions for such trials. Belgium (Art. 31 §5: no fees payable to EC and CA!) and France (Art. L1121-11: 90% reduction for CA approval process) are actually leading the way [34,41]. In the UK, trial fees are graduated depending on the kind of submitted dossier: Phase IV studies, cross-referral dossiers (to an existing CT application) and follow-up protocols (same product and sponsor) are taxed between 140 and 100 £ - representing only 5-10 % of the amount of phase I-III IMPD fees with unknown investigational products. Italian legislation also foresees financial alleviations for non-commercial sponsors, but it is not yet clear to which extent CA related fees become reduced. In Germany, it was possible in the past for non-commercial sponsors, to obtain a fee exemption, but in an opposite move compared to other MS, this alleviation has been recently cancelled[xxv] - IMPD fees now expand solely on the extent of examination.

At a glance, some MS like France or Spain continue to focus in their CA approval on new IMP, i.e. products intended to be investigated for the first time in humans, whereas in other countries such a focus can not be observed.

[xxv] A respective note about fee reduction was present in the first draft of the German 3. Bekanntmachung zur klinischen Prüfung (Version Date 26. Aug 2004), but has been deleted in latest draft version (4 Jan 2005).

4.5 Investigational medicinal products and labelling issues

For Investigational Medicinal Products (IMP), the Clinical Trials Directive allows in recital 14 for facilitations of "trials whose planning does not require particular manufacturing or packaging processes if these trials are carried out in with medicinal products with a marketing authorisation … and on patients with the same characteristics as those covered by the indication specified in this marketing authorisation". Not restricted to non-commercial trials but fitting with a portion of these trials, this statement has been questioned and discussed widely. Labelling of the IMP "intended for trials of this nature should be subject to simplified provisions". The definition of an IMP applies to active substances or placebo tested or being used as a reference in a clinical trial.

Differences in the transposition process of these requirements have been reported regarding co-medications. More comprehensive definitions of IMP in order to overcome differing national view points are requested [see Annex X]. For labelling issues, sponsors of non-commercial clinical trials should be aware that the labelling, the manufacturing permission and importation procedures remain closely linked to national regimentations, therefore asking for an accurate, maybe decentralised handling of these requirements in case of international multi-centre studies. Guidance in some countries explicitly notes the possibility to separate the documentation of these processes from the (Core-)IMPD [32].

German legislation states in line with recital 14 that 'depending on the concept of a specific clinical trial' with marketed medicinal products for which no supplementary manufacturing or packaging steps are required, no outer labelling on containers or packages is needed [31].

4.6 Conduct of non-commercial clinical trials and IIT

The Clinical Trials Directive has raised the standards for the conduct and supervision of clinical trials in the EU. The need to monitor clinical trials, the trial amendment and termination provisions and the creation of a GCP-inspection system at MS and EU level were subject of many meetings and discussions. The new legislative framework is requesting extended resources for regulatory maintenance [73].

Regarding the monitoring of clinical trials, the CTD 2001/20 contains no written obligation towards monitoring activities or frequency but notes "quality requirements" (Art. 1) and the need to provide "assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible". The GCP Directive uses the term "monitoring policies" and refers to ICH-GCP's statement of 'adequateness' [5].

Although in the past some commentaries have stressed the fact that every clinical trial conducted in the future had to been monitored, an analysis of the transposed legislation does not match this view. The function of a monitor has been expressively noted only in the French (L.1121-3) and Spanish (Art. 36) legislation. French legislation puts its focus on the data protection issue and obliges the monitor to keep strict confidentiality, whereas Spanish legislation gives a comprehensive listing of a monitor's function and its obligations. Swedish legislation acknowledges (Ch. 8, 1§) the need for quality control (monitoring) and quality insurance (auditing). A similar distinction of quality assurance and control is incorporated in the Dutch texts (Ch. 3) – describing in a flow chart the monitor's duties: Checking completeness, accuracy, consistency, reliability and procedures. Belgian, German and UK legislation are only mentioning the need for 'compliance with GCP' and the utility of 'adequate quality assurance systems' to guarantee the validity of data.

Apart from these notions, MS have not laid down any provisions for the extent and frequency of monitoring, although the risk assessment differs between a phase I trial with an unknown product and a phase IV study or IIT with a well-established product. In addition, performing monitoring at different depths strongly impact on trials' costs. An exemption hereby is France, where the INSERM and the organisation of public hospitals at Paris (AP-HP) are developing a classification system for monitoring with following levels: A: low risk, B: same as usual care, C: phase III, D: phase I-II, biotherapy etc. For the UK, the idea of risk-assessed monitoring has been previously expressed too [74]. In Germany, a research project has been initiated to develop and validate adequate monitoring-models for IIT [75].

Regarding the trial amendment requirements and termination notifications, MS have followed quite closely the detailed guidance provided by the EU guidance document [10].

Sponsors and investigators of non-commercial trials must note that the number of GCP inspections will multiply at investigational sites – independently from the kind of trial executed - and will trigger again in several MS the payment of fees. Inspections from the EMEA can be reasoned by routine or random sampling, cases of concern or issues identified by inspectors (e.g. in clinical trial authorisation or MA approval dossiers) or can be simply based on 'noteworthy' publications in peer-reviewed journals [Annex X].

For the final study reporting, the lack of many European languages in MedDRA (Medical Dictionary for Regulatory Activities) as compulsory terminology for coding and the fees for MedDRA access are seen as obstacles for non-commercial trials. Regarding the last point, discussions are ongoing between the EMEA and MedDRA that licences for non-commercial trials should be waived [Annex X].

4.7 Informed Consent, data protection and ownership, transparency

Independently of sponsorship, the objective to get the best possible patient safety and data quality is an explicit obligation for any clinical trial. Data protection is a central data management issue and a legal obligation for non-commercial trials too. Today, diversities in national regulations are still in place according to the MS responsibilities for the rights of privacy. The same applies to the topics data ownership and data transparency.

