First experiences with Conditional Marketing Authorisations in the EU: requirements, obligations, initial experiences and perspectives

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List of Abbreviations

AE	Adverse Event
Agency (=EMEA)	European Medicines Agency
AIDS	Acquired Immune Deficiency Syndrome
AR	Adverse Reaction
b.i.d.	twice daily
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorisation
COMP	Committee on Orphan Medicinal Products
CP	Centralised Procedure
CT	Clinical Trial
CYP450	Cytochrome P450
DCP	Decentralised Procedure
DR	Duration of Response
Draft Guideline	Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling into the scope of Regulation (EC) No 726/2004
EEA	European Economic Area (EU + European Free Trade Association, currently: Iceland, Liechtenstein, Norway)
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMEA (=Agency)	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU-CTD	EU Common Technical Document
FDA	Food and Drug Administration (US federal authority that regulates foods, pharmaceutical drugs and medical devices for human use)
FUM	Follow-up Measures
GCP	Good Clinical Practice
GIST	Gastrointestinal Stromal Tumour
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
i. e.	id est
IFN-α	Interferon-alpha

IL-2	Interleukin 2
MA	Marketing Authorisation
MAA	Marketing Authorisation Application Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
MP	Medicinal Product
MRCC	Metastatic Renal Cell Carcinoma
MRP	Mutual Recognition Procedure
MS	Member State (of the European Community)
NOC/c	Notice of Compliance / with Conditions
NTA	Notice to Applicants
ODAC	Oncologic Drugs Advisory Committee
ORR	Objective Response Rate
OS	Overall Survival
PA	Protocol Assistance
PFS	Progression Free Survival
RMP	Risk Management Plan
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
QRD	Quality Review Document
q.t.d.	daily
SA	Scientific Advice
SAE	Serious Adverse Event
SAG-O	Scientific Advisory Group Oncology
SAR	Serious Adverse Reaction
SAWP	Scientific Advice Working Party
SMEI	Severe Myoclonic Epilepsy in Infancy
SPC	Summary of Product Characteristics
t.i.d.	three times daily
TTP	Time to Tumour Progression
U.S., USA	United States of America
WHO	World Health Organisation

	legislation citations and Commission Decisions are printed in *Italics*
[...]	contains explanations within the cited legislation or elsewhere entered by the author

Part I: Regulatory Framework, Requirements and Obligations

1. Introduction

Generally it takes about 8 – 13 years for the development of an active substance including Phase I to Phase III clinical trials (CTs) in human subjects and the registration process until market introduction of the final formulation in the countries of the European Economic Area (EEA).

Patients suffering from serious or life-threatening diseases which are currently incurable or rather difficult to manage survive usually only for a short period of time after the diagnosis and/or are tremendously limited in their quality of life. For these patients access to efficient treatment with innovative medicines fulfilling their unmet medical needs can not come too soon. At the same time the patients' right for efficient, safe, and uniformly high quality medicines must be observed.

In line with the ultimate aim of the pharmaceutical legislation, namely the protection of public health, medicinal products (MPs) for human use may only be placed on the market of countries of the European Community when a marketing authorisation (MA) has been obtained.

Depending on the characteristics of the MP, MA can either be granted

- by the Competent Authority of a Member State (MS) of the European Community as a national MA by registration in only one country, or
- by Mutual Recognition Procedure (MRP) or Decentralised Procedure (DCP), respectively, according to Directive 2001/83/EC as amended by Directive 2004/27/EC[1], or
- by the European Commission in form of a Community Authorisation according to the Centralised Procedure (CP) as introduced into the European pharmaceutical legislation already by Council Regulation (EEC) No 2309/93[2].

Where urgent health needs exist, it has been determined that common Community application and approval procedures are necessary to enable early market access for MPs for new therapies. Based on the already existing regulatory framework of the CP, the European Medicines Agency (EMEA) presented in 2005 in its "Road Map to 2010"[3] the development of a strategy that will improve the regulatory environment for MPs. Furthermore, the strategy will help to stimulate innovation in research and development in the European Union (EU), aiming at offering practicable proposals how these challenges can be met.

With the intention to make much needed and innovative MPs faster available to all patients in the EU, the EMEA announced the implementation of new tools, provided by the newly revised Community Pharmaceutical Legislation. This includes, besides other important initiatives as revised scientific advice (SA) procedures and the possibility of accelerated evaluation of applications for MA, the introduction of the new concept of Conditional Marketing Authorisation (CMA) into the framework of the CP, and the development of Guidelines on the procedural steps necessary for implementation.

Interestingly, equivalent initiatives to the CMA in the EU have already been started by the U.S. Food and Drug Administration (FDA) and Health Canada in the 1980s and 1990s and have been implemented in the local legislation in USA as "accelerated approval"[#4,5], and in Canada as "Notice of Compliance with Conditions" ("NOC/c") [6,7].

Article 14(7) belongs to those parts of Regulation (EC) No 726/2004[8] which entered into force in November 2005. This article introduced for new marketing authorisation applications (MAAs) the possibility into the EU legislation that MPs of major therapeutic interest still in development might be eligible for the granting of a CMA, valid for the whole EU. With acceptance of the Community Authorisation by Iceland, Liechtenstein and Norway the MP will be available for patients in the whole EEA.

To meet the requirements of Article 14(7), Regulation (EC) No 507/2006[9], which became valid according to its Article 13 at the beginning of April 2006, lays down the details for the implementation. It refers to MPs for which the applicant provides a less than complete clinical data package due to incomplete efficacy and safety testing, but is able to demonstrate significant health benefits on early evidence of effects. These effects should be expected to predict the positive outcome from an ultimately comprehensive development. With the purpose to give advice on the scientific application and practical arrangements necessary to implement this Regulation, a *Draft Guideline*[10] was developed.

Before Regulation 726/2004 became effective, the only legislative option provided for early market access for MPs developed against serious or life-threatening diseases and with incomplete clinical data sets was obtaining a MA under exceptional circumstances. The relevant provision, which is still represented within the new pharmaceutical legislation in parallel with the provisions for CMA, features certain characteristics in which it is distinguishable from the application and authorisation procedures for CMAs. One main difference is that this original provision does not include the expectation that in due time the lacking data could be presented and a "full" MA be granted. CMAs are, in contrast, not intended to remain conditional infinitely.

Upon the basis of submission of confirmatory post-approval data derived from the conduct of further clinical studies (as imposed by specific obligations), it is foreseen that the conditional status of the CMA be lifted and be replaced instead by the status of a "normal" (="full") MA in accordance with Article 14(1) of Regulation 726/2004.

In Part I of this Masterthesis an overview is presented over the legal provisions for CMAs which are clarified with the help of the explanations of the *Draft Guideline*.
Part II deals with first experiences with CMAs in the EU, mainly regarding the clinical development and evaluation of the available data based on which CMA for the first three MPs was granted.
Impact and perspectives in the context of CMAs are subsequently discussed in Part III.

[#]which must not be confused with the accelerated assessment procedure provided for in Article 14(9) of Regulation (EC) 726/2004.

2. Conditional Marketing Authorisation - current regulatory framework

2.1. Legal basis and purpose

By Article 14(7) of Regulation 726/2004 the legal provision for CMA was introduced:

Following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency. The list of these obligations shall be made publicly accessible.
By way of derogation from paragraph 1 ["…a marketing authorisation shall be valid for five years], *such authorisation shall be valid for one year, on a renewable basis.*
The provisions for granting such authorisation shall be laid down in a Commission Regulation adopted in accordance with the procedure referred to in Article 87(2).

Following the procedure described in Article 87(2), Commission Regulation 507/2006 of 29 March 2006 was adopted, laying down Community procedures on CMA, subject to specific obligations.

Based on the legal provision of Article 11 of this Regulation, a Guideline was drafted on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006, referred to in the following as "*Draft Guideline*", which forms the basis for requesting or renewing a CMA. It has been released by the Committee for Medicinal Products for Human Use (CHMP) for consultation with stakeholders on 14 December 2006 for a period until 31 March 2007. The feedback of the European Federation of Pharmaceutical Industries and Associations (EFPIA) was recently published[11] (see footnotes in this text indicated by * on relevant points). After finalisation of the consultation, the *Draft Guideline* is intended to be adopted upon which a favorable opinion of the Commission is expected to follow.

The current *Draft Guideline* focuses mainly on the practical arrangements necessary to implement the Regulation 507/2006. Guidance on the scientific application is provided in more general terms. It is envisaged that with updates of the *Draft Guideline* on a regular basis guidance will become more specific and examples, based on the CHMP's expertise with CMAs which is expected to be available until then, will be included.

In the definitions of the *Draft Guideline*'s purpose it is clearly stated that the possibility of obtaining a CMA is only open to new MAAs using the CP, but not to new indications submitted as part of a variation or line extension procedure. In addition, MAs already granted under exceptional circumstances or MAs not subject to specific obligations cannot be changed into CMAs.

2.2. Procedures for granting of a Conditional Marketing Authorisation

A CMA may either be proposed by the marketing authorisation applicant (MAA) or by the CHMP. In both cases the same procedure of subsequent CHMP assessment of the proposal is applied.

Applicant's request for granting of a CMA

The applicant is expected to indicate, in advance of the submission of the MAA, his intention to request a CMA in his "letter of intent".

According to Article 3(1) of Regulation 507/2006, the request itself
…for a conditional marketing authorisation may be presented by the applicant together with an application in accordance with Article 6 of Regulation 726/2004 [which refers to the particulars and documents to be provided according to Directive 2001/83/EC as amended by Directive 2004/27/EC.] *The request shall be accompanied by details showing that the product falls within the scope of Regulation 507/2006 and satisfies the requirements laid down in Article 4(1).*
The Agency shall immediately inform the Commission of applications containing a request for a CMA.

The request shall be included into:

Module 1, Administrative Information And Prescribing Information For The European Union (EU),
Chapter 1.5, Specific Requirements For Different Types Of Applications,
Subchapter 1.5.5, Conditional Marketing Authorisation,

of the European Common Technical Document (EU-CTD)[12] submitted to the EMEA. If there is any doubt whether a MP qualifies for a CMA, advice from the Scientific Advice Working Party (SAWP) may be sought prior to the submission of the MAA by the applicant according to Article 10 of Regulation 507/2006:

A potential applicant for a marketing authorisation may request the advice of the Agency on whether a specific medicinal product being developed for a specific therapeutic indication falls within one of the categories set out in Article 2 and fulfills the requirements laid down in Article 4(1)c [unmet medical needs will be fulfilled].

As outlined by the EMEA in its documents relating to the mandate of the SAWP and to new Scientific Advice (SA) and Protocol Assistance (PA) procedures[13, 14], the SAWP shall provide advice on the justification of whether a specific MP being developed for a specific therapeutic indication is eligible for granting of a CMA*. Furthermore, the SAWP shall provide advice on the acceptability of the development programme for CMAs.

These services are offered in addition to the general SA for applicants for MAAs and PA for designated orphan MPs in accordance with Article 6 of Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products[15]. According to the relevant EMEA Draft Guidance on presubmission meetings[16], there exists a provision for applicants who wish to discuss with the EMEA and rapporteurs their intention to request a CMA and all associated aspects concerning any practical or procedural issues: they may indicate this by ticking "yes" on the presubmission meeting request form under point 24 referring to CMA and provide a draft justification for the conditional approval along with a summary listing of issues to be discussed.

* EFPIA comment: there may also be interest to obtain SA on justification of other requirements, i.e. risk/benefit balance of the product and likelihood to be able to provide comprehensive data.

CHMP proposal for granting of a CMA

One option in the new system is that not the applicant but the CHMP considers it adequate to propose a CMA, according to Article 3(2) of Regulation 507/2006:

The Committee for Medicinal Products for Human Use ..... may, in its opinion on an application submitted in accordance with Article 6 of Regulation (EC) No 726/2004, propose a conditional marketing authorisation, after having consulted the applicant.

Upon agreement of the applicant, such a proposal for a CMA by the CHMP may take place during the scientific assessment of the application for MA. Explanatory reasons for the proposal are to be described in detail in the CHMP scientific assessment report. The proposal and the explanation should be given the earliest possible to the applicant, normally in the day 120 List of Questions, in order to allow for sufficient time for agreement on the details of the specific obligations. These may, if necessary, be discussed in meetings with the rapporteurs and the Agency during the process of the CP*.

CHMP assessment of a request for a CMA

Whether an applicant's request for a CMA is acceptable or not is subject to the scientific review by the CHMP. It is summarised in the CHMP's assessment report on whether the MP falls within the scope of the Regulation 507/2006 and whether the requirements of Article 4 have been met. The same procedure will be applied if the proposal for a CMA comes from the CHMP. For the evaluation of the CMA, the general procedures as laid down in Regulation 726/2004 are to be followed.

If it is decided by the CHMP that the requirements for granting of a CMA are not fulfilled and/or the provided data are not sufficient for evidence of a positive risk/benefit balance, the opinion adopted by the CHMP will be negative**.

In case of adoption of a positive opinion on the granting of a CMA, specific obligations and the timeframe for their fulfillment will be defined and be made publicly available as part of the European Public Assessment Report (EPAR)[17] on the Agency's homepage.

*EFPIA comment: the rapporteur should contact the applicant after the initial assessment at Day 80 to discuss the proposal, in order to address the fulfillment of the requirements for a CMA, before a list of questions is issued at day 120.

**EFPIA comment: reference should be made to whether there exists the possibility for the applicant to request a re-examination.

2.3. Requirements and preconditions to be fulfilled for a Conditional Marketing Authorisation

2.3.1. Medicinal products falling within the scope of a Conditional Marketing Authorisation and justification

In order to fall within the scope of a CMA, a MP must

i) meet the preconditions of Article 3(1) or (2) of Regulation 726/2004 to qualify for the CP, and

ii) belong to one or more of the categories described in Article 2 of Regulation 507/2006.

i) Article 3(1) of Regulation 726/2004 refers to MPs which may only be authorised via the CP (mandatory scope):

No medicinal product appearing in the Annex may be placed on the market within the Community unless a marketing authorisation has been granted by the Community in accordance with the provisions of this Regulation.

According to the Annex of Regulation 726/2004, these are MPs

- *developed by means of one of the following biotechnological processes*
  - *recombinant DNA technology*
  - *controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells*
  - *hybridoma and monoclonal antibody methods*

- *medicinal products for human use containing a new active substance which, on the date of entry into force of the Regulation, was not authorised in the Community, for which the therapeutic indication is the treatment of acquired immune deficiency syndrome* [AIDS], *cancer, neurodegenerative disorder or diabetes,*
and with effect from 20 May 2008 auto-immune diseases and other immune dysfunctions and viral diseases

- *medicinal products designated as orphan medicinal products pursuant to Regulation (EC)141/2000.*

Article 3(2) of Regulation 726/2004 applies to MPs not appearing in the Annex of Regulation 726/2004, but which may nevertheless be eligible for a Community authorisation on the optional scope, if

a) the medicinal product contains a new active substance which was not authorised in the Community at the date of entry into force of the Regulation, or

b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or that the granting of an authorisation in accordance with this Regulation is in the interests of patients at Community level.

ii) according to Article 2 of Regulation 507/2006, the applicant must justify that the MP belongs at least to one of the following three categories:

1. medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases

Justification of the severity or the life-threatening characteristics (fatal outcome) of the disease needs to be demonstrated objectively and quantifiably. For a life-threatening disease it should be possible to collect, count and describe epidemiological mortality data and statistics without too much difficulties. The justification of a disease to be seriously debilitating may be more difficult, its effects on the patients' daily life functions and morbidity need to be established in specific patterns in order to quantify the relevant aspects as objectively as possible.

2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation (WHO) or by the Community in the framework of Decision No 2119/98/EC

Decision 2119/98/EC[18] aims at the set-up of a Community network of an early warning and response system for improvement of prevention and control of a series of categories of communicable diseases. These are described in the Annex of the Decision, including the amendments of Commission Decision 2003/534/EC[19], as

- *diseases preventable by vaccination*
- *sexually-transmitted diseases*
- *viral hepatitis*
- *food-borne diseases*
- *water-borne diseases and diseases of environmental origin*
- *nosocomial infections*
- *other diseases transmissible by non-conventional agents (including Creutzfeldt-Jakob's disease)*
- *diseases covered by the international health regulations (yellow fever, cholera and plague)*
- *other diseases (rabies, typhus, viral haemorrhagic fevers, malaria and any other as yet unclassified serious epidemic disease, including diseases that are caused by agents specifically engineered for the purpose of maximising morbidity and/or mortality upon deliberate release, etc.).*

It has to be justified that the MP is intended to be used in these respective situations, and a reference to the relevant WHO Resolution or Decision or to the measures adopted in the context of the Community Decision 2119/98/EC should be provided. According to the second part of Article 4(1) of Regulation 507/2006, emergency situations as referred to in Article 2(2) are the only cases where a CMA may be granted when comprehensive pre-clinical data or pharmaceutical data have not been supplied*.