Informed Consent procedures are of major importance to guarantee patients' protection. This requisite had been adopted already previously in the legislation of each EU MS. Changes incorporated by the CTD 2001/20 touch the current practice in so far that regulations had to be adapted to EU requirements regarding the Informed Consent of minors and adults unable to give Informed Consent. Therefore MS definitions of the legal representative have been clarified and harmonised to some extent. Regarding clinical research in emergency situations, the question of 'surrogate consent' of critically ill patients without legal representatives and/or family members or partners is solved in a differing way is each MS. A comparative survey about the situation for emergency research in the EU has been recently published [76].

As mentioned, data ownership issues start to play a distinctive role inside definitions of non-commercial sponsors. Related to the sphere of intellectual property rights, a rising demand for regulation has been expressed over the last years, culminating in calls to improved, unbiased practices of trial data publication in order to diminish industry's influence on publications. The current initiative from the 'International Committee of Medical Journal Editors' and the 'Ottawa statement' result in a restricted acceptation of clinical trials for peer-review and publication from July 2005 on: trial protocols must

previously be registered in a publicly available clinical trial register [77,78,79]. Broadly welcomed by the scientific community, this approach carries nevertheless potential pitfalls for European academic research [80,81].

Sponsor-investigators today have to take into account different development stages of transparency policies for clinical trials in the EU: In the UK, clinical trials registers have been set-up since 2001 [82], resulting from an initiative from the ABPI, the UK Cancer Coordinating Committee for Cancer Research and the MRC Clinical Trials Unit [83]. Spanish legislation already incorporates an obligation to publish trial results. Italian legislation asks the investigator for a statement for independent, final publication of results as a prerequisite to classify a trial as non-commercial. In other MS, discussions are ongoing to resolve the emerging development, characterised by lawsuits against pharmaceutical companies[xxvi], single initiatives to enhance the transparency and the trust into commercial drug studies [84] and MS requests to develop the discussion within the European regulatory framework [85].

Although the actual EU legislation does not yet lay down detailed requirements for registry and publication, investigators should be aware of the changing environment and national policies. The mandatory notification of each trial in the EudraCT database and the allocation of a unique clinical trial number are required to submit the IMPD to EC and CA for approval. The provisions laid down in Art. 88a of Directive 2004/27/EC [86] and Art. 57 of regulation 726/2004 (EuroPharm) indicate that later relevant information about clinical trials running in the EU will be made publicly available (Draft ENTR CT/6 [22]).

4.8 Pharmacovigilance-Reporting

The CTD 2001/20 has written down new obligations for trial sponsors: An annual safety report, the reporting of the Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Events (SUSAR) within fixed timelines to the EC and CA as well as the submission of a final report to the authorities. In addition to the requirements of the CTD 2001/20, general reporting rules for manufacturers, sponsors and investigators are reviewed due to the revision of pharmaceutical legislation ['Review 2004', see Annex I]. Nevertheless, pharmacovigilance will remain primarily an area of MS responsibility.

This bunch of new measures has requested all MS to review their pharmacovigilance legislation. In France and Germany, the drug respectively health law has been revised and reflects now the augmented pharmacovigilance standards. In other MS, pharmacovigilance changes were introduced by several decrees, dealing on one hand with general requirements laid own in Directive 2004/27/EC [86] and on the other with pharmacovigilance aspects related to CTD 2001/20 - rendering an overview about the sum of adopted measures difficult. Therefore the analysis will focus exemplarily on one country. In Germany, a recently published guidance document [87] summarizes the new pharmacovigilance modalities. Investigators must report all[xxvii] SAR as well as adverse events, judged to be 'critical' by protocol, to the trial sponsor; physicians should report all (unexpected) adverse events during the therapeutic use of medicinal products to the manufacturer ('spontaneous reports'). For sponsor-manufacturers, a bundle of reporting requirements is in place and include the collection and revision of any data arising from spontaneous reports, case reports from published literature, reports sent from other commercial sponsors (e.g. in case of combination studies or comparator-reporting) or

[xxvi] New York attorney E. Spitzer against an Anglo-Saxon group in case of suppressed trial data on Paroxetine, a selective serotonin reuptake inhibitor. The lawsuit ended with settlement, in which the company committed to putting summaries of the results of all company-sponsored clinical trials into a clinical trials register [84].

[xxvii] Except those identified in the protocol or IB as "not requiring immediate reporting"

other CA, solicited reports (registries, surveys, etc.), and reports from PMS/PASS, including data from non-interventional studies. All these individual case safety reports (ICSR) will be incorporated into the Eudravigilance post-Marketing module, whereas SUSAR from clinical trials will be stored in its CT module.

The raised reporting obligations create several problems for sponsor-investigators:

- Should the pharmacovigilance reporting for Eudravigilance be done by i) the sponsor, ii) the manufacturer (who might support/finance the trial) or iii) the CA?
- How can the sponsor-investigator reporting to a CA of other MS be resolved in case of international multi-centre studies?
- How does a sponsor-investigator get access to other accurate safety information in order to perform its duties of annual reporting or modified risk/benefit analysis?
- How to ensure that a SUSAR really is (still) a SUSAR, if no access to the full database of the IMP is possible, e.g. in case of a commercially available product?
- How to perform reporting for CT starting before 1 May 2004?[xxviii]
- How to organize data management in order to inform all investigators in a multi-centre study timely and to have fresh data available for annual reporting? What timeline has to be respected for the reporting to investigators?
- What about SUSAR reporting in radiotherapy or surgery trials, in which registered drugs are used in the control arm?

At a glance, many questions are still unsolved for the pharmacovigilance reporting of non-commercial trials. The CTD 2001/20 makes no distinction between reporting in early phase drug registration trials and reporting in TOS. Timelines for reporting of SUSAR (7d/15d) are harmonised throughout the EU and the safety reporting for patients' sake has been intensified since May 2004 – some EC already report that they can not deal anymore with the large flood of information – but the new reporting requirements constitutes a challenge for large, international multi-centre non-commercial trials.

4.9 Costs, 'reimbursement' & off-label use

A central element of the CTD 2001/20 is the obligation for any trial sponsor to provide the investigational medicinal product free of charge. For non-commercial study sponsors, this requirement constitutes a supplementary financial barrier to initiate clinical trials – especially in therapeutic indications like cancer where innovative medicinal products are usually positioned by the manufacturers in the top-edge pricing category. The provision of study medication free-of-charge by manufacturers and mechanisms allowing for public take-over of costs or 'reimbursement' are the two principal ways for non-commercial sponsors to charge for the costs of IMP.

Some MS have incorporated procedures into their legislation allowing non-commercial sponsors to provide commercially available medicinal products free-of-charge: Belgium, Sweden, Italy and probably the Netherlands, where a General Governmental Measure (AMvB) will come into force when the new law is implemented – allowing the payment of the cost of registered drugs by another body than the sponsor[xxix].

Italian legislation foresees not only that non-commercial sponsors have access to commercial drugs without providing it free-of-cost, but fixes as well modalities covering insurance costs for public bodies acting as sponsors and uses the income deriving from new fees to 'cover the costs of inspections relating to monitoring of those trials whose sponsor is a public or non-profit agency or facility or a non-profit scientific association'.

[xxviii] Such a provision is foreseen in guidance ENTR/CT4 (p.7).

[xxix] According to Newsletter N° 4 of the Dutch EU Directive Implementation Working Group (6 May 2004).

The Swedish law contains similar provision for the costs of an IMP. An 'application for exemption' should be submitted to the MPA at the same time as the application for authorisation of the trial. Exemption may be granted, for example, "in trials where the IMP is used in accordance with the market authorisation (TOS)". Interestingly, it is the Swedish MPA which is charged to decide about cost take-over in contrast to Italy, where the EC decides, if the status of a 'no-profit study' can be applied for a trial and subsequently IMP reimbursement is accepted [50]. An exemption from the IMP-furnishing-for-free principle in case of trials within the product's labelling range is also provided by Belgian law.

In paediatric oncology, clinical trials were used in the past to legalize the off-label use of medicines in children. Because nearly all cytotoxic drugs were never tested in such populations for regulatory purposes, non-commercial trials are urgently needed to set-up medical evidence in these patients and to allow easier reimbursement for the concerned drug regimen, used 'off-label'. The new paediatrics regulation [18] is proposed, to change this unsatisfactory situation [88,89,90]. It is hoped that in 5-10 years the situation in paediatrics might improve.

'Off-label use' is common in rare malignancies too. As commercial drug development programmes are most often run in just a few cancer indications due to the limited time of intellectual property protection, preferring those with high incidences, some rare cancer types are lacking to a certain degree innovative medicines too. Non-commercial studies often test in such rare cancers commercially available, still patent-protected drugs that are widely used with a well-known safety profile in large indications. Due to the limited number of patients especially in smaller MS, such trials of public interest must often be carried out in form of international multi-centre studies in order to test efficacy and safety in a confirmative way. Concerns are tremendous that these trials will suffer most from the impact of the CTD 2001/20 due to lack of advocacy and funding [Annex X]: the financial, administrative and reporting efforts are enormous if e.g. in smaller MS the one participating, investigative site is able to enrol only 1-2 patients per year. Today, only the Swedish legislation has taken into account the situation allowing for public cost take-over of IMP classified as "orphan drugs with a small retailing volume".

An opposite move has been recently observed in Germany. As mentioned before on page 15, not legislative action but a decision of Germany's High Court for Social Affairs from July 2004 has considerably shaken all sponsors carrying out clinical research in Germany. Stating that "any trial-related costs in drug trials are to be paid in total by the trial sponsor" and prohibiting public sickness insurance funds that were willing (!) to take over in part indirect costs related to the hospital stay of patients due to the participation into a clinical trial[xxx], to do so, many sponsors and some university hospitals stopped to carry out clinical research. In order to resolve the situation, the German BMGS has announced in a publicly available letter [91] that the specific situation of clinical studies including TOS is taken into consideration by the 14th Amendment of the German Drug Law [92] requesting a proportionate participation of sickness funds in clinical trials to reduce the sponsors' financial duty to trial-related overhead costs. In other MS, similar provisions have been incorporated for years into social and reimbursement law to arrange the need for continuous medical research and the promotion of public health by innovation on the one hand and the obligation for public health insurance systems on the other to apply to the principle of an economic, effective use of resources in order to limit public health expenses to an affordable level. The French practice of hospital-based experts who evaluate in cooperation with investigators and pharmacists study-related extra costs compared to standard therapy, has proved to be a reliable method to evaluate economic aspects of clinical trials – independently from the nature of the sponsor.

[xxx] By the argument that the patient required in any case medical care (treatment/hospitalisation) independently of the decision to participate into a clinical trial.

5 SPECIFIC IMPLEMENTING STATUTES FOR THE USE OF INVESTIGATIONAL MEDICINAL PRODUCTS IN MS

Outside of clinical trials, a patient has limited possibilities to gain access to medicinal products not yet approved for his/her specific medical condition. Such exceptions include:

- Compassionate use of an investigational product,
- Off-label use of a medicinal product, which is approved for a different indication,
- Importation of a medicinal product from another country.

Apart from off-label use and single-patient-use importation, which remain to be ruled by MS legislation, specific compassionate use regulations are put in place in only two MS: France and Italy [93,94]. The EU Directive 2004/27/EC allows in Art. 5(1) for national regulations in terms of supply of unapproved medicinal products [95]. Applying above all to single-patient use of unlicensed medicinal products, the directive's article can be interpreted as the legal basis for compassionate use in Europe. In order to give patients with serious and life-threatening diseases missing therapeutic alternatives better access to innovative medicinal products, the Regulation EC No. 726/2004 expressively underlines in Art. 83 the MS right to make drugs "available for compassionate use" [19].

The Italian decree from 2003 addresses both standard compassionate use situations:

- a single, 'nominative' use of an unapproved drug on a physician's demand,
- a group-wise use for patients either treated before with an IMP inside a clinical trial or for patients with rare and/or life-threatening diseases requiring such therapeutic alternative.

The requesting physician constitutes a kind of protocol as defined in the decree and submits it to his EC. In parallel, the MoH has to been notified. Medicinal products used for compassionate use are delivered free-of-charge from the authorised pharmaceutical manufacturer. Data gained from compassionate use can be used to support MA dossiers.