* EFPIA comment: this might be unnecessary restrictive. Besides such emergency situations, there may be other situations where for a product for use in a life-threatening disease the risk/benefit evaluation might be considered positive for granting of a CMA, even in absence of, for example, non-clinical data.

3. medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000

according to which a MP shall be designated as an orphan MP if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made,

or

that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

Commission Regulation EC No 847/2000[20] on the procedure for the designation of medicinal products as orphan MPs describes in Article 2(1) and (2) by which information the prevalence of a condition in the Community should be documented and its life-threatening or chronically debilitating nature be justified. If orphan designation will be obtained based on expected insufficient return of necessary investment, the data to be provided should include estimations, statements and justifications of all costs and incentives.

Irrespective of the applicable alternative, in order to obtain orphan designation the sponsor must prove that either no other (satisfactory) method of diagnosis, prevention or treatment of the condition in question exists, or, if a treatment already exists, that the MP in question is of significant clinical superiority to patients affected by the condition. This should be demonstrated by presentation of details on already existing methods and justification by scientific and medical literature and other relevant information.

For requesting a CMA for a MP on grounds of Article 2(3) of Regulation 507/2006, a copy of the Commission Decision on the designation as orphan MP should be provided.

2.3.2. Requirements for Conditional Marketing Authorisation

According to Article 4(1) of Regulation 507/2006,

A conditional marketing authorisation may be granted where the Committee finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements [a-d] *are met:*

a) the risk/benefit balance of the medicinal product as defined in Article 1(28a) of Directive 2001/83 is positive.

Article 1(28a) provides for an evaluation of the positive therapeutic effects of MPs regarding any risk relative to quality, safety or efficacy of the MP regarding patients' health or public health.

For a "normal" MA, the risk/benefit evaluation is based on therapeutic confirmatory (randomised and controlled) CTs providing convincing evidence of a positive balance. Since a CMA will be granted based on less than comprehensive clinical data*, evaluation of the positive therapeutic effects of the MP in comparison to the risks for patients' or public health should be demonstrated, based on robustness and validity of the results on safety and efficacy.

Hence, the applicant should agree in the frame of a SA procedure on the size of safety databases for appropriate definition of the safety profile of the MP in question. It has to be outlined how confirmation of the positive risk/benefit balance will be obtained in further studies.

b) it is likely that the applicant will be in a position to provide the comprehensive clinical data.

A prerequisite will be to obtain comprehensive** data regarding effects on other endpoints, long-term effects, effects in special populations or identification of responders with the completion of still ongoing or new studies. Thus, evidence of a positive risk/benefit balance in the approved indication should be confirmed.

The still open questions regarding safety and efficacy need to be clearly defined in advance. Also, a rationale needs to be identified on how comprehensive data, derived from more mature data sets or additional studies, may be analysed. It should focus on methods to demonstrate coherence of these data with the already available data on primary and secondary endpoints, and how the new data may contribute to a better estimation of efficacy and safety of the MP.

* EFPIA comment: an explanation is missing what is meant by "less than comprehensive clinical data". EFPIA proposal: inclusion of the option that CMAs in serious or life-threatening diseases may be granted based on efficacy on a surrogate endpoint, with the specific obligation to confirm clinical benefit based on a clinical endpoint, such as overall survival (OS).

** EFPIA comment: what will happen if the applicant provides non-robust or equivocal data? Would CHMP consider not renewing the CMA?

Further, the applicant must demonstrate the quality and feasibility of the studies he plans to perform, in order to eliminate as soon as possible uncertainties deriving from the lack of incomprehensive data. A specific timeframe has to be agreed upon for completion of the data*.

(c) unmet medical needs will be fulfilled

Unmet medical needs are defined by Article 4(2) of Regulation 507/2006 [in accordance with Article 3(1)b of Regulation 141/2000 on orphan MPs, but not restricted to orphan indications] as

condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community, or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to affected patients.

Just as required for orphan drug designation, applicants should present a critical review of already available methods of prevention, diagnosis or treatment of the respective diseases. This will serve as a base to justify that these methods are not satisfactory, or that significant improvement of clinical safety or efficacy would provide a major therapeutic advantage to affected patients**, and that therefore an unmet medical need exists. If no such methods are already in place, the applicant should show the necessity of the introduction of new methods.

Demonstration of the extent of fulfillment of unmet medical needs by the MP has to be justified by quantifiable data of medical or epidemiological character on a case-by-case basis. Major advantages of the MP to affected patients should be robustly evidenced by data obtained in well controlled, randomised controlled CTs*** comparing the new methods to already existing methods in respect to efficacy and safety (evidence-based demonstration of benefit). Criteria may be, for example, impact on improvement of morbidity or mortality of patients affected by the respective disease, or onset and duration of the condition.

d) the benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The applicant must show and justify which benefits to public health are to be expected by immediate availability of the product on the market, in comparison to the risks associated with still incomplete clinical data. This should be supported by all available objective and quantifiable epidemiological information. On the other hand, all risks connected with a delay of availability of these MPs to seriously ill patients until the missing data have been obtained have to be taken into account.

* EFPIA comment: if this is not feasible, would it be possible to extend the time period permitted to provide confirmatory evidence?

** EFPIA comment: specific populations (for example, elderly) should be taken into account.

*** EFPIA comment: comprehensive robust evidence from well conducted controlled trials is an ideal and is in contradiction to the earlier statement that CMA can be based on less than comprehensive data.

2.3.3. Fulfillment of Specific Obligations

It should be ensured that the right balance is struck between preventing market access of MPs obtaining an unfavourable risk/benefit balance, and facilitating MA for MPs fulfilling unmet medical needs of patients suffering from life-threatening or serious debilitating diseases. Therefore it was necessary to make CMAs subject to specific obligations, as laid down in Article 5 of Regulation 507/2006:

1. By way of specific obligations, the holder of a conditional marketing authorisation shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk/benefit balance is positive and providing the additional data referred to in Article 4(1).
In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

When a CMA is granted, the specific obligations and time schedule for their completion and for presentation of the relevant data are included in Annex II.C of the respective Commission Decisions[21] and detailed in the Letter of Undertaking of the marketing authorisation holder (MAH). Depending on many factors including all already existing data, intended treatment aims and target populations, specific obligations have to be determined by the Agency on a case-by-case basis and may vary strongly in each individual case of CMA.

According to "EMEA Current Thinking on CMA"[22], commitments may include ongoing studies to be finished and/or new studies to be performed in order to clarify any outstanding questions on quality, safety and efficacy. These may be studies on pharmacology, dose-response and therapeutic use in order to refine the understanding of benefits and risks, and therapeutic confirmatory studies essential to demonstrate efficacy. General guidance on the concept and conduct of the studies may be derived from Guidelines E8, General Considerations for Clinical Trials[23] and E9, Statistical Principles for Clinical Trials[24] of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

A particular element of specific obligations may be the collection of post-marketing pharmacovigilance data including intense safety monitoring measures, in order to allow informed judgment by the CHMP while assessing the positive risk/benefit balance on the occasion of the annual renewal.

2. The specific obligations referred to in paragraph 1 and the timeframe for their completion shall be clearly specified in the conditional marketing authorisation.

According to "EMEA Current Thinking on CMA" [22], the Agency will assess in the course of the renewal procedure whether the specific obligations are fulfilled and whether there exists compliance with the timeframe for obligations.

3. The Agency shall make the specific obligations and the timeframe for their completion publicly available.

According to the relevant EMEA Reflection Paper "EMEA Summary for the Public"[25], an EPAR will be prepared at the end of every centralised evaluation process, providing a summary of the grounds for the positive CHMP opinion. After deletion of commercial confidential information by the EMEA according to the EMEA's general principles[26], the public has the possibility to obtain the relevant information, including information regarding specific obligations, via the Agency's homepage.

Product information

In line with the new EMEA transparency policy measures[27], Article 8 of Regulation 507/2006 lays down relevant provisions regarding clear information to healthcare professionals and their patients on the conditional nature of the MA:

Where a medicinal product has been granted conditional marketing authorisation in accordance with this Regulation, the information included in the summary of product characteristics and package leaflet shall contain a clear mention of that fact. The summary of product characteristics[28] [representing Annex I of the Commission Decision] *shall also contain the date on which the conditional marketing authorisation is due for renewal*.*

According to the current version 7.2 of the annotated QRD template[29], it is foreseen that into section 5.1, Pharmacodynamic properties, of the summary of product characteristics (SPC) the following statement should be included:

"This medicinal product has been authorised under a so-called "conditional approval" scheme.
This means that further evidence on this medicinal product is awaited.
The European Medicines Agency (EMEA) will review new information on the product every year and this SPC will be updated as necessary."

In Annex II.C to the Commission Decision on a CMA ("Specific obligations to be fulfilled by the marketing authorisation holder") the study programme is to be outlined which the MAH should fulfill within a specified time frame. Its results are to be taken into account in the risk/benefit evaluation during the assessment of the application for a renewal.

*****EFPIA comment: some standard wording and its exact location in the SPC would be appropriate to be described in the SPC-Guideline and to be indicated in the Quality Review Document (QRD) template [comment of the author: this has already been integrated into the QRD, see below].

2.3.4. Periodic Safety Update Reports (PSURs) and Renewal of Conditional Marketing Authorisation

PSURs

Adequate provision for enhanced pharmacovigilance for MPs under CMA is very important. The general requirements for PSURs on MPs granted MA via CP, laid down in Article 24(3) of Regulation 726/2004, have been taken up by Article 9 of Regulation 507/2006. Accordingly, the MAH should maintain detailed records of all suspected adverse reactions (ARs) within or outside the Community which are reported to him by healthcare professionals. He should submit these reports, accompanied by a scientific evaluation of the risk/benefit balance of the MP, to the Agency and MSs as PSURs immediately upon request or at least every six months following the granting or renewal of a CMA.

Pharmacovigilance requirements relevant for each individual CMA are to be included into Annex II.B ("Conditions of the Marketing Authorisation") to the respective Commission Decision.

Renewal of a CMA

Usually, according to Article 14 of Regulation 726/2004, MAs need to be renewed only once after five years and are afterwards valid infinitely.
For CMAs, Article 6(1) of Regulation 507/2006 provides that

1. After its period of validity of one year the conditional marketing authorisation may be renewed annually.

To initiate a renewal procedure, Article 6 (2), describes that

2. The application for renewal shall be submitted to the Agency at least six months before the expiry of the conditional marketing authorisation, together with an interim report on the fulfillment of the specific obligations to which it is subject **.*

The requirements for renewal applications are explained in the *Draft Guideline* on CMAs; they apply to the annual renewal of CMAs only, replacing the requirements of Annex 2 of the Notice to Applicants' (NTA) "Guideline on the Processing of Renewals in the Centralised Procedure"[30] (relevant footnote on page 8 of the *Draft Guideline* on CMAs).

*EFPIA comment: report of interim progress is out of date at time of review. Reports closer to the renewal expiry date would better represent the current state.

**EFPIA comment: can a proposal be included for an update of the SPC based on data that have become available as part of the specific obligations? This would be important information for health care professionals and patients.

To enable the CHMP to review the specific obligations and assess their fulfillment according to the agreed schedule, and to confirm that the risk/benefit balance of the respective MP is positive, the MAH should provide certain annually updated information along with the CMA renewal application[#]. This information is different from that to be provided within the usual five year renewal for MAs in accordance with Article 14(1) of Regulation 726/2004.

The information should include at least:

a) a chronological list of all follow-up measures (FUMs) and specific obligations submitted since obtaining the CMA

b) SPC, Annex II, labelling and package leaflet (one relevant example)

c) an interim report to demonstrate which specific obligations have been resolved at which time point in order to enable an evaluation of the probability that the still missing data will be provided by the MAH. Although the structure and content of an interim report may vary depending on the available data and the type of CTs, certain requirements should be fulfilled regarding the optimal format and key elements.

The following items should be contained within the interim report:

- title page and synopsis, addressing the study plan and design
- introduction describing the developmental status of the studies and still outstanding issues
- accrual specifics and their implications for timing of the final analysis
- description of characteristic issues in accordance to screening and exclusion criteria
- description of (serious) adverse events in the treatment groups according to their severity and body system level
- timing and outcome of interim or final analysis
- details of study conduct including protocol deviations and treatment compliance

d) based on PSUR data and data on safety and efficacy otherwise collected since granting of the MA, a clinical expert statement addressing the current risk/benefit balance of the MP (and in exceptional cases, also non-clinical or quality expert statements may be required)

e) data related to specific obligations and / or PSURs where the due date for submission of such data coincides with the renewal application.

[#]The presentation of renewal applications shall follow the provisions of the EMEA post-authorisation Guidance document[31], which will be updated in due time to reflect CMA renewal procedures.

Based on the results of this assessment, obligations may be retained or modified, or a positive risk/benefit balance may be considered as established. If data agreed upon in specific obligations can not be provided, it may be decided by the Agency that the CMA will not be prolonged[#]. If a product is considered harmful, or is lacking therapeutic efficacy, the MA may be suspended, revoked, withdrawn or varied.

The reporting of CTs should be performed in the conventional format of the study report according to the provisions of ICH Guideline E3[32].

On the fifth renewal of the CMA, the MAH will, together with the interim report on the fulfillment of specific obligations, provide all information as listed in Annex 2 of the NTA "Guideline on the Processing of Renewals in the Centralised Procedure"[30].

According to Article 6 (3) of Regulation 507/2006,

3. The Committee shall assess the application for a renewal, on the basis that the risk/benefit balance is to be confirmed, taking into account the specific obligations contained in the authorisation and the timeframe for their fulfillment, and shall formulate an opinion as to whether the specific obligations or their timeframes need to be retained or modified. The Agency shall ensure that the opinion of the Committee is given within 90 days following receipt of a valid renewal application. That opinion shall be made publicly available.

On acknowledgement of receipt of a valid renewal application by the EMEA, the renewal procedure will be started in accordance with the starting dates published on the EMEA website[33]. Within 90 days the CHMP assesses the renewal application, upon which a positive or negative opinion will be published on the EMEA website[34].

In addition, according to Commission Regulation (EC) No 658/2007[35] which was established further to Article 84(3) of Regulation 726/2004, financial penalties may be applied as consequence to infringement of certain obligations laid down in connection with the MA. Its Article 1(9) refers explicitly to failure to observe the specific obligations associated with CMAs which are mentioned in Article 14(7) of Regulation 726/2004. Furthermore, according to Article 84(3) of Regulation 726/2004, the Commission will publish the names of the MAHs involved and the amounts of and the reasons for the financial penalties imposed ("name and shame").

In order to ensure that MPs for which the renewal application is submitted within the deadline are not removed from the market until a Commission Decision is reached (except for reasons related to public health), Article 6(4) of Regulation 507/2006 was implemented:

[#]comment of the author: this statement within the *Draft Guideline* may partially answer to the EFPIA comment ** on page 9 of this text regarding consequences on provision of non-robust or equivocal data. In addition, as detailed in Article 6(3) of Regulation 507/2006 – see below – the possibility of modifying the specific obligations exists.

4. Once a renewal application has been submitted in accordance with paragraph 2, the conditional marketing authorisation shall remain valid until a decision is adopted by the Commission in accordance with Article 10 of Regulation (EC) No 726/2004.

This means also that the MA ceases to be valid on the expiry date if the MAH does not apply in time or does not apply at all for the renewal.

After the Commission adopts a positive opinion according to Article 10 of Regulation 726/2004, the renewed authorisation is valid for one year, starting at the previous expiry date.

2.3.5. Switch from Conditional Marketing Authorisation to "full" Marketing Authorisation

In his submission of the data*, either at the time of renewal or at the time the data have to be provided for fulfillment of the last remaining specific obligations, the MAH should indicate that in his view a change to a "full" MA is possible, and present in support an updated product information and clinical expert statement.

Article 7 of Regulation 507/2006 provides that

Where the specific obligations laid down in accordance with Article 5(1) have been fulfilled, the Committee may at any time adopt an opinion in favour of the granting of a marketing authorisation in accordance with Article 14(1) of Regulation 726/2004.