The French ATU constitutes a more comprehensive framework merging elements of compassionate use (single 'ATU nominative' and collective 'ATU de cohorte') and conditional MA. Applicable for drugs that have shown strong evidence of clinical efficacy and an acceptable toxicity, the cohort ATU is limited to drugs for which a MA procedure is ongoing or actively pursued by the respective manufacturer. Valid for one year, the cohort ATU can be renewed. The drug costs are covered by the French Social Security.

In other countries, compassionate use had been done until now under the umbrella of existing MS clinical trial regulations, often in form of 'open protocol studies'. As the situation is seen as unsatisfying, unequal on a European level and not in line with the amended legislations after transposition of the CT Directive 2001/20/EC, the EU Commission and the EMEA are actually elaborating the three acts described already in Ch. 1.3[xxxi]. Intended to enhance patients' access to innovative therapies, the guidelines on 'compassionate use' and 'exceptional circumstances', both not yet available, and to a minor extent 'conditional marketing authorisation' [20] will impact on MS legislation.

In contrast to the French ATU, 'compassionate use' will on the European level be clearly separated from the authorisation of a conditional MA and will apply the free-of-charge principle for IMP. For academic sponsors, the new provision might allow to gain therapeutic experience with new medicinal products, to build medical evidence in form of (retrospective?) evaluations of compassionate use experiences and to offer cancer patients innovative therapies. Therefore compassionate use programs for patient groups might serve to address therapy optimisation needs in form of incorporated therapeutic use programs/studies.

[xxxi] Respective acts are actually foreseen for MS legislations, e.g. in Germany by the 14. AMG-Novelle [92].

6 NON-COMMERCIAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS WITHOUT ANY MARKETING AUTHORISATION

This chapter analyses two specific border-line cases regarding clinical trials with products that have not yet obtained a MA within the EU.

Following cases can be distinguished:

The active drug substance has not yet been authorised neither in the EU nor in other ICH-regions. The drug substance is i) already included into a clinical development plan of a pharmaceutical company or ii) is developed and manufactured itself by an independent research laboratory or the academic institution.

The first case refers to drug development programs as carried out e.g. by the National Cancer Institute (NCI) in the United States, who runs own trial and development plans among others for rare cancer populations or for new substances (e.g. hypothesis testing for new therapeutic classes), for which a commercial clinical development is not foreseen. Due to the prospective character of such trials (which might trigger subsequent clinical development programs) and the necessary risk-assessment for such IMP, for which no extensive safety data exists, such trials must be considered in any case as interventional. If a pharmaceutical company agrees to provide the IMP, the research institution should be considered as Contract Research Organisation (CRO), able to take over some or all sponsor duties (according ICH-GCP 5.1.8[5]) for that trial, but quality issues and GMP questions remain in such case in general in charge of the manufacturer. If the research institution has developed itself the IMP, the institution bears all sponsor-responsibilities.

In both scenarios, full accordance with the provisions of the CTD 2001/20 for interventional trials must be assumed by institutions conducting such trials. The patient protection issue in clinical research projects from non-commercial sponsors, testing self-developed new therapeutic instruments, e.g. engineered haematological cell lines or biotech-derived immunological products, has been a driving force for the law-makers in Europe to subject the conduct of all clinical trials to the same applicable GCP-standard.

7 FEASIBILITY SCENARIOS: INITIATION AND CONDUCT OF NON-COMMERCIAL TRIALS IN THE EU - A CRITICAL DISCUSSION

In order to discuss the impact of the transposition process of CTD 2001/20 on the conduct of clinical trials in a concrete manner, three hypothetical 'case studies' are developed in the following. The cases, each with an 'evidence-based medicine' proved background, are chosen in a way to critically highlight borderline situations and problems specifically arising for IIT in oncology in the context of the new regulatory environment.

Case 1: Studies for the evaluation of radiotherapies or surgical techniques are not subject of the CTD 2001/20. For such investigation into humans, rules are given primarily by the GCP principles and the related EU and MS legislation. It is of particular interest to pose the question how a randomised multi-modal trial, which adds chemotherapy (or radiotherapy) to an existing (multi-modal) therapy, should be handled by the authorities.

Case 2: The definition of a non-interventional trial requires attention: A non-randomised 'trial', using drugs 'in accordance' with their MA, not requiring additional diagnostic methods compared to standard care and intended to enhance tolerability of an existing standard care, is primarily of non-interventional character. But any prospective context (hypothesis generation, sample number calculation, elaboration of a 'treatment protocol', 'assigning' patients to that 'treatment protocol') classifies such activity as interventional.

Case 3: Labelling of modern drugs is based on phase III trials with highly specific and somewhat homogenous patient populations. A 'line extension' of a narrow label can mean to use the drug in earlier-stage patients (in general in better health condition, associated with a reduced co-morbidity and a better drug tolerability) or to use the drug in other late-stage patients with cancers of another organ system known to behave similar in terms of susceptibility, resistance and tolerability. The question of interest is, if the actual regulatory environment facilitates one direction of such prospective evidence-building.

Case 1 Sequential chemo- and radiochemotherapy in inoperable stage III NSCLC

Background: A meta-analysis in 1995 has shown an advantage for sequential radiochemotherapy (CT-RT) in inoperable, locally advanced non-small cell lung cancer (NSCLC), compared to radio-therapy (RT) alone (Cancer Coll Group, BMJ 1995). US Phase III studies (ECOG4588/RTOG8808) confirmed these findings (Sause, JNCI 1995). Significant advantages were observed also for simultaneous radiochemotherapy (RTCT), compared to RT (Schaake-Koning, NEJM 2000). By comparing CT-RT and RTCT, a significant survival advantage could be shown for RTCT (Furuse, JCO 1999) despite of significant haematological toxicities. Both approaches incorporating platinum-based chemotherapy are currently part of national consensus recommendations (e.g. in Germany RTCT, see Thomas, Pneumologie 2002), the ESMO thereof recommends CT-RT (ESMO Minimum Recommendation, Ann Oncol 2005). A phase I/II study has indicated an advantage for an intensifying combination of both approaches (CT-RTCT) (Willner, Lung Cancer 2001), using Paclitaxel-Carboplatin. Since, several large phase III trials in NSCLC confirmed the superiority of platinum regimen compared to platinum free doublets, and the superiority of Cisplatin towards carboplatin.