If the CHMP assessment of the newly submitted data confirms that all specific obligations have been fulfilled, the CHMP recommends the granting of a "full" MA. The reasons for this proposal are detailed in the CHMP assessment report including revised or updated product information, if appropriate.
Changes not related to the submission of results of specific obligations should be submitted as variations to MAs.

Although it might be assumed that such a newly obtained MA not subject to specific obligations any more would now be valid infinitely, this is not the case. In the Draft Reflection Paper on criteria for requiring one additional five-year renewal for centrally authorised medicinal products[36] is described the following procedure: upon switch, the now "full" MA will be valid for 5 years according to Article 14(1) of Regulation 726/2004. At the time of renewal, the CHMP can recommend unlimited validity or consider requiring one additional 5 year renewal according to Article 14(2) of Regulation 726/2004.

* EFPIA comment: in order to convert the CMA to a "full" MA, it would be helpful to have more details on the procedural steps and documentation required.

Part II: Initial Experiences with Conditional Marketing Authorisations

3. Preface: Considerations regarding Clinical Trials in the Frame of Conditional Marketing Authorisations

In contrast to the "full" MA[#], for which Phase III studies have to be fulfilled to demonstrate the therapeutic benefit and to provide the basis for a risk/benefit evaluation, the instrument of CMA allows for MA earlier in the development, under the condition that the relevant Phase III studies are completed and submitted after approval. Generally, only Phase III CTs may be missing in order to qualify for CMA, although in the special cases referred to in Article 2(2) of Regulation 507/2006 also non-clinical or pharmaceutical data may be incomplete.

According to "EMEA's current thinking on CMA"[22], Table 1 presents guidance on which data provide a basis for CMA, and which data have to be subsequently filed for confirmation in order to obtain a "full" MA.

Table 1

Basis for approval	Confirmation
Short-term results (soft endpoints)	Long-term results (hard endpoints)
Interim analysis of randomised clinical trials	Further analysis
Selective approval (CMA in target indication, low proportion of responders)	Studies to identify patients likely to benefit and studies in special populations: change of product information
Biomarker (exploratory - Phase II single-arm or randomised)	Clinical outcome of randomised controlled clinical trials of Phase III in the same or related indication

[#] see Annex II (General overview over the phases of clinical development of medicinal products) for requirements on clinical trials leading to "full" MA.

4. Clinical Development of new medicinal products granted Conditional Marketing Authorisation

Since entry into force of Regulation 507/2006 and until early September 2007, three MPs were granted CMA. The CTs on which CMA was based were performed in accordance with Good Clinical Practice (GCP)[37] and the Ethical Standards of the so-called Clinical Trial Directive 2001/20/EC[38]. In the case of Diacomit®, the development programme lasted ~25 years and a number of clinical studies were initiated before the current ICH/GCP guidelines came into force. However, according to the applicant, the studies followed all ethical guidelines in practice at the time of conduct of the studies.

Due to the new policy of transparency in the work of the EMEA[27] and its scientific opinions to the public, an overview over evaluation and decision on each of the three products could be extracted from the EMEA homepage via the respective links and is presented in the following.

4.1. Sutent® (sunitinib) [39,40]

On 30 August 2005 Pfizer Limited submitted an application for a first MA for Sutent® through the CP, as the MP fell within Article 3(1) (mandatory scope) and points 3 (treatment of cancer) and 4 (designated orphan MP) of the Annex of Regulation 726/2004. The sponsor had not previously requested SA or PA.

The active substance of Sutent®, sunitinib, is an oral tyrosine kinase inhibitor that targets and blocks the signaling pathways by competitive inhibition of the ATP binding site of multiple selected receptor tyrosine kinases, as vascular endothelial growth factor receptors (VEGFR-1, -2, -3), platelet-derived growth factor receptors (PDGFR-α, -β), stem cell factor receptor (KIT).

Sunitinib was described to be used for the treatment of patients with one of two types of cancer:

- Gastrointestinal stromal tumour (GIST), which is a sarcoma of the stomach and bowel. GIST affects about 14000 patients in the EEA, predominantly middle-aged or elderly, and is considered as life-threatening. Sunitinib is to be used in patients with tumours that can not be surgically removed or have spread to other organs, and where treatment with imatinib mesylate or other anti-cancer medicines is not possible due to resistance or intolerance (exhibited by ~70 % of the patients).
- Advanced and/or metastatic stages of renal cell carcinoma (MRCC), affecting the cells of the renal tubules or already spread to other organs, after failure of interferon-alfa (IFN-α) or interleukin-2 (IL-2) therapy.

Successful treatment of these patients fulfills an unmet medical need because these patients have only a short survival time associated with significant morbidity, and because the efficacy of the only other available treatment is limited and by many patients not well tolerated. The number of patients affected by these diseases is low, and the applicant could show that there are no similarities to any already authorised orphan MP according to Article 3 of Regulation 874/2000. In addition, substantial differences exist in the mechanism of action and the structural aspects of the active ingredient sunitinib to imatinib.

Therefore, the Committee for Orphan Medicinal Products (COMP) adopted a positive opinion on orphan medicinal product designation (EU/3/05/267 and EU/3/05/268) for Sunitinib to Pfizer Limited on 10 March 2005[41#].

In light of the overall data submitted and the scientific discussion within the Committee, the CHMP issued on 27 April 2006 a positive opinion for granting a CMA to Sutent® which was therefore the 27th orphan MP to receive a positive CHMP opinion[42] (see 4.1.3.).

The decision was based on the following studies and data presented:
In total, 15 clinical pharmacokinetic Phase I-III studies with sunitinib were conducted, including 8 studies in healthy subjects, 1 study in patients with acute myeloid leukemia and 6 studies in patients with solid malignant tumours. No pharmacodynamic studies were conducted directly in humans, since no adequate biomarker reactions had been identified.

4.1.1. Clinical Efficacy

The clinical programme in the GIST indication consisted of two efficacy studies.

Patients included into both studies were at least 18 years old with histologically proven GIST who had experienced disease progression during prior imatinib therapy or who were intolerant to imatinib. Treatment was given in 6-week cycles, with 4 weeks of daily 50 mg of sunitinib or placebo administration, followed by a 2-week off-treatment period.

#although the MP is presently no more indicated as orphan MP on the EMEA page of the Sutent® EPAR; upon research, no explanation on reasons for this change could be found by the author. Possible reasons for removal as designated orphan MP from the Community Register of orphan MPs according to Article 5(12) of Regulation 141/2000 may be

a) request of the sponsor for removal, or

b) that the criteria for designation as orphan MP as laid down in Article 3 of Regulation 141/2000 are no longer met.

Alternative c), end of the period of market exclusivity as laid down in Article 8 of Regulation 141/2000, can be excluded since CMA was only obtained in July 2006.

- Phase III, double blind, placebo-controlled, multicenter pivotal trial (study A618004) with 312 patients, ongoing at the date of CHMP review.

  The randomisation scheme was 2:1 (207 patients were randomised to the active substance, 105 to placebo).

  The primary objective of this study was to compare Time to Tumour Progression (TTP) between patients receiving sunitinib and patients receiving placebo. At a planned interim analysis when ~50% of the required number of progression events has occurred, statistically significant benefit of sunitinib over placebo (median TTP of 27.3 weeks versus 6.4 weeks) was shown.

  This was supported by analysis of the secondary endpoint Progression Free Survival (PFS) (24.6 weeks in the sunitinib arm, 6.0 weeks in the placebo arm) and increased Overall Survival (OS) (2 times higher for sunitinib than for placebo). These interim results were sufficiently good for the study to be discontinued early and for the patients of the placebo arm to be switched to sunitinib treatment.

- Supportive Phase I/II single-arm, open-label, multicenter study (RTKC-0511-013) with 55 patients, completed at the date of initial MAA. Results of this study confirmed consistency in the endpoint TTP (34 weeks) with the pivotal trial.

In the MRCC indication, clinical efficacy is based on data from the following studies with similar designs:

- Phase II single-arm, open-label, multicenter, pivotal trial (study A6181006) with 106 patients, still ongoing at the date of CHMP review.

- Supportive Phase II single-arm, open-label, multicenter trial (study RTKC-0511-014) with 63 patients, completed at the date of initial MAA.

Both studies were non-randomised and not controlled.

Study participants were at least 18 years old, with histologically proven MRCC and not amenable to therapy with curative treatment, with failure or intolerance to prior cytokine therapy (IL-2 or IFN-α).
They received 50 mg sunitinib daily for 4 weeks, followed by 2 weeks of rest in repeated 6-week cycles. It was foreseen that doses could be reduced to 37.5 or 25 mg in the event of toxicity.
The primary objective of these two studies was to demonstrate anti-tumour efficacy as Objective Response Rate (ORR). Interim analysis after mean duration of 34 weeks in study RTKC-0511-014 and after 23.6 weeks in the still ongoing study A6181006 revealed the medium ORR to be ~25% (laboratory assessment) and ~36% (investigator assessment).

Analysis of Duration of Response (DR), PFS and OS in sub-populations, defined by age, gender and race, showed no clinically significant differences.

No randomised controlled trials and no comprehensive clinical efficacy trials with sunitinib in MRCC patients refractory to prior cytokine therapy were submitted with the initial MAA.

Further ongoing studies at the time of CHMP opinion for granting CMA were

- clinical trial A6181034, from which data were requested in the specific obligations and expected by September 2006 (see 4.1.4.)
- open-label continuation studies (RTKC-0511-017 and A6181030) were offered to patients in the GIST indication, MRCC indication and other cancers, who were expected to benefit from further sunitinib treatment (14 GIST patients, 18 MRCC patients).

4.1.2. Clinical Safety

The most important serious adverse events (SAEs) associated with sunitinib treatment, and therefore representing the most important risk, were pulmonary embolism, thrombocytopenia, tumour haemorrhage, febrile neutropenia and hypertension (all experienced by 1% or less of the treated patients). The most common treatment-related adverse events (AEs), experienced by at least 20% of the patients, were fatigue, gastrointestinal disorders, stomatitis, vomiting, skin discolouration, nausea, dysgeusia and anorexia. Furthermore, cardiac toxicity was an important risk identified with sunitinib.

Due to the limited size of the safety database there were still uncertainties, but nevertheless the safety profile was considered as justified in view of the unmet medical needs of these patients with no other treatment options. It was required that the applicant introduced specific procedures concerning the safety of the product.

Several studies already finalised or still ongoing during CHMP review were of particular relevance to address specific safety issues:

- A6181005, completed QT study
- A6181077, ongoing randomised Phase II study of sunitinib versus standard care for previously treated breast cancer patients
- A6181079, ongoing hepatic impairment study, Phase I.

Further safety issues addressed in at the time of CHMP review ongoing CTs were in relation to hypertension, haemorrhage, anaemia, hypothyroidism, thromboembolic events, phototoxicity, carcinogenicity, gastrointestinal perforation, fatigue and drug-drug interactions due to Cytochrome P450 (CYP450) regulation.

The CHMP considered that the pharmacovigilance system as described by the applicant fulfilled the regulatory requirements. This was based on the risk management plan (RMP) which the applicant submitted, since a number of safety issues, including long-term toxicity, required routine pharmacovigilance, periodic monitoring and review of target AEs and SAEs from ongoing CTs on a regular basis.

The CHMP was of the opinion that no additional risk minimisation activities were required beyond those included in the product information. It required an updated RMP according to the Guideline on Risk Management Systems for Medicinal Products for Human Use[43] to be submitted at the same time as the PSURs, within 60 days of an important milestone reached, when the results of a study became available, or at the request of the Competent Authority.

4.1.3. Risk/Benefit Assessment

The CHMP considered that sunitinib fulfilled the requirements of Article 4 of Regulation 507/2006 and issued a positive opinion for granting of a CMA, based on the following grounds:

GIST

- The clinical benefit of sunitinib in the treatment of GIST was demonstrated in studies A618004 and RTKC-0511-013 in relevant clinical endpoints such as TTP and OS in patients who had failed or were unable to tolerate prior imatinib therapy. Taking into account that the safety profile was acceptable, the risk/benefit balance of sunitinib in the claimed GIST indication was considered positive.
- No satisfactory methods of treatment have been authorised in the Community for patients with GIST after failure of imatinib mesylate treatment. Therefore, the CHMP considered that in these patients unmet medical needs would be fulfilled by treatment with sunitinib.

MRCC

- For the MRCC indication, the CHMP considered that comprehensive clinical data in relation to efficacy were not supplied. The reason was that the two studies A6181006 and RTKC-0511-014 of which data on clinical efficacy were derived, were not randomised and the effects of sunitinib on clinical endpoints could not be properly quantified.

Nevertheless, the Oncology Scientific Advisory Group (SAG-O) concluded, upon being consulted by the CHMP, that the Phase II data provided a manageable toxicity and convincing evidence of a clinical benefit. This was based on the consideration that the observed high ORR (>35%) in MRCC patients who failed prior cytokine-based treatment was unlikely to have occurred spontaneously. However, ORR is no direct measure of clinical benefit, which would generally require the presence of effects in terms of PFS and OS.

- The SAG-O considered it likely that the observed ORR would translate into a clinically relevant effect on PFS and OS. Results from ongoing randomised Phase III study A6181034 (see 1.4.1.), when available, might provide supportive evidence to confirm the conclusions based on the Phase II trials.
- Based on the advice of the SAG-O and taking into account the favourable safety profile, and in view of the efficacy of the product and the poor prognosis of patients, the CHMP reached the following conclusion: the benefit to public health of the immediate availability on the market of Sutent® outweighs the risk inherent in the fact that additional data were still required for the indication MRCC.
- No satisfactory methods of treatment have been authorised in the Community for patients with MRCC after failure of cytokine-based treatment. Therefore, the CHMP considered that in these patients unmet medical needs would be fulfilled by treatment with Sutent®.

However, because comprehensive data on PFS or OS were not available in the MRCC indication, the CHMP recommended on 26 April 2006, after consultation with the applicant, the granting not of a “full” but of a CMA. This was based on the falling of sunitinib within the scope of Regulation 507/2006, with particular reference to Article 2, and its being subject to the specific obligation for provision of results of the already ongoing study A6181034.

In addition, with reference to Article 8 (market exclusivity) of Regulation 141/2000, the CHMP considered sunitinib not to be similar as defined in Article 3 of Regulation 827/2000 to other authorised orphan MPs for the same therapeutic indication.

In his 26 April 2006 “Letter of Undertaking” the applicant presented in the attached RMP measures to be fulfilled post-authorisation; in addition to the specific obligation of the assessment of study A6181034 (see 4.1.4.), two more complementary analyses were listed within the SPC:

- analysis of efficacy and safety data in subgroups of patients for whom the dose was reduced
- provision of further information on possible pharmacodynamic markers, such as the target receptor tyrosine kinases or the inactivating mutation of the von-Hippel-Lindau tumour suppressor gene.

On 19 July 2006, the European Commission adopted the decision; thus the MA for Sutent® represents the first CMA granted in the framework of the CP of the European Community#, initiated by the CHMP, for the following indications:

"Sutent® is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Sutent® is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alfa or interleukin-2 based therapy.

Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC."

4.1.4. "Full" Marketing Authorisation in the EU[47-51]

In order to fulfill the specific obligations post-marketing as requested by the CHMP, the final analysis of completed study A6181034 was provided by Pfizer Limited as a part of the application for Extension of Indication to include first-line treatment of patients with advanced MRCC. In addition, the MAH applied for switch from CMA to a "full" MA in the frame of a Type II variation.

Study A6181034 was an open-label, multicenter, international Phase III study, evaluating the efficacy and safety of single agent sunitinib compared to IFN-α as first-line systemic therapy in patients with treatment-naïve MRCC. 750 patients at least 18 years old were included and 1:1 randomised for IFN-α treatment or treatment with sunitinib 50 mg/day in 6-week cycles of 4 consecutive weeks of treatment, followed by a 2-week off period.

Primary endpoint for clinical efficacy was PFS; this was 47.3 weeks for the sunitinib treated group versus 22.0 weeks for the IFN-α treated group.

#

After receiving a priority review in the USA, approval for Sutent™ was on 26 January 2006 granted by FDA for treatment of delay of tumor growth in the indication GIST after disease progression on, or intolerance to, imatinib mesylate, and for treatment of advanced MRCC by reduction of tumor sizes[44] .