Concept: To test CT-RTCT compared to CT-RT in a large phase III setting, using a 3rd-generation platinum-doublet (CIS/VINO) for chemotherapy-induction and concomitant use.

Regulatory status: Both drugs are authorised in the indication, (Cisplatin: EU approved in 1996, labelling "small-/non-small cell lung cancer"; Vinorelbin: EU approved in 1989, labelling: "mono-therapy or combination with Cisplatin in stage III/IV NSCLC") and are widely used in NSCLC. Vinorelbin is in major EU markets still a drug of choice for NSCLC (very high retailing volume).

Protocol Synopsis: International multi-centre, randomised phase III study. A sample size of around 370 patients is required to detect a 10% difference in 1-y-survival (70% vs. 60%; 2-sided log-rank, α=0.01, β=0.20). Follow-up planned for 5 years. PFS and toxicity secondary endpoints. The toxicity of both arms has been investigated in previous phase II studies (Ruíz, Proc ASCO 2001; Carabantes, Proc ASCO 2001), the dose-limiting toxicity is linked to RT (esophagitis °III/IV).

Regulatory questions: Both drugs are used within their labelling, their safety profile is well known. Does the extension of the dosing schedule (prolonged, hence simultaneous use in the experimental arm) constitute an intervention in terms of the CTD 2001/20? From the radiologist's point of view, the main question is, if the phase II tested radiation volume (60 Gy for RT & RT/CT) can be maintained. Could this trial been set-up as a radiotherapy trial in SE, UK and IT with solely EC approval? Would the trial in France be approved by the DGS (Direction Général de Santé), if later on French investigative sites join the study group - or by the AFSSAPS, if the trial is judged to fall under the medicines legislation in France? If the trial has to be run under the CTD 2001/20 legislation, the realisation of the study concept might strongly depend on the Italian decision, if the IMP can be applied free-of-charge there. Should therefore the trial be set-up simultaneously in SE and UK or should the Italian decision be awaited? Would the latter strategy be feasible in case that a UK-based charity or hospital is foreseen (and willing) to take over "sponsorship"?

Assessment: The sponsorship and funding issues will constitute central problems to be solved - like in almost all future international IIT, in which public sponsors are requested to take over liabilities outside their home country. Both drugs are either generic (CIS) or at the end of their life-cycle (VINO), so support from the MA holders ought not to be expected. In addition, the non-harmonised scope of legislations for biomedical research shows up as another big challenge. Other questions regard the status of radiologists – it has to be clarified if each radiology department (often administrative independent hospital entities) constitutes an own investigative site in addition to the medical oncologists administering the chemotherapy at each investigative site.

Case 2 Split-course therapy in metastatic transitional cell cancer

Background: The MVAC regimen has been the standard treatment for locally advanced and metastatic urothelial cancer for the past 15 years. In a pivotal, randomised phase III study with 400 patients, the combination of Gemcitabine and Cisplatin has shown to be equally efficient in terms of survival and progression-free survival, but less toxic (von der Maase, JCO 2000). Based on this favourable risk-benefit ratio, the regimen has been approved and became a widely accepted regimen in bladder carcinoma. In the following, a large EORTC study has investigated the combination, adding Paclitaxel as third drug (results not yet published). Other groups have modified the four-weekly dose regimen (GEM 1000 mg/m² d1,8,15; CIS 70 mg/m²d2) in order to improve compliance whilst maintaining dose intensity, because 50% of patients require a dose reduction on days 8 and 15 (Soto Parra, JCO 2002). In other platinum sensitive tumours like NSCLC or Ovarian cancer, splitting of the cisplatin dose has shown to be an adequate measure to reduce toxicities in combination regimen and to avoid extensive hydration and co-medication aid.

Concept: To test split-course cisplatin (40 mg/m² on d2+9 in combination with the favourable dosage of GEM on d1+8 (q3w)) in a cohort of 46 patients. The investigative site has used the q4w regimen routinely but liked to reduce the percentage of patients (40%) with grade III/IV toxicity.

Regulatory status: Both drugs are authorised in the indication, (Cisplatin is labelled for "mono-/ combination-chemotherapy in bladder carcinoma"*; Gemcitabine for: "locally advanced or metastatic bladder carcinoma in combination with other cytostatics").

Protocol Synopsis: Phase II non-randomised, based on the Fleming design**, α=0.01, β=0.20). The regimen is expected to reduce the event rate of grade III/IV thrombocytopenia, neutropenia & nausea (combined score) at 50% (primary objective): max. 9 toxicity events in 46 patients.

Regulatory questions: Both drugs are used within their labelling. No additional monitoring or diagnostic procedures are required, no assignment in advance to a particular therapy strategy is necessary. Is this 'trial' an interventional one, if the changed therapeutic use is observed systematically in 46 patients to have a statistically interpretable result?

Assessment: The investigator should seek advice at his EC, to know if this investigation has a) to be submitted to the EC (in general yes) and b) if it constitutes an intervention according to the CTD 2001/20. MS legislation in Spain, Italy and Germany actually let some space to consider such a prospective research project as non-interventional.

* To be noted: Some generic versions of Cisplatin include this late line extension, whereas other ones (including the originator product) do not contain this labelling. ** All biometrics calculations are done using: Machin D, Campbell MJ et al. Sample Size Tables for Clinical Studies. 2nd Ed., Blackwell Science, London, 1998.

Case 3 Explorative investigation of a recently authorised monoclonal antibody

Background: Monoclonal antibodies (MAb) are state-of-the-art medicinal products that have recently led to significant therapeutic advantages - among others in breast cancer, non-Hodgkin lymphoma and the colorectal carcinoma (CRC). Clinicians around the world actually investigate these newly available drugs in clinical settings and indications that are not yet approved.

Concept: An university-based investigative site (e.g. in Germany) might work out two investigational plans: a) to test MAb X in earlier stage CRC patients (adjuvant therapy) or b) to investigate the drug in oesophageal cancer (2nd line salvage therapy), as this tumor is known to present a promising high receptor status of MAb X's target protein on the tumor cell surfaces.

Regulatory status: MAb X is authorised for the use in late-stage colorectal cancer in chemotherapy refractory patients.