On 26 May 2006 Health Canada issued a NOC to Pfizer Canada Inc. for the drug product PrSutent* after granting priority review for the evaluation of this product. Health Canada approved PrSutent* for the treatment of gastrointestinal stromal tumor (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance[45].

On 17 August 2006 PrSutent* was approved by NOC/c for the treatment of MRCC after failure of cytokine-based therapy or in patients who are considered likely to be intolerant of such therapy[46] .

As secondary efficacy endpoints to be analysed in the proceeding course of the study were defined:

- ORR, which appeared to be 5 x higher in the sunitinib group than in the IFN-α group
- TTP, which was 47.9 weeks for sunitinib versus 22.3 weeks for IFN-α
- DR, which was 40.9 weeks for sunitinib but not applicable for IFN-α
- patient reported outcomes (PROs), providing also subjective data including reference to improvement of symptoms, overall quality of life and social/emotional well-being on three validated instruments. The data showed for the sunitinib arm a better statistically and clinically relevant reported outcome than in the IFN-α arm. An oral, once-daily administration of sunitinib makes outpatient treatment possible, therefore contributing to quality of life benefits.

Taken together, these results were sufficient to demonstrate a treatment advantage for sunitinib compared with IFN-α.

The clinical safety profile of sunitinib as presented by the data of study A6181034 was generally corresponding with the data on the risk/benefit balance presented in the MRCC portion of the initial MAA. It was considered as tolerable, since AEs were generally not severe enough to provoke discontinuation and were considered mostly as able to be managed effectively by specific therapies.

The CHMP decided that the new efficacy and safety data available for treatment-naïve patients with MRCC were consistent with the positive data presented in the initial MAA for patients with cytokine-refractory MRCC. The new data confirmed the initial data by a significant improvement in PFS and a robust improvement in ORR compared with IFN-α in the treatment-naïve MRCC patient population. In addition, in the sunitinib arm better PROs were recognised compared to the IFN-α arm.

Therefore, the CHMP considered the submitted data from Study A6181034 sufficient for the conclusion that the clinical data on sunitinib in total were comprehensive. It agreed on 18 October 2006 on extension of the indication and on the amendments to be introduced into the SPC and package leaflet.

Furthermore, the evidence of compliance with the specific obligations submitted by the MAH was reviewed. Since all specific obligations stated in Annex II.C of the Commission Decision for the original CMA were fulfilled, the Committee recommended on 11 January 2007 that the CMA for Sutent® should be switched to a "full" MA in accordance with Article 7 of Regulation 507/2006 and Article 14(1) of Regulation 726/2004. Annex II.C should be revised accordingly, and the indication regarding MRCC should be changed as follows:

"Metastatic Renal Cell Carcinoma (MRCC)
Sutent® is indicated for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC)."

Therefore, the failing of prior cytokine therapies is no longer a prerequisite for the use of Sutent® in the indication MRCC.

4.2. Prezista® (darunavir) [52-56]

On 4 January 2006 an application for MA through the CP was submitted to the EMEA by the applicant Janssen-Cilag International NV for the antiviral MP Prezista®. The MP fell within Article 3(1) (mandatory scope) and point 3 of the Annex of Regulation 726/2004 (treatment of human immunodeficiency virus (HIV) infection).
SA from the CHMP on quality, non-clinical and clinical aspects of the dossier was received by the applicant on 23 May 2003 and 21 January 2005 (for comparison: for Sutent® and Diacomit® (see above and below) no SA was requested prior to the application).

Application for an accelerated assessment procedure according to Article 14(9) of Regulation 726/2004 was rejected by the CHMP on 26 January 2006.

Prezista® contains a new active substance: the protease inhibitor darunavir, which inhibits the normal reproduction speed of the virus by slowing down the replication rate. It was developed for highly treatment-experienced HIV-patients who failed more than one previous treatment consisting of nucleotide or non-nucleotide reverse transcriptase inhibitors or inhibitors to cell infection (entry inhibitors) in combination with a protease inhibitor. Therefore those patients have few or no remaining treatment options left.

CMA as requested by the applicant[53 #] was granted based on the data and studies described in the following:

4.2.1. Clinical Efficacy

The clinical programme consisted of

- studies on characterisation of the pharmacokinetic profile of darunavir, following single and multiple administration, with or without low dose of ritonavir
- two Phase II randomised open-label, controlled, proof-of-concept, short-term treatment (14 days) studies in treatment-experienced patients (TMC114-C201 (N=34) and TMC114-C207 (N=50)), finalised already at the date of application.

[#]although the author could not find out whether the request was made at the date of application or later during CHMP assessment

In study C201, darunavir was administered as oral solution (without ritonavir) to HIV patients in doses between 400 mg twice daily (b.i.d.) to 1200 mg three times daily (t.i.d.). In study C207, darunavir oral solution was administered with ritonavir to HIV patients in doses of darunavir/ritonavir 300/100 mg b.i.d., 600/100 mg b.i.d and 900/100 mg daily (q.t.d). Ritonavir acts by slowing down the metabolisation rate of darunavir, thus leading to an increase of its plasma levels. In these studies a dose-related activity of darunavir was observed and the applicant considered that combination of darunavir and ritonavir was justified. Data were provided to prove bioequivalence between oral solution and the commercial / Phase III tablet. The proof-of-principle studies and their relevance to dose-finding Phase IIb studies were therefore considered acceptable.

- two main, at the date of CHMP opinion still ongoing randomised, controlled, partially blinded, international Phase IIb CTs (TMC114-C202 = POWER 1 with 319 patients and TMC114-C213 = POWER 2 with 318 patients) which had previously been discussed during SA. The objective was to demonstrate efficacy of the proposed dose regimen by analysis of dose-response and effects on the viral blood load and on the immune system. HIV infected adults not responding to their current HIV treatment, including a protease inhibitor, were enrolled; in the past, these patients had taken on average 11 antiviral medicines, including 4 protease inhibitors for HIV treatment. Exclusion criteria were any current AIDS defining diseases, allergy or hypersensitivity to the excipients, and evidence of active liver disease.

  In these studies, efficacy of darunavir taken in combination with low-dose ritonavir (tablets in doses between 400/100 mg q.t.d. to 600/100 mg b.i.d.) was compared to efficacy of other protease inhibitors, selected on the patients' predicted response and previous treatment. In addition, all patients took a combination of other anti-HIV medicines which provided the best chances of reducing the HIV levels in their blood.

  The primary objective in the original protocols was to evaluate the dose-response relationship of the regimen's antiviral activity at 24 weeks. An interim analysis of both studies revealed a higher antiviral activity of darunavir/ritonavir in the 600/100 mg group and thus all randomised patients were switched to this recommended dose. The objective of the trials was then amended to a proof of efficacy based on the proportion of patients whose viral load decreased at least by 1.0 $\log_{10}$ or more (= primary endpoint) measured after 24 weeks of treatment. This was observed in ~70% of the patients taking darunavir compared to only ~21% of the patients taking the comparator protease inhibitor. However, this low portion of reacting patients receiving in the comparator group may be explained by the non-availability of protease inhibitors predicted to be active.
  In both trials, the results obtained for the other virologic response categories (secondary endpoints, defined as decrease of viral load by at least 0.5 $\log_{10}$ relative to baseline, or proportion of patients with a viral load < 400 or < 50 copies/ml) confirmed the findings of the primary efficacy endpoints.

- two open-label trials in protease-inhibitor experienced patients (POWER 3 =TMC114-C215 with 431 patients + TMC114-C208 with 29 patients), ongoing at the date of CHMP review. Interim 24-week and 48-week data were provided.

  Supportive data on efficacy of the 600/100 mg b.i.d. darunavir + ritonavir dose compared to control were obtained from the POWER 3 analysis on long-term safety and tolerability. Patients included were even more advanced than in trials C202 and C213; virologic response rate, defined to be a 1.0 $\log_{10}$ decrease in viral load versus baseline accounted for 65% of the patients who started directly with the recommended dose and reached week 24.

The efficacy of darunavir was not examined in children nor in HIV infected treatment-naïve patients.

4.2.2. Clinical Safety

Clinical safety data of darunavir with ritonavir were limited to the analysis of data from the interim analysis of the two ongoing Phase IIb trials (C202, C213), supported by data of de novo patients from the two open label trials (C215/C208), starting directly with the recommended dose. A total of 810 patients received treatment with the recommended dose of darunavir and ritonavir 600/100 mg b.i.d. Therefore, the safety database, especially with regard to the final recommended regimen and formulation, contained only a limited number of patients.

Overall, 15% of these patients reported SAEs, mostly in isolated cases; the most common SAE was pneumonia. 15 deaths after treatment with any dose of darunavir/ritonavir were observed (but none of them considered as possibly related to treatment).
Discontinuation due to AEs was observed only infrequently. Most common AEs reported were diarrhoea (11.5%), nausea (8.8%), nasopharyngitis (8.3%), headache (7.2%), fatigue (4.7%), pyrexia (4.1), furthermore abdominal pain, constipation, flatulence of abdomen, dyspepsia, anorexia, vomiting, insomnia and hyperglyceridaemia. Protease inhibitor class-related events were prospectively looked at as cardiac-related, lipid-related, liver-related and glucose-related AEs.

Appropriate warnings were advised to be included into the SPC that patients taking Prezista® may be at risk of lipodystrophy, osteonecrosis, immune reactivation syndrome or diabetes mellitus/hyperglycaemia. As expected for antiretroviral MPs, patients with co-existing liver conditions (including hepatitis B or C infection) can have an increased frequency of treatment emergent live function abnormalities. Therefore, Prezista® is contraindicated for patients with severe liver problems and should be taken with caution by patients with mild or moderate hepatic impairment. Contraindications include further patients taking rifampicin for tuberculosis treatment, St. John's wort against depression, or medicines metabolised over the same pathway as Prezista®.

So far the safety profile seemed consistent with that of other protease inhibitors.
However, the lack of head to head comparative Phase III studies versus comparators in similar therapeutic indications precluded a definitive conclusion related to the safety profile of darunavir compared to other protease inhibitors.

In the RMP submitted by the applicant it was addressed that there is a need to further characterise the safety profile, and a risk minimisation plan was included; final results from ongoing studies were to be submitted as part of the FUMs during post-authorisation.

4.2.3. Risk/Benefit Assessment

The CHMP considered that darunavir fulfilled the requirements of Article 4 of Regulation 507/2006 and issued a positive opinion for granting of CMA, as requested by the applicant, based on the following grounds:

- The clinical benefit of darunavir was demonstrated based on evidence of the two main randomised controlled studies comparing safety and efficacy of darunavir in combination with low dose ritonavir to other ritonavir-boosted protease inhibitor combinations.

- Although only a limited safety database existed and supplementary safety data derived from randomised controlled Phase III trials were necessary (see below), the safety profile was considered for the time being acceptable. The risk/benefit balance of Prezista® as defined in Article 1 (28a) of Directive 2001/83/EC was considered positive for the treatment of HIV infection in highly pre-treated adult patients who failed one or more regimen containing a protease inhibitor.

- As specific obligations, specified in Annex II.C of the Commission Decision, comprehensive clinical data on efficacy, tolerability and safety of darunavir compared with other treatments had to be provided from additional CTs.
  This included two studies on the interactions of the medicines, to be finalised until the third quarter of 2008.

  Since these trials were already ongoing at the time of CHMP opinion, the CHMP considered it likely that the applicant will be in the position to provide the demanded comprehensive clinical data in due course. The results of these trials will be taken into account for the risk/benefit evaluation during assessment of the application for renewal.

- Despite the fact that other MPs had shown activity for treatment of the advanced disease, there still remains a large unmet medical need, and the availability of satisfactory methods for treatment are of immediate relevance to the affected patient population.

Based on the submitted RMP, the CHMP decided that the routine pharmacovigilance system described by the applicant fulfilled the regulatory requirements. But it was of the opinion that additional pharmacovigilance activities were needed to investigate some of the safety concerns in more detail.

On 14 December 2006, the applicant provided a Letter of Undertaking on the specific obligations and FUMs (including (cross)-resistance data, interaction data, data in patients with hepatic impairment, in children and adolescents and in HIV-infected treatment-naïve patients) to be fulfilled post-authorisation.

In conclusion, the CHMP considered that Prezista®'s benefits to public health (in view of the efficacy of the product and the poor prognosis of the target population) and its immediate market availability outweigh the risk caused by the lack of comprehensive safety data. It recommended therefore on 14 December 2006 the granting of a CMA in the following indication:

"Prezista®, co-administered with 100 mg ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI).
This indication is based on week-24 analyses of virological and immunological response from 2 controlled dose range finding Phase II trials and additional data from uncontrolled studies (see section 5.1 of the Summary of Product Characteristics). In deciding to initiate treatment with Prezista® co-administered with 100 mg ritonavir careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents.
Genotypic or phenotypic testing (when available) and treatment history should guide the use of Prezista®."

Based on this positive CHMP opinion, the European Commission granted a CMA valid throughout the EU for Prezista® to the applicant Janssen-Cilag International NV on 12 February 2007.[#]

[#] Prezista™ was on 23 June 2006 approved through accelerated approval by the US FDA to be co-administered with a low-dose of ritonavir for the treatment of treatment-experienced HIV patients under the provisions of 21CFR314.51[57].

On 28 July 2006, Health Canada issued a NOC/c to JansenOrtho Inc. for [Pr]Prezista*, based on the review of data on quality, safety and efficacy. The Authority considered that the risk/benefit profile of [Pr]Prezista*, co-administered with 100 mg ritonavir and other antiretroviral agents, is considered favourable for the treatment of HIV infection in treatment-experienced adult patients who have failed prior antiretroviral therapies[58].

4.3. Diacomit® (stiripentol) [59-63]

The applicant Biocodex, France, submitted an application for MA through the CP to the EMEA on 25 April 2005 for Diacomit®. The MP fell within Article 3(1) (mandatory scope) and points 3 (treatment of neurodegenerative disorders) and 4 (designated orphan MP) of the Annex of Regulation 726/2004. SA or PA were not previously sought.

Stiripentol was granted orphan MP status EU/3/01/071[64] on 05 December 2001 in accordance with Article 3 of Regulation 141/2000 in the indication "Treatment of severe myoclonic epilepsy in infancy (SMEI)", on calculation of a prevalence of 0.4 per 10000 EU population.

The product was not licensed in any other country at the time of submission of the application.

SMEI (also known as Dravet's syndrome[65,66]) is characterised, according to the last classification of Epilepsy syndromes by the International League Against Epilepsy[67], by family history of epilepsy or febrile convulsions, associated with seizures including loss of consciousness in children, beginning during the first year of life.
The seizures never come under control, with secondary development of myoclonic jerks and partial seizures. Psychomotor development is retarded from the second year of life onwards. The disease has a very unfavourable prognosis for epilepsy and cognitive development, the average development quotient of affected subjects varies between 20-40 after ~5 years of age.
Therefore the disease is considered as one of the most deleterious syndromes among childhood epilepsies.

Experience with this form of epilepsy shows that it is very resistant to most forms of currently available treatment. Consequently, there exists an urgent unmet medical need.

Preliminary uncontrolled studies had already shown the potential utility of the active substance stiripentol in combination with other anti-epileptic agents. However, it is not fully understood how stiripentol employs its anti-convulsant activity.

It may be due to

- inhibiting of synaptosomal uptake of the neurotransmitter gamma-aminobutyric acid , or
- increasing the activity of other anti-epileptic medicines by inhibition of CYP 450 isoenzymes (particularly 3A4, 1A2, 2C19), involved in the hepatic metabolism of these MPs.

The positive opinion adopted by the CHMP on 19 October 2006 for granting of a CMA for Diacomit® was based on presentation of the studies and data described in the following.

4.3.1. Clinical Efficacy

The dossier contained four pharmacokinetic studies performed in healthy subjects in the 1980s to determine bioavailability and enantiomer metabolism.

The main development programme consisted of two pivotal efficacy studies conducted in the target population. Four supporting studies and three other open studies assessed efficacy of stiripentol in all forms of epilepsy. The main theme throughout the development programme was the use of stiripentol in combination with other anticonvulsants rather than in monotherapy. The primary efficacy criterion was an overall reduction of seizures. Data regarding the target patient population were derived from the following studies:

- Two at application date already finalised pivotal double-blind, multicenter, placebo-controlled, randomised efficacy studies of two-months duration in the target population (STICLO-France and STICLO-Italy). They included, due to the rarity of the disease, only 66 children between 3 and 18 years of age with a diagnosis of SMEI and at least four tonic-clonic seizures per month. Since identical protocol designs were applied, comparison and pooling of the data was allowed. The patients received 50 mg/kg/day stiripentol versus placebo, in co-medication with valproate and clobazam. The objectives of both studies were
    - to demonstrate efficacy of stiripentol as add-on therapy to clobazam and valproate in children with SMEI and refractory seizures
    - to study the safety profile of the combination
    - to document steady state concentration of stiripentol and concomitant medications.