Protocol Synopsis: Phase I/II study to confirm the dose established in metastatic CRC in the new patient collective (a six-patient cohort tested in advance with intra-patient dose escalation) and to investigate response rate in 30-50 patients (Simon-two-stage-design for each setting). The MA holder of MAb X agrees to provide commercial ware free-of-charge to the investigative group.

Regulatory questions: Is any specific alleviation for non-commercial trials applicable for the two concepts? How can the trial be performed and what obligations have to be respected regarding the IMP? Is simplified labelling feasible in this situation? Does a simplified IMPD fulfil the requirements of the CA?

Assessment: The trial is interventional. In accordance with the new legislation, the IMP can be provided free-of-charge. An advice of the CA is required to clarify if the simplified labelling

according to Art. 14 of the CTD 2001/20 can be applied. Regarding this point, MS legislations are slightly differing in the transposition of the directive and allow diverging interpretation.

For IMPD submission, the sponsor-investigator must clarify in cooperation with the CA how far he can simplify the dossier (assuming that no letter of authorisation exists to cross-refer to the data submitted by the MA holder for other ongoing clinical trials). German legislation would allow for a SmPC-submission plus clinical report, listing the known clinical evidence in case that the product is used outside of the labelling, specified hereby as differing "indication, dosing regimen, therapy duration, application form". Such a 'close proximity' rule is very useful to facilitate such explorative testing in oncology and would favour the conduct of the trial in Germany. Anyway, no evidence if available, if the CA differentiates between the testing in an earlier stage of disease in the same anatomical area (adjuvant CRC therapy) and the testing in another organ class (2nd line therapy in oesophageal cancer).

These case studies are intended to make the incertitude better understandable clouding on the set-up of many clinical trials under the new legislative. Especially borderline trials (in terms of the legislations' scope and the Directive's new classifications) are concerned.

The last question in Case 3 is of particular interest, as future rules established either by national CA or the Clinical Trials Facilitation Group will influence the expectant handling of off-label use in the MS. For this high-calibre topic of future guidance, it is interesting to see how the question is handled within the United States.

8 A LOOK ACROSS THE BORDERS: THE REGULATIONS OF THE FOOD AND DRUG ADMINISTRATION FOR THE CONDUCT OF NON-COMMERCIAL STUDIES IN THE USA

In the USA, the regulatory framework for clinical trials is constituted in a different manner. Any clinical experimentation with a medicinal product not yet marketed in the US requires an Investigational New Drug (IND) application. The IND concept focuses on drugs (=products) in contrary to the CTD 2001/20 dealing with clinical studies (=processes). Exemptions from IND[xxxii] are granted in case that i) a study is not intended to support FDA approval of a new indication or a significant change in labelling; ii) the study is not intended to support a significant change in the advertising of a product and iii) the study does not involve a route of administration, a dosage level or a use in a patient population that 'significantly increases the risks' of the use of the product. Studies run with an IND exemption must respect IRB and Informed Consent regulations and must be conducted in accordance with Part 312.7 of the Code of Federal Regulations.

The cited listing contains a definition of 'non-commercial study', underlines the required distance between clinical research and promotional activities and establishes the principle of 'significant risk increase' as decision instrument whether a proposed study falls under the IND rules (=interventional) or gets an exemption (=non-interventional).

As IND applications entirely cover the pre-marketing life-cycle of a product, specific rules for studies run by an IND exemption were issued by the US Department of Health and the Food and Drug Administration (FDA). Table 5 lists the existing guidance documents.

The guidance document from December 1998 points out that data from "experienced, independent cancer trials organizations" with well-established quality assurance procedures might be used as "alternative sources of clinical study data" in order to promote supplemental applications for new uses of cancer treatment products. The FDA states that data and analyses from these sources has found "generally to be highly

[xxxii] According to US Code of Federal Regulations (CFR), Title 21, Ch. V, Part 312.2(b)

credible and reliable". Afterwards, a guidance document has been issued in October 2001, to lay down minimum data and quality for independent trials providing data for marketing applications.

Document Type	Document name	Date issued	Scope of Application	Ref
Guidance for Industry	FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biol. Products	December 1998	CDER/CBER	96
Guidance for Industry	Cancer Drug and Biological Products – Clinical Data in Marketing Applications	October 2001	CDER/CBER	97
Guidance for Industry	IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for Cancer Treatment	January 2004 (Rev. 1)	CDER/CBER	98
Guidance for Industry	Available Therapy	July 2004	CDER/CBER	99
Guidance for Industry	Reports on the Status of Post-marketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997	Draft guidance April 2001	CER/CBER	100
Report	Report to Congress Reports on Post-marketing Studies [FDAMA 130]			101

Table 5: US guidance ruling non-commercial trials and post-marketing studies in the US

Non-commercial studies not intended for later label changing are described in the IND exemption guidance document from January 2004. The FDA position on IND exemptions is risk-assessment based. Increased risk is defined as a deviation in the planned investigation from approved-label-use. In oncology, "modifications of labelled dosing recommendations are common", the same is stated for 'off-label use': "Such treatment of individual patients with approved drugs within their clinical practice does not require an IND". Any systematic practice should be subject of an IRB review, if doubts occur, if such a study 'significantly increases the risk'; the FDA offers advice on the applicability of the IND exemption on request. Studies in oncology that are generally IND-exempted include

- Single-arm, phase II trials using marketed drugs to treat cancer different from that indicated in the approved labelling, but at similar doses and schedules,
- Phase I oncology trials of marketed drugs if judged appropriate for the patient population (i.e. patients with residual cancer) without existing effective therapy,
- Studies of new combinations, if these combinations have been described in the 'professional medical literature'[xxxiii],
- Studies of new routes or schedules of administration not described in labelling[xxxii],
- Studies of high-dose therapy, if using adequately evaluated regimens appearing to have an acceptable therapeutic ratio.

Studies generally not exempted include

- Studies of cytotoxic drugs in patients in which cytostatics are not standard therapy,
- Studies of adjuvant chemotherapy in populations of low risk of recurrence and beneficial survival benefit produced by existing therapies,
- Studies involving substitution of new agent of unproven activity in settings where standard therapy provides a cure or increase in survival, and again

[xxxiii] An initial study of the new drug combination should have ordinarily been performed under an IND.

- Studies intended to support approval of a new indication or change of labelling.

The FDA's point of view offers space to IND-exempted, 'non-interventional' trials in phases I-II in late-stage cancer patients without therapeutic alternatives[xxxiv]. Interestingly this series of guidance documents is intended to cancer – similar documents are not available for other indications except – to a certain degree – for anti-HIV drugs. The FDA conception shows that clinical cancer research and prospective therapeutic use research has gained specific acknowledgement and promotion by the US regulatory system.

Last, but not least, US regulatory guidance exists for phase IV studies too. The draft document from April 2001 describes the scope of post-marketing studies, carried out in most cases as part of post marketing study commitments in line with the accelerated approval procedure or the paediatrics regulation. A post-marketing study might be conducted as well on a sponsor's initiative without any request or requirement by the FDA. Applicants may conduct post-marketing studies on their own initiative for a variety of reasons, including the evaluation of a new indication or a new delivery system for a drug. Such studies can also been used to gather additional information about product safety, efficacy, or optimal use. Post-marketing studies are also used to evaluate chemistry, manufacturing, and control (CMC) issues, which are important for ensuring consistency and reliability in drug production. They are reviewed by the FDA according to the rules laid down in section 506B of the Federal Register.

9 CONCLUSION AND OUTLOOK

It must be noted that conclusions drawn from the analysis of the transposition process described in Chapter 4 must be regarded with caution. The results are obtained by i) a comparison of legal texts and their 'interpretation' (based on personal/professional experience, background and viewpoint); ii) the inclusion of third-party articles, statements and presentations coming either from scientific & regulatory journals (a portion of them in form of letters and editorials – hence not peer-reviewed) or from the internet. Therefore this report is not fully validated, because it is not possible to verify independently statements, data and figures reported from cited sources.

European-wide regulations for non-commercial trials constitute an intricate task from the legal point of view as these trials have specific characteristics: they are a part of public scientific research which continues to be authorised, initiated and financed by public institutions in the MS. Also, important issues of non-commercial trials are linked to liability and financial agreements with public health and social security bodies – an area which remains according to the EU treaty under the "responsibility of the MS". Today, rules for non-commercial trials within the EU continue to be divergent, as they are partly influenced by EU harmonisation enforcements and partly ruled by MS-specific provisions.

The eight countries analysed in this thesis were chosen in terms of their capacity to fund non-commercial research [70], their (patient) population [102] and their activity into clinical cancer research [103] – granting the first two categories double weight.

The MS have transposed the requirements of the CTD 2001/20 respecting their legal obligations. Therefore areas which were specified by detailed European guidance are harmonised to a certain degree through the Union. In technical issues like timelines for the trial authorisation process, harmonisation has been reached. More general questions

[xxxiv] Herein the US system is clearly positioned with regard to the last question posed in Ch. 7.

are still open for non-commercial as well as commercial clinical trials: Will studies be evaluated similarly throughout the MS? Do comparable views for risk/benefit assessment exist? How to deal with negative opinions in single MS in case of multi-centre studies?

For non-commercial trials, the new European legislation framework does not facilitate the conduct of interventional studies. Sponsor liability issues, raising worries regarding insurance conditions, missing structural and educational support to set-up trials and funding problems are repeatedly listed among the major hurdles [104,105,106].

In oncology new vertical (between therapy forms) and new horizontal disharmonies (between member states) can be stated, favouring e.g. radiotherapy and surgery trials in countries, which have separate legislations for interventional drug studies and for other forms of therapeutic trials. Like in other indications, the 'single EU-sponsor' concept ultimately stops EU-wide multi-centre cancer trials. A reinforcement of clinical research at national level might therefore be expected. In this context questions have been raised if the enforcement of measures does result in a better 'protection' of patients as the number of initiated trials and therefore the access of patients to innovative therapies and, in most cases, to an enhanced quality of medical care and follow-up seems to slow-down [107]. Because registers and statistics about clinical trials were not routinely maintained in the past, the quantitative impact of the CTD 2001/20 on the number of trials can only be estimated. Table 6 is an attempt to list the available data on trial statistics.

Country/ Year	Non-commercial trials [% of total]	Cancer trials # [% of total n]	Cancer trials [non-co. vs. co.]	Paediatric oncology [no-c. vs. c.]	Ref.
FR 2002	24% (of 1260)		45% / 55%	74% / 24%	108
IT 2000-04*	23% (of 2459)	31% (of 2459)	46% / 54% **	No data	109
IT 2002	No data (of 545)	34% (of 545)		No data (of 135)	109
DE 2002+	No data (of 1494)				110
NL 2002	No data (of 659)				111
UK 2002§	(~30%) (3069)				112
DE 2004-05++	17% (of 65)				110
EMEA 2004-05°	14% (of 2917)				113

Table 6: Available figures about clinical trial conducted in some EU MS 2000-2004 (* until June 2004, **n=756 trials total, +Summarized figures for BfArM and PEI, ++Data from PEI for Aug 04 – Mar 05, °Mai 04 - Mar 05, §All permissions for trial conduct including DDX and CTX, DDX is used as a surrogate for non-commercial trials, #Oncology & haematology trials)

Interesting is the conformity of the French and Italian data regarding the proportion of non-commercial trials rising from 24 (all indications) to 45 percent for cancer trials. As presumed this portion rises again in paediatric oncology. The first available figures regarding the post CTD 2001/20 era are not yet mature to allow any interpretation. Regarding cancer trials, first statements from funding bodies (UK NCRN) and research organisations (EORTC) indicate a 30-50 % decline of new trials submitted for research grants or for protocol review. Due to the inadequate data for the pre-authorisation era, it will remain difficult to quantify the impact of the CTD 2001/20 on the number of non-commercial trials conducted in the EU. Italy, where an official trial notification system is in place since 2000, may produce the next years the most valuable impact indicators.