  The main efficacy measure (primary outcome) was the number of patients who "responded" to treatment (= reduction of seizures in the second month of treatment of at least 50% versus the number in the month before start of treatment).

  Secondary endpoints were
    - percentage of children whose number of seizures decreased by at least 50% in the 2nd month of treatment compared to baseline on a 30-day basis
    - percentage of children withdrawn from the trial
    - number of seizures during the comparison phase
    - time lapsed until the same number of seizures as baseline was experienced.

- One supportive study (STEV) with 233 epileptic patients, 25 of them diagnosed SMEI between the age of 2 and 15 years, with 12 weeks treatment duration. This study was already completed at the date of application. The Objective Response Rate (ORR), which was defined as change in seizure frequency in this study, formed the basis for the hypothesis that stiripentol could be effective in SMEI.

  However, this study provided insufficient information, and since the design was uncontrolled, variations in dosage were possible and many patients were lost to follow-up. Therefore no definite conclusions could be drawn from the results of this study regarding efficacy of SMEI treatment.

- One at the date of CHMP review still ongoing open study (STILON), representing the only long-term study (3-5 years) with 45 SMEI patients of different age in the frame of a compassionate use programme in France. The study includes follow-on patients responding in the previous epilepsy studies. In this way the long-term effect of stiripentol treatment in the STICLO studies could be assessed.

No dose response studies were conducted.

Although efficacy in animal models had been claimed, the anti-epileptic activity of stiripentol could not be demonstrated clinically, since no stiripentol monotherapy study was performed.
In the target indication, the studies compared the efficacy of stiripentol and placebo when they were added to the children's existing treatment with clobazam and valproate. The following reduction of clonic and tonic-clonic types of seizures was found: 67% of the patients in STICLO-Italy and 71% in STICLO-France responded to the added stiripentol treatment, whereas only 5% and 9%, respectively, of the patients in the placebo group responded. Efficacy was evaluated only on clonic and tonic-clonic types of seizures. The impact on psychomotor development was not determined and would have required a longer duration of treatment.

It was not clear whether the seizure reducing effect observed in stiripentol treated patients, but not in the placebo group, was due to stiripentol or to increased levels of the other anti-epileptic medicines. However, as in the stiripentol group the clobazam levels were significantly higher than in the placebo group, it is plausible that the reduction in seizure frequency observed could be ascribed to the concentration of the co-medication, and simple increase of the clobazam dose might have reached the same effect.

Therefore, comparison of additional effects of stiripentol to maximum safe doses of co-medication (clobazam and valproate) was necessary and consequently requested by the CHMP as specific obligation (see 4.3.3.).

4.3.2. Clinical Safety

Due to the diversity among the study designs, patient populations and doses used, it was not possible to summarise data on exposure according to dosages or exact duration of exposure. AEs could not be consistently and adequately related to plasma levels of stiripentol.

The heterogeneousness of the patient populations in the pivotal studies (children and adolescents of different age groups with SMEI) and in non-pivotal studies (adults, and children and adolescents of different age groups and with different types of epilepsy), made it impossible to perform a formal safety analysis according to demographic factors.

However, overall, the AE profile did not raise major concerns. Potentially drug-related AEs concerning mostly the central nervous system and the gastrointestinal tract (as loss of appetite, weight loss or weight gain, anorexia, insomnia, drowsiness, hypotonia) appeared to be common. Although they were often severe in intensity, they appeared to be reversible, especially with adjustments of the co-medication dose. It was also assumed that some of the observed AEs may have been related to the elevation of the serum concentration of the co-administered compounds. Furthermore, for the safety evaluation of stiripentol, it had especially to be observed that stiripentol inhibits the CYP450 isoenzyme 2C19 which leads to reduction of the clearance of several anti-epileptic drugs.

No adequate studies were performed to address concerns about the potential of adverse effects on the cognitive function, behaviour and psychomotor development. The applicant committed to address these issues post-authorisation as FUMs and specific obligations as well as in the RMP.

The CHMP considered that the proposed pharmacovigilance activities described by the applicant in his EU-RMP regarding safety concerns, AEs and drug interactions fulfilled the regulatory requirements. No additional risk minimisation activities were required beyond those included in the product information. The following pharmacovigilance activities to investigate safety concerns were agreed upon:

• A close monitoring of gastro-intestinal problems, particularly when stiripentol is combined with valproate.

• A close monitoring of the frequency of neurological problems under doses of drugs frequently used with stiripentol such as clobazam.

In addition, the applicant committed to establish an EU-wide post-marketing safety study to collect data on safety issues including specific concerns identified by the CHMP as necessary to be monitored; these are failure to thrive, neutropenia and hepatotoxic potential, psychomotor development and behaviour.

4.3.3. Risk/Benefit Assessment

Although it could be shown that in specific combinations with clobazam and valproate, stiripentol at a fixed dose of 50 mg/kg/day had an effect on tonic-clonic epilepsy in SMEI patients, the data were too limited to assess the relative contribution of stiripentol to seizure control in SMEI. The same effect of reduction of seizures may have been achieved by simple increase of clobazam and valproate concentration in the placebo group. In order to clarify this issue, the applicant agreed to conduct a pivotal efficacy study using maximum tolerated doses of these substances; for such a study, the applicant sought SA and PA from the CHMP.

Since the safety of stiripentol could only be demonstrated in a very limited population under the proposed optimal dose of 50 mg/kg/day, correlation of AEs with serum levels could not be performed and therefore could not be established as a tool to guide on therapy. However, as the data on the fixed dose did not raise major safety concerns, safety issues were considered as resolved.

Although the applicant had applied for "full" MA, the CHMP adopted a positive opinion for granting of only a CMA. It considered that Diacomit® fell within the scope of Regulation 507/2006 with reference to Article 2 and fulfilled the requirements of Article 4 based on the grounds that

(a) The risk/benefit balance of stiripentol for the treatment of SMEI was acceptably demonstrated, since in two placebo-controlled pivotal studies a significant improvement in controlling the seizure frequencies was obtained.

(b) As specific obligations and FUMs (see below) the applicant committed to provide the results of clinical studies to better understand the role of stiripentol in seizure control, either through its intrinsic anticonvulsant activity or through its effects on the metabolism of the adjunctive treatment with clobazam and valproate in SMEI patients.

(c) The CHMP considered that an unmet medical need for patients with SMEI will be fulfilled, because the seizures associated with the disease can never be completely controlled with conventional antiepileptic drugs, and striripentol is expected to improve the control of seizures in these patients.

(d) The availability of stiripentol is expected to be the last alternative to improve severely affected patients. Since there is evidence of efficacy in the data provided – although the role of stiripentol needs to be better understood – the CHMP presumed that the benefit to public health of the immediate market availability of Diacomit® is greater than the risk inherent in the fact that additional data are still required.

Therefore, the recommendation of the CHMP on 18 October 2006 for the granting of a CMA for Diacomit® included the following specific obligations:

1. A randomised placebo-controlled double-blind clinical trial over 12 weeks using stiripentol as an add-on therapy in ~ 40 paediatric patients with Dravet's syndrome (SMEI) not adequately controlled with clobazam and valproate by 2009 (STP 165).

2. A bioavailability study of stiripentol after single oral administration of two 500 mg formulations (capsule and sachet) in 24 healthy male volunteers by 2007 (STP 166).

The applicant provided a Letter of Undertaking on the specific obligations on 17 October 2006 and included additionally the commitment to the following FUMs:

- A population pharmacokinetic study in Dravet's syndrome (SMEI) patients treated with stiripentol, valproate and clobazam.
- An *in vitro* study investigating enzymes that catalyse phase-1 reactions for prediction of possible effects of other drugs on stiripentol.

Based on the positive CHMP opinion, the European Commission granted to Biocodex on 4 January 2007 a CMA for Diacomit® valid throughout the EU.

4.4. Comparison of the three medicinal products already granted Conditional Marketing Authorisation under the new pharmaceutical legislation

The following Table 2 summarises issues of the CT programmes of the three MPs which were relevant for obtaining CMA.

Table 2

Comparative summary of the clinical trial programmes on which CMA of Sutent®, Prezista® and Diacomit® was based

Indication / Medicinal product	Study Number	Design	Number of sub-jects	Dosage/dosage form	Treatment duration	Study status	Endpoints
GIST / Sutent®	RTKC-05-11-013 (supportive study)	Single-arm, open-label, multicenter, Phase I/II (after failure of imatinib)	55	50 mg sunitinib q. d. capsule	6 weeks cycles (4 weeks exposure, 2 weeks off)	completed at the date of initial application	≥ 50% improvement in median TTP over placebo
GIST / Sutent®	A6181004	Double-blinded, placebo controlled, multinational, Phase III efficacy study (after failure of imatinib)	312 (207 active drug)	50 mg sunitinib q. d. capsule	6 weeks cycles (4 weeks exposure, 2 weeks off)	ongoing at the date of CHMP review for CMA, interim analysis presented	primary: ≥ 50% improvement in median TTP over placebo secondary: PFS, OS, ORR, DR
MRCC Sutent®	RTKC-05-11-014 (supportive study)	Single-arm, open-label, multicenter, not randomised, not controlled Phase II	63	50 mg sunitinib q. d. capsule	6 weeks cycles (4 weeks exposure, 2 weeks off)	completed at the date of initial application	Primary: ORR Secondary: TTP
MRCC / Sutent®	A6181006 (pivotal study)	Single-arm, open-label, multicenter, not randomised, not controlled Phase II	106	50 mg sunitinib q. d. capsule	6 weeks cycles (4 weeks exposure, 2 weeks off)	ongoing at the date of CHMP review for CMA, interim analysis presented	Primary: ORR Secondary: TTP, DR, OS (not reached at time of application)
MRCC / Sutent®	A6181034 (continuation of study A6181006 after CMA for full MA)	Open-label, 1:1 randomised, controlled, multinational, Phase III	Total: 750	50 mg sunitinib q. d. capsule	6 weeks cycles (4 weeks exposure, 2 weeks off)	ongoing at the date of CHMP review for CMA, completed at the date of CHMP review for full MA	Primary: PFS Secondary: TTP, DR, OS, PRO
GIST/ MRCC / Sutent®	RTKC-05-11-017/ A6181030	Open-label continuation study for patients in GIST, MRCC and other cancers who would benefit from further treatment	24 GIST 18 MRCC	50 mg sunitinib q. d. capsule.	6 weeks cycles (4 weeks exposure, 2 weeks off)	ongoing at date of CHMP review for "full" approval	Primary: ORR Secondary: TTP, DR, PFS, OS

Indication / Medicinal product	**Study Number**	**Design**	**Number of sub-jects**	**Dosage/dosage form**	**Treatment duration**	**Study status**	**Endpoints**
HIV / Prezista®	TMC114-C201 (Proof of principle) Europe dose ranging study	Randomised, controlled, open-label, Phase IIa	34	darunavir / ritonavir oral solution 400 / - mg b.i.d. 800 / - mg b.i.d. 800 / - mg t.i.d 1200 / - mg t.i.d.	Short term (14 days)	finalised at the date application	dose finding
HIV / Prezista®	TMC114-C207 (Proof of principle) Europe dose ranging study	Randomised, controlled, open-label, Phase IIa	50	darunavir / ritonavir oral solution 300 / 100 mg b.i.d. 600 / 100 mg b.i.d. 900 / 100 mg b.i.d.	Short term (14 days)	finalised at the date of application	dose finding
HIV / Prezista®	TMC114-C202 (POWER 1) USA, Argentina main study	Randomised,controlled, partially blinded, Phase IIb, followed by an open-label period on the recommended dose of darunavir with low dose ritonavir	319	darunavir / ritonavir tablet (400 / 100 mg q.d.) (800 / 100 mg q.d.) (400 / 100 mg b.i.d) 600 / 100 mg b.i.d.	Long-term efficacy study (144 weeks)	ongoing at the date of CHMP review, 24 week interim data presented	Primary: viral load decrease $\geq 1.0 \log_{10}$ secondary: viral load decrease by $\geq 0.5 \log_{10}$ relative to baseline proportion of patients with viral load < 400 or < 50 copies/ml
HIV / Prezista®	TMC114-C213 (POWER 2) multinational main study	Randomised, controlled, partially blinded, Phase IIb, followed by an open-label period on the recommended dose of darunavir with low dose ritonavir	318	darunavir / ritonavir tablet (400 / 100 mg q.d.) (800 / 100 mg q.d.) (400 / 100 mg b.i.d) 600 / 100 mg b.i.d.	Long-term efficacy study (144 weeks)	ongoing at the date of CHMP review, 24 week interim data presented	Primary: viral load decrease $\geq 1.0 \log_{10}$ secondary: viral load decrease by $\geq 0.5 \log_{10}$ relative to baseline proportion of patients with viral load < 400 or < 50 copies/ml
HIV / Prezista®	TMC114-C215 (POWER 3) multinational supportive study	Randomised, open-label, Phase IIb controlled	431	darunavir / ritonavir tablet 400 / 100 mg b.i.d 600 / 100 mg b.i.d.	Long-term safety and tolerability study (144 weeks)	ongoing at the date of CHMP review, 24 and 48 week interim data presented	Primary: viral load decrease $\geq 1.0 \log_{10}$ secondary: viral load decrease by $\geq 0.5 \log_{10}$ relative to baseline proportion of patients with viral load < 400 or < 50 copies/ml
HIV / Prezista®	TMC114-C208 (POWER 3) Europe supportive study	Randomised, open-label, Phase IIb controlled	29	darunavir / ritonavir tablet 400 / 100 mg b.i.d 600 / 100 mg b.i.d.	Long-term safety and tolerability study (144 weeks)	ongoing at the date of CHMP review, 24 and 48 week interim data presented	Primary: viral load decrease $\geq 1.0 \log_{10}$ secondary: viral load decrease by $\geq 0.5 \log_{10}$ relative to baseline proportion of patients with viral load < 400 or < 50 copies/ml

Indication / Medicinal product	**Study Number**	**Design**	**Number and age of sub-jects**	**Dosage/dosage form** **Oral administration in two dosage forms (capsules and sachets)**	**Treatment duration**	**Study status**	**Endpoints**
Epilepsy / Diacomit®	STEV 2-center	Phase II Single-blinded, prospective	25 in indica-tion SMEI, age 2-15 years	60-90 mg/kg q.t.d., switch to 65-83 mg/ kg q.t.d.	12 weeks	completed at the date of application	Change in seizure frequency
Epilepsy / Diacomit®	STILON (France)	Open label, observational, compassionate use programme	45 in indica-tion SMEI, age n. a.	Variable dose, few SMEI patients received >60mg/kg q.t.d. stiripentol and other anti-convulsant co-medications	3 – 5 years	ongoing at the date of CHMP review	
SMEI / Diacomit®	STICLO-FR	Double blinded, 1:1 randomised, placebo-controlled, multicenter	42 age 3-18 years	50 mg/kg q.t.d. stiripentol / ≤ 30 mg/kg/q.t.d. valproate / ≤ 20 mg/q.t.d. clobazam	2 – 3 months	completed at the date of application	Primary: number of responders in each group (= those with > 50% reduction of seizure frequency during 2nd month of treatment). Secondary: percentage of children whose number of seizures decreased by ≥ 50% in the 2nd month of treatment compared to baseline
SMEI / Diacomit®	STICLO-IT	Double blinded, 1:1 randomised, placebo-controlled, multicenter	24 age 3-18 years	50 mg/kg q.t.d. stiripentol / ≤ 30 mg/kg/q.t.d valproate / ≤ 20 mg/q.t.d. clobazam	2 – 3 months	completed at the date of application	Primary: number of responders in each group (= those with > 50% reduction of seizure frequency during 2nd month of treatment). Secondary: percentage of children whose number of seizures decreased by ≥ 50% in the 2nd month of treatment compared to baseline

Although the three MPs were developed for the treatment of totally different indications (cancer, HIV, epilepsy in infancy), all of these diseases fell within the mandatory scope for the CP according to Article 3(1) and under point 3 of the Annex of Regulation 726/2004. Sutent® and Diacomit® fell additionally under point 4 (orphan MPs) of the Annex. All three were considered MPs of high significance, since they were intended to treat life-threatening and seriously debilitating illnesses.

Sutent® and Diacomit® were developed against rare diseases (although Sutent® was in early September 2007 not any more indicated as designated orphan MP in its EPAR on the EMEA homepage). Prezista®, in contrary, was meant for a high proportion of the population worldwide which was expected to grow even more in numbers within the next years.
This was reflected by the different number of patients enrolled into the respective CTs with the three MPs: recruitment of larger numbers of patients for Phase II trials with darunavir seemed even easier than for Phase III trials performed in the indications of rare cancers with sunitinib. Patient recruitment for the epilepsy trials with stiripentol was obviously the hardest task, since the disease is not only rare, but the target SMEI patients are children and adolescents. They constitute a very heterogeneous population concerning age and developmental stage, and in addition a vulnerable population with all associated difficulties.

Applications for MA for the three products were submitted to the Agency between April 2005 and January 2006, granting of CMAs by European Commission Decisions between July 2006 and February 2007. The shortest period of time between submission of the CP application and granting of the CMA was 11 months for Sutent®. It took 13 months for Prezista®, and the longest, 21 months, for Diacomit®, due to the long clock-stop. Clock-stops are provided for in Article 7(c) of Regulation 726/2004 in order to give the applicant sufficient time to supplement the application according to the request of the CHMP or to prepare oral or written explanations. Therefore, it may be assumed that the provision of the answers to the respective requests was more difficult for Diacomit® than for Sutent® or Prezista®.

The clinical development of the three MPs was at very different progress stages at the time of application for MA: in the case of Sutent®, the data provided on efficacy and safety for the indication GIST were mainly derived from a Phase III trial, and would already have been sufficient for “full” MA in this indication. Although the Phase III trial was still ongoing at the time of application, the independent Data and Safety Monitoring Board decided that the primary endpoint had been met, and the blinded study was consequently discontinued. All remaining patients were allowed access to open-label sunitinib treatment.

For the second indication (MRCC) only one more, already ongoing, Phase III trial had to be finalised in order to provide all required comprehensive data and to obtain “full” MA. The trial’s objective was confirmation that the effects observed on the surrogate short-term endpoint ORR translated into the clinically relevant long-term endpoints PFS

and OS. The positive CHMP opinion for indication change to first line treatment and lifting of the conditional state was already obtained half a year after CMA.
After approval for the target population, the continuation of open-label studies will serve to identify further patients likely to benefit from the treatment, what may in the long run lead to a change of the product information.

In the case of the CMA application for Prezista®, although already Phase II studies had included a large number of patients, demonstration of clinical efficacy of darunavir was based solely on the interim analysis of the week 24 virological response from two Phase II trials. Clinical efficiency was defined by the surrogate endpoint of "reduction of viral load after 24 weeks of treatment". Use of an ultimate clinical endpoint would have prolonged the trials' treatment duration until a time point not acceptable for fulfillment of unmet medical needs.

The lack of Phase III studies comparing the treatment with other protease inhibitors in similar therapeutic indications precluded definitive conclusions on efficacy and the safety profile of darunavir. Only a small safety database existed regarding the recommended dose of darunavir/ritonavir 600/100 mg b.i.d. Thus, long-term data (144 weeks) on safety, efficacy and tolerability were still to be provided, as well as data on other studies (mostly interaction studies), which were imposed as a large package to be fulfilled in the frame of specific obligations.

However, CMA was granted for Prezista® since the overall risk/benefit balance was considered positive and there is an urgent medical need for the treatment of HIV in highly pre-treated patients when other treatment regimens have failed.

In the cases of Sutent® and Prezista®, the studies were obviously well planned, designed and conducted in a straightforward way, and were directed to the target population. At least for Prezista®, the possibility may have existed to take prior examples of CT programmes in the same indication as guidance.

For Diacomit®, the historical trial programmes were not very well designed for the SMEI indication; much less CT data than for Sutent® and Prezista® were available at the time of MAA for Diacomit®. In addition, the data were very difficult to interpret regarding efficacy. This was due to the low number of patients affected and to the broadly varying doses and dosage forms of the administered substance stiripentol, in combination with another anti-convulsant co-medication. Only two pivotal efficacy studies (with a fixed dose of stiripentol in combination with fixed doses of valproate and clobazam) delivered significant data in the SMEI target population. These trials were of only two to three months duration with the primary clinical endpoint "reduction of seizures", therefore permitting no information about continued use.

In contrast, for Sutent® and Prezista®, long-term studies with exactly designed dose regimen and more homogenous target populations than for the studies with Diacomit® were already completed or were still ongoing at the time of the respective CHMP review.

Therefore, the lack of long-term efficacy trials with stiripentol was an issue: at the time being, the observational STILON study served as the only source for long-term data, but this study will not provide informative hard data because of the different patients enrolled and the different dosages used.

The fact that only 34 patients were treated with stiripentol in a controlled design in the STICLO-studies, and that these patients provided a very heterogeneous population, rendered interpretation of the available data rather difficult. Several issues were still unresolved, for example regarding comparability of the bioavailability of the dosage forms used in the different studies (sachets and tablets). Another question was whether the observed anti-epileptic effects were due to the active substance stiripentol or to increased levels of the co-administered anti-epileptic medicines. In contrast, for the active substances sunitinib and darunavir the mechanisms of action were clearly defined.

The only possibility to get some clarity of the relevance of stiripentol in the treatment of SMEI will be to evaluate whether stiripentol as an add-on therapy, using maximum safe doses of clobazam and valproate, will provide additional positive effects. Fulfillment of this obligation is expected only in 2009, due to the difficulties associated with indication and recruitment.

Although the amount of comprehensive data and the number of patients included into the CTs provided for in the Diacomit® application dossier were much less compared to the data provided / patients treated in the studies on Sutent® and Prezista®, there remain not as many specific obligations to be fulfilled with Diacomit® than with Prezista®.
This may be due to the fact that comparative Phase III trials on the target population might have been considered as very difficult to perform because of the low prevalence of the condition, and due to difficulties regarding an appropriate study design. This includes the fact that during long-term treatment the paediatric patients will reach another age group and therefore data interpretation will need to be adapted. Furthermore, comparison with other treatments is impossible because no other treatment options exist.

The three cases show that EMEA and European Commission are readily utilising the CMA approach for very serious conditions where the medical need is considered urgent and little or no other alternative treatments exist. The precondition is that the requirement for a positive risk/benefit balance is fulfilled, even if the submitted CT data on efficacy are not yet comprehensive and the available safety data can not yet totally dispell all safety concerns.

Comparison of the three cases also indicated that the less comprehensive data will be available at the time of submission, generally the more specific obligations and FUMs have to be expected to be agreed upon by the applicant in his “Letter of Undertaking”.

The time frames obliged for their fulfillment seem to be realistically adapted to the probable availability of sufficient numbers of patients to be included into the trials, the probable duration of recruitment and conduct of the trials, and the subsequent evaluation of the collected data. For the example of Sutent® in the indication MRCC, fulfillment of the specific obligations within the envisaged timeframe could already be demonstrated.

However, for Prezista®, and particularly for Diacomit®, it remains to be seen whether it will be possible for the MAHs to perform the required studies within the envisaged time frames, and especially if the trials will deliver the expected results to grant a “full” MA in due course. For other MPs developed for the treatment of HIV, it was already demonstrated that comprehensive data could be collected to justify a switch to a “full” MA from a temporary MA (granted as “under exceptional circumstances”, presumably because no provisions for the alternative of CMA existed at the time).

Even for Diacomit®, a switch to “full” MA was obviously considered to be reasonably likely in due course in spite of all associated difficulties, since otherwise rather a MA under exceptional circumstances would have been recommended by the CHMP.

5. Comparison of Marketing Authorisations under Exceptional Circumstances and Conditional Marketing Authorisations

Before entry into force of the new European pharmaceutical legislation, the only option for applicants in the EU who were unable to present comprehensive clinical data at the time of dossier submission was applying for a temporary MA in form of "marketing authorisation under exceptional circumstances".

This possibility was firstly defined in Council Directive 75/318/EEC[68] of 1975 as amended by the Annex of Commission Directive 91/507/EEC[69] of 1991. The amended Part 4G (Documentation for Applications in exceptional circumstances) represented the legal provision for application for MA under exceptional circumstances, reserved for situations in which complete clinical data would not be available for justified reasons:

When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on the quality, efficacy and safety under normal conditions of use, because:

- *the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or*
- *in the present state of scientific knowledge comprehensive information cannot be provided, or*
- *it would be contrary to generally accepted principles of medical ethics to collect such information,*

marketing authorization may be granted on the following conditions:

a) the applicant completes an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile;

b) the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and for a radiopharmaceutical, by an authorized person;

c) the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

This provision became subsequently valid for MPs falling into the scope of the CP, since Regulation 2309/93/EC of 22 July 1993 took up this provision in its Article 13(2), which entered into force in the frame of Title II on 1 January 1995 as follows:

In exceptional circumstances and following consultation with the applicant, an authorisation may be granted subject to certain specific obligations, to be reviewed annually by the Agency.
Such exceptional decisions may be adopted only for objective and verifiable reasons and must be based on one of the causes mentioned in Part 4 G of the Annex to Directive 75/318/EEC.

Changes relating to pharmacovigilance aspects regarding MAs under exceptional circumstances were introduced into Article 14(8) of Regulation 726/2004 which was based on the former Article 13(2) of Regulation 2309/93.

Article 14(8) provides that

In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I [Part II, 6.] *to Directive 2001/83/EC* [which are the same reasons as described in Part 4 G of Directive 75/318/EEC].
Continuation of the authorisation shall be linked to the annual reassessment of the risk/benefit balance.

The provision for obtaining a CMA features certain characteristics in which it is distinguishable from the application and authorisation procedure under exceptional circumstances.

The following Table 3 shows the main differences according to "EMEA current thinking on CMA" [22]:

Table 3

Conditional Marketing Authorisation	**Marketing Authorisation under Exceptional Circumstances**
- granted before all data are available; it is expected that comprehensive data will be provided	- it is assumed that comprehensive data can never be provided, for example because the disease is too rare; medical ethics (i.e. it would be unethical to submit seriously ill patients to extensive tests); stage of scientific knowledge
- authorisation valid for one year (renewable)	- annual assessment of the risk/benefit balance
- obligations: further clinical trials to verify the risk/benefit balance, which is initially based on preliminary evidence from an ultimately comprehensive development	- obligations: specific procedures, in particular concerning safety
- data package: initial data and fulfillment of obligations to provide the missing data = normal MA	- data package: initial data and fulfillment of obligations < normal MA (comprehensive data not expected)

The fulfillment of any specific obligations imposed as part of the MA under exceptional circumstances aims at the provision of information on safety and efficacy of the MP; usually it is not considered as possible to compile a full dossier containing sufficient clinical data. However, the option that a MA under exceptional circumstances could nevertheless be switched into a "full" MA was not excluded explicitly for those cases where the MAH may finally be able to present comprehensive data on efficacy and safety under normal conditions of use and no specific obligations remain.

This has, for instance, been demonstrated by the example of Aventis' Taxotere® for cancer treatment, which gained a full MA although initially granted a MA under exceptional circumstances. Another example is Boehringer Ingelheim International GmbH's Viramune® for part of combination therapy for the antiviral treatment of HIV-1 infected patients with advanced or progressive immunodeficiency (see Annex I of this Masterthesis).

MA under exceptional circumstances was used a lot in the past because there was no other scheme for applicants in the EU not able to present comprehensive clinical data at the time of dossier submission. It may be presumed that the new opportunity of application for CMA may be considered as a convenient approach to faster market access by applicants who are not yet in the possession of sufficient data for a "full" MA but see a good chance to achieve this package in the foreseeable future. Applications for MAs under exceptional circumstances should, in contrast, since entry into force of Regulation 726/2004 only be submitted in those cases where it may realistically not be expected to provide sufficient data in due course. According to the Guideline on procedures for the granting of MAs under exceptional circumstances[70], MAs under exceptional circumstances should not be granted when a CMA is more appropriate.

An overview representing several MPs which have obtained a temporary MA under exceptional circumstances via the CP in Europe during the recent years is shown in Table 4 in Annex I of this Masterthesis (extracted from IDRAC[71] and the relevant EPARs on the Agency's homepage[17]). It includes MPs granted MA under exceptional circumstances under the old and already under the new legislation, although it does not claim completeness. It also includes the three MPs granted CMA so far for comparison purposes.

Interestingly, most MPs granted approval under exceptional circumstances under the "old" pharmaceutical legislation were MPs for the treatment of HIV and various kinds of cancers; many of the latter were designated orphan MPs based on the low prevalence of the condition in the European population.

Since validity of Regulation 726/2004, only three MPs developed for the treatment of cancer were considered for MA under exceptional circumstances, namely

- Evoltra®, for the treatment of acute lymphoblastic leukemia. As the product is intended for the treatment of affected children, representing only a small part of the population, it may truly be impossible to provide the essential data on safety and efficacy for a "full" MA.

- Atriance®, designated orphan MP, for treatment of T-cell leukemia; a positive CHMP opinion for MA under exceptional circumstances was released, but no Commission Decision yet published (early September 2007).
- Yondelis®, designated orphan MP, for treatment of soft tissue sarcoma by binding to DNA and prevention of multiplying of tumour cells; a positive CHMP opinion for MA under exceptional circumstances was released, but no Commission Decision yet published (early September 2007).

Other indications than cancer and HIV are now in the focus for MAs under exceptional circumstances. For example, Advagraf® has been developed for prophylaxis and treatment of transplant rejection in adult kidney or liver allograft patients, and the orphan MP Naglazyme® is used for the treatment of Mucopolysaccharidosis in paediatric patients.

Further MPs granted MA under exceptional circumstances have been developed for influenza prophylaxis: Daronrix® (by Glaxo Smith Kline Biologicals S.A.) and Focetria® (by Novartis Vaccines and Diagnostics S. r. l.) are examples for MPs made by new biotechnological processes. They are intended to be applied as prophylaxis against influenza in an officially declared influenza pandemic situation. In case of an outbreak the virus can widely spread in a very short time because of lack of immunity. Therefore, the objective behind these mock-up vaccines is to have in the event of a pandemic situation MPs in place which can be changed quickly in form of a variation to include the responsible virus strain.
These are classical examples for situations in which sufficient data for a “full” MA are not considered ever to be provided, neither at the time of MA nor later.

Interestingly, Prezista® by Janssen-Cilag International NV and Aptivus®[72] by Boehringer Ingelheim GmbH, both containing an HIV protease inhibitor as active substance, have been granted temporary MA for second line treatment in the same indication: treatment of HIV-1 infection, co-administered with low doses of ritonavir in highly pre-treated adult patients who failed treatment with other protease inhibitors. In both cases it was considered that the risk/benefit balance is positive, but not all formal studies on the MP’s safety and efficacy have yet been completed.

But for Prezista®, CMA was granted at a time when Regulations 726/2004 and 507/2006 were already in force and therefore the conditions for the granting of a CMA were clearly outlined. In the case of Aptivus®, Regulation 726/2004 was not yet in force and therefore the MA for Aptivus® could only be granted as MA under exceptional circumstances accompanied with imposed specific obligations. Yet, it may be speculated that Aptivus® might become another case where a MA originally granted under exceptional circumstances will be transformed into a “full” MA upon provision of all comprehensive data.

Part III: Impacts and Perspectives of Conditional Marketing Authorisations

6. Discussion

With the new Regulations 726/2004 and 507/2006, supported by the *Draft Guideline*, the legal provision for CMA was introduced into the EU pharmaceutical legislation. Precondition for receiving a CMA is a high probability that the applicant can fulfill the imposed specific obligations and the FUMs in order to provide the missing data on CTs in due time for obtaining of a "full" MA.

6.1. Perspectives for patients

Advance in knowledge and technology have greatly increased expectations of patients for improved healthcare, especially in serious and life-threatening diseases.

In line with their role to protect the public from not efficient and unsafe MPs, regulatory authorities must judge on the acceptability of the risk/benefit balance of a specific MP before they grant access to the market. This provides especially a challenge in cases of serious and life-threatening diseases.

For example, oncologic MPs are usually highly toxic but this is accepted because of their positive influence on the disease, the symptoms or prolongation of survival time. Similarly, for other life-threatening and serious diseases probably leading to death if untreated, a relatively high level of known risk and some uncertainty about potential risk must be weighed against improved survival or quality of life by effective treatment. In these cases, where unmet medical needs exist for seriously ill patients, it may be more acceptable to license MPs with a higher risk than would be acceptable for MPs not intended to treat serious or life-threatening diseases[73].