Italy and Sweden might be the countries gaining most on attraction for the conduct of future non-commercial trials - primarily due to the comprehensive alleviations in terms of cost take-over for IMP. The political pragmatism to create a positive research

environment starts to be paid off by an increasing number of applications [114] and a very positive perception of the new conditions[xxxv]. Belgium, after the UK and in line with the Netherlands a country with a (historically) very huge amount of clinical trials carried out per habitant [42], might be able to obtain the density of research due to its pragmatic, low-administrative provisions and allowances, like in the Netherlands, for cost take-over. The Belgian co-ordinated EC-CA system will probably attract phase I trials.

The UK, long time leading in the EU, has undertaken considerable efforts to assess the impact of the CTD 2001/20 [37] in advance. Its provisions to solve the tricky task of responsibilities for public sponsors are exemplary [69]. Nevertheless, for the UK (declining from a high level) like for France and Spain, the transposition of the CTD 2001/20 in MS law will probably result in a slow-down of non-commercial clinical research activities. A specific situation is observed in Germany where an assessment of the impact is difficult due to the interfering High Court decision on trial costs (see Ch. 4.9), resulting in wide-ranging reluctance of non-commercial sponsors to get involved into clinical trials. An easement of the situation is expected by the 14. AMG-Novelle [92].

Medical research will continue to constitute in clinical oncology as in other areas of medical practice a vehicle for professional acceptance and reputation. It can be presumed that the willingness of physicians and institutions to carry out clinical research and publish its results continues to exist. As a result of enforced financial and administrative barriers to conduct clinical studies with medicinal products, a move towards questions that can be answered by non-interventional trials might be seen in the near future.

For medical oncologists, it might be more rewarding to set-up trial projects focussing on radiotherapy and surgical techniques. Future ESTRO trials may exclude France and the Netherlands to a certain degree. Phase III trials optimising polychemotherapeutic approaches, used e.g. in Small-cell lung cancer or Non-Hodgkin lymphoma, will particularly be attracted by exemptions from the IMP free-of-charge concept and by provisions for trial-adapted monitoring.

Apart from such regulatory-strategy reflections where to conduct a specific clinical trial in the EU, much international teamwork is needed to resolve borderline questions, created by the new legislation:

- Do multi-modal radiotherapy trials incorporating 'standard care' chemotherapy fall in any case under the provisions of the CTD 2001/20 – a query at EU & MS-level?
- Where ends the 'proximity' to the SmPC-labelling and how far a CA is willing to advice and set-up rules for a "proximity test"? ("Essential proximity"!)
- Does a systematic therapeutic use investigation in heavily pre-treated, late-stage patients without therapeutic alternatives necessitate an 'interventional trial'?
- Should therapeutic use research to some extent be incorporated into the category of non-interventional research?

Until now, only a very limited number of comparative law and comparative regulatory studies have been published [76,104,115,116]. The authors remark how complex the actual framework became after transposition of the CTD 2001/20.The ongoing adaptation of the GCP-Directive and recent guidelines will ask for further regulatory activity at MS level. Due to the numerous open questions and the missing harmonisation, further actions towards a unified trial authorisation process are desired. The proposal of a single trial approval and opinion process has been expressed recently [117]. In public discussions the wish for such simplification becomes apparent as well [Annex X].

[xxxv] Galletti P. Commentary: Italy's new renaissance. GCP Journal, May 2004.

10 SUMMARY

The issue and transposition of the Clinical Trials Directive 2001/20/EC constitutes a landmark for the clinical research process in Europe. Put into place under the auspices of the European Commission's DG Enterprise, the Directive and its enclosed guidelines set forth a modified framework of rules for pivotal studies conducted by commercial sponsors. Founded on the unifying principles of GCP, the Clinical Trials Directive and the GCP-Directive 2005/28/EC regulate as well the conduct of non-commercial studies.

This master-thesis is aimed to investigate the impact of the European legislative process and its transposition into national legislation on the future conduct of non-commercial clinical studies and IIT. The analysis is focussing on clinical cancer research representing an area of unmet medical need and a major scientific, medical and socioeconomic challenge. Carried out in form of a comparative study, the transposition of the Clinical Trials Directive and the present clinical research environment in eight EU Member States (Germany, UK, France, Spain, Italy, Belgium, Sweden and the Netherlands) is analysed in order to depict a picture of the actual status quo of clinical research in the EU.

At a glance, the easiness for physicians to carry out medical research on human beings has been diminished. Today, sponsor liability issues, the provision of drugs free-of-charge, raising worries regarding insurance conditions, missing structural and educational support to set-up trials and funding problems are named as major hurdles to conduct non-commercial trials. The new framework asks for considerable administrative and regulatory maintenance and requires the implementation of quality assurance systems.

A discrepancy between the goals of the directive (enforcement of patient protection, enhanced drug quality standards for clinical trials, elimination of red-tape, R&D speed-up and transparency) and the results might be stated regarding the set-up of the initial GCP framework in the EU. Nevertheless patient protection is enforced especially in case of non-commercial clinical trials carried out with investigational medicinal products not manufactured GMP-conform in the past. Such GMP or GCP deviations were assumed to occur more frequently in case, manufacturing processes took place at university-based plants or at biotech spin-offs.

Regarding the future regulatory process, the scenario remains unclear. The GCP-Directive now gives Member States more flexibility, to rule investigator-initiated trials able to show enormous public health benefits. Of interest is, if Member States follow the actual SmPC-ruled classification system for IIT ("essential proximity") or if they develop like in the US a risk-assessment approach offering physicians more choice in patient-focused research.

11 LIST OF ANNEXES

Annex I Review : Recent Developments in European Pharmaceutical Law 2004: A legal Point of View

Annex II Source Materials Germany : 'Nicht- kommerzielle/-interventionelle Studien'

Annex III Source Materials France : 'Les essais institutionnels'

Annex IV Source Materials UK : 'Charity or University trials / Non-interventional trials'

Annex V Source Materials Belgium : 'Expérimentation non-commerciale'

Annex VI Source Materials Sweden : Non-commercial/-interventional studies

Annex VII Source Materials Netherlands : Non-commercial / observationnel studies

Annex VIII Source Materials Spain :'Estudio post-autorizacíon / Estudio observacional '

Annex IX Source Materials Italy : 'Expérimentazione non-commerciale / Studi osservazionali'

Annex X Conference Rapport : Examining the Value and the Impact of the EU Clinical Trial Directive – One year into the new European GCP Reality

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Declaration

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

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