In case of standard MAs, the level of knowledge about the safety of the new compound is usually quite satisfactory: only rare ARs are not yet seen at this stage of development. However, as several cases also in the recent past have shown, no guarantee can be given that SARs only become obvious once the new drug is administered by thousands or even millions of patients. By granting CMA on the basis of a very limited safety data base the European Authorities accept an increased risk for the patients to suffer from unknown ARs. This increased risk can only be justified in serious or life-threatening diseases when available information is thoroughly evaluated and when the process can ensure close collaboration with the MAH in generation of additional safety data.

For example, MRCC patients were most probably not exposed to a higher risk of experiencing unexpected or more serious ARs during treatment with Sutent® under CMA than patients using alternative anti-cancer treatment granted a "full" authorisation. This is because solid safety data had already been provided for the GIST indication, and in the course of evaluation of the CT data provided for "full" application it was determined that the initial safety profile was confirmed.

In contrast, when using Prezista®, there may exist a certain risk for patients to experience not yet observed ARs and SARs, since the safety database for the recommended dose is still limited. However, since Prezista® is to be administered in cases where most other available treatments have previously failed, Prezista® may provide the last option for affected patients. In this regard, patients are supposedly much more willing to put up with the possibility of ARs, even severe ones, since their life is at stake. They are most probably already used to cope with disagreeable ARs caused by the treatment with previous medications and have already arranged their daily life accordingly.

The available safety database for Diacomit® at the time of CMA granting was very limited due to the very small target population available for enrollment into the two controlled CTs. Therefore, parents of concerned children had to make a very difficult decision before they agreed to their child's treatment with this new drug. However, probably a large part of the paediatric patients (and their parents or peers) are ready to give Diacomit® a try. They understand their seizures to be very derogating for their daily life and functioning, and the danger to hurt themselves during tonic-clonic seizures (biting of the tongue, falling down, damaging of limbs or head, etc.) must not be underestimated. In these circumstances ARs are probably perceived as less incommodating as long as the quality and quantity of the seizures can be significantly improved.

Since it is not the Regulatory Authorities but the patients suffering from serious and life-threatening diseases who may potentially gain benefit from a new and innovative MP, and who ultimately take the risk of experiencing ARs, processes should be in place to involve patients into decisions about the acceptable risk/benefit ratio of new MPs. Such a process exists in the decision on acceptable risks in CTs: every trial needs to be approved by one or several independent ethics committees. European legislation requires that each ethics committee must have patient representatives. The requested percentage of the total number of ethics committee members, however, varies from country to country.

Yet, the involvement of patient representatives in the decision on acceptable risk in MAs is still very limited[74]. Mostly due to a lack of structural preconditions, there are presently only rare mechanisms where patient organisations may contribute to all aspects of development, approval and access to MPs throughout the EU.

Besides fundamental lack of financial means, a problem may be associated with the particular circumstances of the patients themselves, namely that chronic and severe illnesses reduce personal energy and financial resources. Since it is difficult to summon up the necessary strength and steadfastness to organise successful activities, infrastructure funding and other forms of support need to be provided by the EU, foundations, commercial sponsors and wealthy individuals. As discussed already at the EPPOSI workshop in Barcelona in 2002[75] would patient groups by such measures enabled to determine and formulate their needs. Furthermore, they could develop their activities and send their delegates as representatives in decision making bodies at all relevant stages of drug development and regulatory processes.

A positive example is the Cancer Liaison Programme[76] developed by the FDA. It includes a process for recommending, recruiting and training patient representatives to serve on cancer-related advisory committees, such as the Oncologic Drugs Advisory Committee (ODAC) which is consulted by the FDA for guidance. Furthermore, the FDA has established a Cancer Drug Development Patient Consultant Programme which aims at the incorporation of the patients' perspective into the drug development process. Patients serve as consultants in the CTs phase and are involved in topics like CTs design, endpoint determination, and patient recruitment strategies.

In Europe, the SAG-O provides the CHMP with guidance on the approvability of cancer drugs (as it was performed in the case of Sutent®). But unlike the ODAC, which holds its meetings in public so that they can be attended by anyone with an interest in the topics under discussion, SAG-O's meetings take place in private and without any patient representation within the group.

However, initial initiatives have recently been developed within the EMEA to integrate patients into the development of different aspects of MPs. The EMEA Road Map to 2010[3] aims at the involvement of patient associations in the recommendation for granting or renewing CMAs as well as at converting them into "full" MAs or taking any negative action on such CMAs. Also, the Road Map provides for the implementation of the necessary measures to adequately inform the public on actions taken in relation to CMAs. Regarding new approaches to increase transparency and communication[27], particular attention will be given to the development of effective communication tools for patients and healthcare professionals, especially in relation to new community legislation concepts such as CMAs.

Patients' and consumers' organisations wishing to participate in EMEA activities may apply at the EMEA by using a specific link[77]. Already 16 organisations, including the European Cancer Patient Coalition (ECPC), the European Federation of Neurological Associations (EFNA) and the European AIDS Treatment Group (EATG) have been included in the list of patients' and consumers' organisations fulfilling the criteria for involvement into the EMEA activities.

6.2. Perspectives for the pharmaceutical industry

Although special provisions for financial compensation have already been implemented, especially when rare diseases are concerned, the risk of investment into studies intended to lead to CMAs in life-threatening and serious diseases may seem not always profitable in the long run. Associated difficulties for marketing authorisation applicants (MAAs) / MAHs may be somewhat minimised by the provision of market introduction at early stages of development made possible by CMA. Thus, market advantages over competitors and in addition a good reputation may be gained. However, this should never be the only and ultimate motivation for a decision to apply for CMA; it should never be neglected that an ethical responsibility exists for MAAs/MAHs to provide to the public access to adequate and efficient treatment for life-threatening and serious diseases as soon as possible.

A potential disadvantage of an early access to the market through a CMA may be the fact that more SARs or ARs may arise during continuation of ongoing or new trials than expected from evaluation of the initial data. Or possibly a satisfactory level of efficacy can not be demonstrated[#] what may lead to a risk/benefit balance not as positive as anticipated. In addition, data gathering may prove more complicated than expected or even impossible, and consequently deadlines for submission of the required comprehensive data may not be observed. Therefore a risk of financial penalties in case of unkept timelines, removal of the MP from the market, and public "name and shame" may be imminent as consequence.

Furthermore, the CMA status will generate the extra work of yearly renewal and of many variation applications for the MAH, which is very time- and cost-intensive. Therefore, it is important in cases when it is the CHMP who proposes CMA that this is done in agreement with the applicant, and it is essential to be sufficiently sure that the applicant will be able to fulfill the obligations agreed upon. Hence, before application for CMA, it is advisable that the pharmaceutical enterprise should perform an intensive risk analysis.

Whereas for Prezista® it was the applicant who requested for CMA[53], the proposal for CMA for the products Sutent® and Diacomit® was made by the CHMP.

It remains to be awaited how the procedures will develop in the future, i. e. if mostly the applicants or mostly the Agency will propose that a MP may fulfill the requirements for granting rather of a CMA instead of a "full" MA. It may be speculated that some applicants might try to apply for "full" MA at first, and if this is not acceptable, will follow the Agency's proposal for a CMA.

[#] Iressa (gefitinib) by AstraZeneca, which was approved in May 2003 by the FDA via "accelerated approval"[4] in the indication "advanced non-small cell lung cancer", constitutes an example that it is not always possible to provide comprehensive data. The drug was approved initially based on a study using ORR as surrogate endpoint, but these data could not be confirmed by the results of a further study using OS as clinical endpoint, as required by the FDA. Therefore, the FDA approved in June 2005 a new labelling that limits the use of Iressa to patients who have or are currently benefiting from Iressa treatment[78].

As an alternative, the EFPIA[11] proposed that the following procedure should be included into the *Draft Guideline* as acceptable from a procedural point of view: if an applicant for MA, although he believes that his submission qualifies for "full" approval is however not entirely certain, he may include a justification why his data meet at least the criteria for CMA. If the CHMP reaches the opinion in the course of assessment that the data do not qualify for "full" approval, this justification may anticipate a possible request from the CHMP for information to substantiate the fulfillment of the requirements for CMA.

Equivalents to the European CMA have already been earlier introduced in Canada under the NOC/c policy[6,7] and in the USA as accelerated approval[4,5]. A strengthening of the collaboration with associations of the pharmaceutical industry in these countries as well as with and between the Regulatory Authorities will be particularly important in this innovative field. This may especially be true regarding learning from former activities and avoiding mistakes which may have already lead in the past to problems in these countries.

In this context, one focus should be directed to potential problems in connection with data gathering and another to the possibility of the use of biomarkers in the frame of CTs for CMA. Furthermore, request of SA should be strongly recommended to applicants for CMA (see below).

6.3. Considerations on the conduct of clinical trials and data gathering

As described in the Guideline on Clinical Trials in small populations[79], the usual Phase III CTs enrolling several hundred patients may not be practical or even possible for rare serious or life-threatening diseases. This is because subjects for large trials may simply not be available in sufficient numbers.
In general, the need for statistical significance should be weighed against the need for clinically relevant and interpretable results, the latter being the most important.
If internal controls are not possible in trials relevant for CMA applications, patient registers in forms of large-scale databases monitoring the natural history of a given disorder could provide a virtual placebo group. Against this virtual placebo group the effectiveness of a new drug could be measured, given robustness and acceptability of the data. In addition, this approach may contribute to a solution of the problem that patients with serious disorders are mostly unwilling to risk being in the placebo group, as discussed at the EPPOSI workshop[75].

Moreover, if patients have already received the MP after CMA, especially in orphan indications, specific caution has to be taken when planning further studies, as too few treatment-naïve patients might be left for enrollment into the new studies. Often, therapeutic confirmatory trials are not feasible in an approved orphan indication as it is unethical to withdraw patients, especially severely ill patients, from an efficient and well tolerated treatment to enroll them into a CT.

In the absence of facilities for undertaking CTs on MPs designed for the treatment of specific disorders, establishment of networks with experienced staff to provide the necessary capacity and expertise would certainly be helpful. Such initiatives may contribute to more flexibility for CTs in serious and life-threatening diseases, especially the rare ones, and promote regulatory acceptance.

For all these approaches it will be important that more intense dialogue takes place between scientists, patients and commercial investors using expert regulatory support. This will help to develop scientifically sound alternatives to traditional CT procedures and to achieve better acceptance by Health Authorities, also and especially in respect to CMAs. Furthermore, regulatory assessment should be flexible enough to accept different approaches of data gathering if it is ensured that patients' interests are protected.

6.4. Role of Biomarkers and Surrogate Endpoints

Especially for life-threatening, seriously debilitating and other serious indications the time frame for the development of new treatments is vital. Waiting to assess the relevant clinical endpoints which are defined as characteristics or variables indicating how a patient feels or functions, or how long a patient survives, poses a dilemma. Therefore clinical endpoints in trials on medicinal products for serious diseases are frequently subject to scientific discussions[80].
It is commonly acknowledged that endpoints are needed that can be measured earlier, easier or more frequently, and with higher precision without being affected by other treatment modalities[81].

Biomarkers have already become increasingly useful and important in the early process of development of new MPs, since they may provide predictive information for CTs on patient-subpopulations that might respond to a new MP, or are susceptible to side effects. Therefore patient selection and recruitment, especially in trials for orphan MPs, may be enhanced by the use of biomarkers.

However, until recently biomarkers have not been considered to be able to truly predict and quantitatively measure the clinical relevance of efficacy and safety of an MP; their role in the evaluation of the outcome of CTs in respect to the licensing of MPs is still limited. For Health Authorities, proof of a positive risk/benefit ratio based on hard clinical endpoints is generally the decisive factor. Only in very few indications biomarkers have been validated as surrogate endpoints that show a high predictive value for a relevant clinical endpoint[82].

In the frame of the new European pharmaceutical legislation and especially for CMAs for serious and life-threatening diseases, biomarkers and surrogate endpoints may gain special importance. Current developments have demonstrated that FDA (FDA's critical path initiative[83]) and EMEA have been willing to accept validated biomarkers (e. g. tumor progression in cancer indications) as alternative to survival outcome because of

the inability of seriously ill patients to afford any delay. However, depending on the type of disease, Health Authorities expect survival data to be generated in refractory cases.
An example for this practice is demonstrated by Sutent® in the indication MRCC. CMA was granted mainly on the efficacy data provided regarding the surrogate endpoint ORR, and the company was asked to collect further information to demonstrate the drug's effect on important time-related endpoints (OS, PFS).

Surrogate endpoints are most useful when not only applicable for a specific CT, but when effects can be translated into general clinical benefit.
For anti-HIV MPs, 24-week data on reduction of viral load have generally been accepted by Health Authorities as surrogate endpoint for granting of MAs under exceptional circumstances, and recently they have also been accepted for granting of CMA for Prezista®.
In the indication HIV use of long-term (for example, 48-week) data on viral load reduction has become so established and well validated that this endpoint has replaced survival as clinical endpoint[84]. Already since 1997 several anti-HIV MPs[#] have been granted "full" approval in the EU using endpoint data on increase in C4 cell counts and reduction of viral load alone[85].

Generally, a pre-determined plan how to supplement clinical studies with further evidence to support clinical benefit, safety and risk/benefit assessment should be provided or will be part of specific obligations imposed on the sponsor in the frame of CMA. It should carefully address methodological issues of interim analysis and further analysis. Demonstration of the causal linkage of surrogate endpoints to changes in a clinical endpoint or symptoms may be supported by epidemiological data, although such data may be limited when there are very few patients[79].

An important role has been attributed to genomic biomarkers. Since they can reflect expression, function or regulation of a gene, they are defined in ICH Guideline E15[86] as "a measurable DNA or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other intervention". If DNA and RNA are the targets of the MP, the characteristics may vary in relation to treatment response and exhibit changes long before physiological effects may be detected.

In summary, biomarkers and surrogate endpoints may play an increasingly important role in order to get relevant and reliable information at early stages of CTs (i.e. before finalisation of Phase III studies). Especially when intending to go the route of a CMA, demonstration of the presumed positive risk/benefit balance as required according to Article 4 of Regulation 507/2006 may be based on the evidence provided by validated biomarkers, although completion of further studies is still pending.

[#]Crixivan®, Epivir®, Norvir®, Invirase®, Fortovase®, Viramune®

In the interest of the waiting patient, it would be important to harmonise provisions for acceptance of biomarker-derived CT data and surrogate endpoints in the regulatory procedures of CMA in the EU and of accelerated approval in USA and NOC/c in Canada.

Furthermore, cooperation amongst the Health Authorities and with pharmaceutical companies in common initiatives would help to define criteria for prioritising diseases and therapeutic areas for which surrogacy of the most promising biomarkers could be assessed. As outlined at the EMEA/EFPIA workshop on biomarkers[87], this may be a step forward to innovative methodological approaches for the design and conduct of future CTs. These approaches may contribute to regulatory acceptability of surrogate endpoint data for CMAs.

6.5. Role of Scientific Advice

Interestingly, Sutent® for which the applicant had not requested SA or PA was granted CMA and only a half year later "full" approval, demonstrating that apparently the CT concept was well elaborated and performed even without SA.

For Prezista®, it may be assumed that the SA provided by the CHMP helped to smooth the way for a straight conduct of the trials by the applicant and speedy evaluation of the CMA submission dossier by the Agency. Especially since several HIV MPs have already been granted MA (many of them – at least initially - under exceptional circumstances), it can be presumed that extensive knowledge exists within companies and within the Agency on issues of relevance for the planning and conduct of the essential CTs.

In the case of the designated orphan MP Diacomit®, CHMP's SA and PA was not requested during the planning phase for the initial MAA. Yet, this support might have been helpful, especially because of the rarity, uniqueness, complexity and the low prevalence of the disease intended to be treated and the broad differences within the very special and highly sensitive target population.
However, SA and PA were only sought for the design of CTs imposed as specific obligations.

MA applicants are generally advised to request SA from the CHMP not to dismiss important issues which should be addressed in a CT and not to expose patients to inadequate or super fluent trials, especially those patients already suffering to an enormous degree from their disease. In addition, for designated orphan MPs, PA offered by the collegial work from EMEA's SAWP, CHMP and the Committee on Orphan Medicinal Products (COMP) should be requested early in the development of the MP. Furthermore, special CHMP scientific advisory groups have already been established which can provide particular expertise for specific indications (for example for oncology, viral diseases, diabetes, and neurological diseases).

An important element in fostering the collaboration of FDA and EMEA is the implementation of a pilot programme for parallel SA of both Regulatory Authorities[88,89]. The goal of this pilot programme is to provide a mechanism for sponsors, EMEA and FDA assessors to exchange their views on scientific issues during the global development of new MPs.

The expected advantages from such interactions are increased dialogue between the two agencies and sponsors from the beginning of the lifecycle of a new product, a deeper understanding of the bases of SA, and the opportunity to optimise product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies. Particular focus of this pilot programme lies on issues of critical importance for patients, such as SA for medicines for rare diseases and oncology. It may be very helpful to identify right from the beginning appropriate trial designs which are acceptable to the Competent Authorities for CMA (EMEA) or accelerated approval (FDA), respectively.

It may have to be considered whether SA should be made mandatory for applications intended for CMA because in critical situations a "unilateral" attempt of the applicant can lead to rejection of the CMA application. In consequence, important products for unmet medical needs may not be accessible for patients early. In particular, the special form of SA offered by the Agency to potential applicants for CMA according to Article 10 of Regulation 507/2006 should become mandatory: this SA helps to decide on whether a MP developed for a specific therapeutic indication falls within one of the categories outlined in Article 2 and whether it may fulfill the requirements laid down in Article 4(1)c (fulfillment of unmet medical needs) for obtaining a CMA.

Another crucial topic for SA on suitability of the CMA approach should be discussed very early in the development: the likelihood to assemble a full dossier. SA may indicate whether application for CMA or MA under exceptional circumstances would be more appropriate and accordingly direct the CT programme.

However, applicants need to understand that SA can not provide an assurance for a positive CMA opinion and that SA is only a tool to address whether the planned studies are adequate for the request for CMA.

6.6. Conditional Marketing Authorisation in relation to other new regulatory procedures

Orphan MPs

It may be expected that for orphan MPs, intended to treat rare serious and life-threatening diseases, the opportunity of application for CMA will be used quite frequently. Two of the MPs already granted CMA (Sutent® and Diacomit®) have been designated orphan MP according to Article 3 of Regulation 141/2000, what provides a basis for eligibility for CMA according to Article 2(3) of Regulation 507/2006.
It has to be considered that Orphan *designation* criteria are independent from the criteria qualifying for CMA.

Regenerative medicines

New therapies within the EU will constitute a particular challenge with respect to the adequacy of the legal tools. Especially for advanced therapy MPs[90] facilitation of early Community market access may become essential. Tissue engineering, which combines various aspects of medicine, cell and molecular biology, materials science and engineering for the purpose of replacing human tissues, presents often the last treatment hope for patients affected by serious and life-threatening diseases.
Therefore the possibility to obtain CMA will certainly provide a very important tool in this innovative biotechnological area.

Accelerated assessment procedures[#]

A provision was introduced into the European pharmaceutical legislation by Article 14(9) of Regulation 726/2004 and described in the Guideline on the procedure of accelerated assessment[93] that an applicant may formally request for accelerated assessment procedure of an MAA and should duly substantiate this request. Precondition is that the MP falls into the scope of Article 3(1) or (2) of Regulation 726/2004 and is considered to be of major interest for public health, particularly in relevance to therapeutic innovation. The normal 210 day assessment period as laid down in Article 6(3) of Regulation 726/2004 is reduced to 150 days at maximum.[##]

Especially applications requesting a CMA (or a MA under exceptional circumstances) may in addition be eligible for an accelerated assessment procedure according to Article 14(9) of Regulation 726/2004. The applicant for MA should present arguments to support the claim that the MP introduces a new method of therapy or improves existing methods, thereby addressing to a significant extent the greater unmet medical need for maintaining and improving the health of the Community.

CMA speeds up patients' access to MPs by impact on development of MPs (i. e. pre-MAA) whilst accelerated assessment impacts how quickly the Health Authorities review the MAA (i. e. post-MAA). Via accelerated assessment, MA and market introduction could take place even two months earlier than it would be possible for a MP granted "only" CMA. In cases of severe diseases a combination of application for CMA and application for accelerated assessment could even increase benefits to public health by saving the life of more patients or enhancing their quality of life earlier.

[#]Equivalent to the EU accelerated assessment procedure are

- the US Priority Review[91], setting the target date for the FDA for completing all aspects of a review and taking an action on the application (approval or not approval) at 6 months (instead of 10 months in Standard Review) after filing date
- the Canadian Priority Review[92], which reduces Health Canada's timeframe to 25 calendar days for submission screening and 180 calendar days for submission review.

[##]The first MP for which, upon application for "full" MA, an accelerated assessment procedure according to Article 14(9) of Regulation 726/2004 was concluded successfully after 147 days is Soliris® from Alexion Europe SAS for the treatment of haemolysis[94].

Compassionate use programmes

Compassionate use means that MPs falling within Article 3 of Regulation 726/2004 but which have not (yet) been granted MA are made available, for humanitarian reasons, to groups of patients suffering from serious or life-threatening diseases. This is realised by way of exemption from Article 6 of Directive 2001/83/EC which provides that a MP may only be put on the market after approval by the responsible Competent Authority.

As a precondition for the performance of compassionate use programmes according to Article 83(2) of Regulation 726/2004, the MP must be subject to a MAA in accordance with Article 6 or must be undergoing CTs. At least data from Phase II CTs must be available which demonstrate efficacy of the MP and enable assessment of a positive risk/benefit ratio, as the Guideline on Compassionate Use[95] provides.

In some MS compassionate use measures have been implemented into the national law, for example in France by the "Authorisations Temporaire d`Utilisation Unit" (ATU) programmes via Articles L.6121-12 and R.5121-68 to 5121-76. For patients suffering from serious or life-threatening diseases, compassionate use may offer a perspective to be continuously supplied with the respective MP until MA is granted, which may be in form of CMA.

It would be unethical to deprive patients, particularly those who participated in CTs and gained benefit from the study medication, from access to the MP until MA is obtained and the product marketed. But it has to be clearly understood that compassionate use programmes can not, and are not intended to, substitute CTs. Therefore, they must not impair the conduct of CTs, which have the aim to prospectively collect further information on the risk/benefit balance in order to obtain as soon as possible MA (or at least CMA) and to supply as many patients as soon as possible with important MPs available on prescription.

However, the impact of extensive compassionate use activities on the interest in achieving CMA needs to be considered. In MS where compassionate use is widespread, there may be less pressure to request a CMA. In contrast, in MS where compassionate use measures are lacking, there may be *per se* more pressure to submit an application for CMA early to avoid delays in market availability of new treatment options.

6.7. Important open issues and remarks on the Draft Guideline on Conditional Marketing Authorisation

- According to the *Draft Guideline*, a CMA does only apply to the first MA for a new MP but not to new indications submitted as part of a variation or extension procedure of an already existing MA or CMA. Is it nevertheless possible to apply for a CMA for a new indication of an already in another indication authorised product, for example in a stand-alone application under a new trade name?

EFPIA[11] believes that it should be allowed to MAHs

- to file variations to "full" MAs or to CMAs for new indications meeting all conditions for being authorised as CMAs

- to file a "full" MA to a CMA in case of availability of comprehensive clinical data supporting a "full" MA in a new indication.

- Although the *Draft Guideline* determines that "full" MAs, and MAs under exceptional circumstances can not be changed into CMAs, there is no provision on whether a CMA may be changed or not into a MA under exceptional circumstances. Such an option would be imaginable for cases where it shows unexpectedly, due to changed circumstances and in deviation from the former point of view at the time of granting of a CMA, that the MAH will probably never be able to supply comprehensive data. However, if the MP is nevertheless considered important for the treatment of serious and life-threatening diseases and the risk/benefit balance is positive, it may be decided that the MP should continue to be accessible for patients via change of CMA into MA under exceptional circumstances.

- The *Draft Guideline* gives no timelines for agreement on details of specific obligations.

- The PSUR schedule has not been clarified: according to Article 9 of Regulation 507/2006, PSURs for CMAs are to be submitted every 6 months until conversion into a "full" MA. For products with "full" MAs, PSURs should be submitted every 6 months for 2 years, then annually for 2 years, then every three years according to Article 24(3) of Regulation 726/2004. Since conversion of CMA can take several years, it is not clear what should be the periodicity of the PSUR submission after conversion to "full" MA.

- Neither in Regulations 726/2004 and 507/2006, nor in the *Draft Guideline* is explanation provided for the timeframe in which the MP has to be marketed after granting of CMA. Along with Article 14(4) of Regulation 726/2004, at latest three years after MA a product must be placed on the Community market, otherwise the MA ceases to be valid (sunset clause).
  For CMAs, this long period before validity would cease does not make any sense, since CMAs are *per se* intended to be made accessible to patients as soon as possible after approval. Thus, there remains the need for explanation in the current legislation. Possibly, there exists an opportunity that this issue may be resolved as a specific agreement between the MAH and the Agency, and the timeframe may be decided upon on a case-by-case base.

7. Conclusion and outlook

Until early September 2007 three MPs have been granted CMA. These initial experiences have already demonstrated that with introduction of the provision for CMA into the new EU pharmaceutical legislation a very useful tool has been established. Access to new and innovative MPs a few months earlier than it would be possible via "full" MA is highly appreciated by patients suffering from serious and life-threatening diseases, often rare ones, with no treatment alternatives. Due to the characteristics of the disease, this may save their life or contribute earlier to a better quality of life. In cases where unmet medical needs exist for severely ill patients it is more acceptable to license MPs with a higher risk than could be accepted for MPs not intended to treat serious or life-threatening diseases.
These are the main reasons for permitting CMA to new MPs for which efficacy and safety data are not yet comprehensive at the date of approval.

A prerequisite must be assurance of critical observation of a positive risk/benefit balance. A further precondition must be a high probability that the applicant can fulfill the imposed specific obligations of collecting post-authorisation comprehensive clinical data. Upon presentation of these data, the CMA is foreseen to be switched into a "full" MA. Thus, CMA is demarcated against the provision for MA under exceptional circumstances, which should only be used in cases where the presentation of comprehensive data in due course may realistically not be expected. Examples for such recent MAs under exceptional circumstances relate to MPs intended for prophylaxis of infectious diseases in an officially declared pandemic situation.

Regulatory decision making will in the future be based more and more on biomarkers and surrogate endpoints, especially in the framework of CMA, since they can predict the outcome of clinical benefit at early stages of CTs. In order to save precious time for the patients waiting for efficient and safe treatment, this new generation of markers may be used instead of, or in combination with, traditional clinical endpoints, given that they become well validated.
An important role in this context will presumably play genomic biomarkers, reflecting expression, function, or regulation of genes. If changes upon administration of the active substance can be measured as DNA or RNA characteristics, these markers may serve to deliver important information much earlier as conventional endpoints and can contribute intensely to the CT design for CMAs.
Thus supported, the CMA approach will help the pharmaceutical industry to accelerate the duration until market introduction in cases of important MPs developed for the fulfillment of unmet medical needs in severe illnesses.

Patients as the ultimate concerned party wish to obtain more influence in all aspects of regulatory decision making, particularly when MPs for serious or life-threatening diseases are involved. They strive especially for participation in the regulatory risk/benefit assessment of such new drugs and in decisions on acceptability of potentially associated risks. Since the power of individual patients is limited, patient

organisations are currently in creation and first initiatives to become involved into the activities of decision making bodies have already been started.

For the pharmaceutical industry there exist many benefits associated with CMA, for example market access earlier than competitors, a good reputation and financial advantages. But also the risk exists that the enterprise will finally not be able to provide the missing data agreed upon by granting of CMA. Further disadvantages may be additional costs and a heavy workload associated with the annual renewal and the presumably high number of variation applications due to continuous creation of new information on the MP.

For Regulatory Authorities, even judgment on the acceptability of the risk/benefit balance for MPs in the standard MA procedure is often not an easy task. But MPs destined for the CMA route may provide special challenges because they are intended for the treatment of severely ill patients. Thus, Regulatory Authorities must weigh case by case improved survival or quality of life against a certain level of insecurity in relation to potential risks.
Therefore it would be of advantage for all concerned parties if dialogues on scientific issues between sponsors and Health Authorities in Europe and the USA would be intensified. An important element in fostering the collaboration of EMEA and FDA has been the implementation of a pilot programme for parallel SA of both Authorities. Further common initiatives should become established and widened in the future with the focus on optimisation of the global product development. This will contribute to allow to severely ill patients early access to innovative MPs which are nonetheless as safe as possible.

If feasible, the combination of application for CMA and for accelerated assessment should be considered. This would make MPs intended to be authorised by CMA even two additional months earlier available for patients, thus increasing even more their benefits to public health.

It is expected that the newly implemented regulatory basis for CMA and first experiences with this new tool will facilitate the discussion on how the system can be improved and how the CMA route could be widened in the future. Provision of further guidance on how to handle specific aspects and upcoming questions in the course of CMA would be very helpful.

8. Summary

For patients suffering from serious or life-threatening diseases efficient treatment can not come too soon. With the intention to make much needed and innovative MPs faster available to all patients in the EU, new tools were implemented into the European pharmaceutical legislation. One of them is the concept of CMA, the legal provision of which was introduced by Article 14(7) of Regulation 726/2004 into the framework of the CP. Regulation 507/2006 lays down details on CMA, and a supporting *Draft Guideline* was developed to give advice on the scientific application and practical arrangements to implement this Regulation.

Accordingly, MPs are eligible for CMA in cases where comprehensive clinical data on safety and efficacy are less than complete at the date of application but are considered reasonably likely to be completed and presented to the CHMP in due time after approval. Usually, all necessary pre-clinical and pharmaceutical data should be available at the time of application for CMA.

To qualify for CMA, a MP must belong at least to one of the following categories:

- MP intended for treatment, prevention or diagnosis of seriously debilitating or life-threatening diseases
- designation as orphan MP by the EU Commission in accordance with Article 3 of Regulation 141/ 2000
- MP intended to be used in emergency situations, responding to European Community- or WHO-recognised health threats. Only in this case it is possible to obtain CMA without complete non-clinical or pharmaceutical data, subject to completion through the specific obligations process.

As precondition for granting CMA, fulfillment of unmet medical needs and a positive risk/benefit balance must be demonstrated by comprehensive scientific evidence. The risks inherent in the fact that additional data on efficacy and safety of the MP still need to be provided must be outweighed by the benefits to public health through patients' early access to the product.

The CMA is valid for one year on a renewable basis. At the occasion of annual reassessment the MAH is obliged to present the status of fulfillment of the imposed specific obligations. These may contain ongoing studies to be completed or new studies to be conducted in order to demonstrate a positive risk/benefit balance.

Until early September 2007, CMA was already granted for three MPs which were developed for the treatment of different serious and life-threatening diseases: cancer, HIV and SMEI. Two of these MPs were previously granted orphan designation. The data provided in the CMA application dossier were at divergent stages of completion, reflecting the different phases of progress of the CTs on the respective MP. This was due to very varying study designs, restricted availability of patients for recruitment for the CTs in the orphan indications, especially in SMEI, and to considerable differences of basic knowledge about the respective disease's background.

Sutent®, the MP for the treatment of cancer, has meanwhile already obtained "full" MA. The relevant CTs have shown the greatest progress at the time of application, compared to the two other products: only one already ongoing study in the indication MRCC had to be finalised in order to present the comprehensive data on safety and efficacy required for "full" MA. Therefore, Sutent® may constitute a prime example for utilisation of CMA and possibly encourage other applicants to proceed likewise.

Prezista® and Diacomit® are still subject to specific obligations; it is expected that the MAHs can fulfill them in due course within the scheduled timeframes.

Because of the very different history and circumstances which may be associated with MPs intended for CMA – as the three examples already indicate - great flexibility will have to be proven in the future. Regulatory Authorities will need to adapt to the different situations in order to perform an adequate estimation on whether preconditions for CMAs are fulfilled.

Patient organisations raise their voice to get involved into the regulatory review process of CMAs as the ultimately concerned stakeholders of the drug development process. Patients often have a different point of view than regulators regarding the risks they are prepared to take when weighed against the potential benefits of a new MP. Therefore, initiatives to participate patients in the regulatory risk/benefit assessment of new drugs for serious or life–threatening diseases are already in the phase of creation. Such initiatives need to be combined with appropriate financial support to patient organisations, transparency of information on the new medicinal products and safety surveillance after CMA has been granted for the MP.

For the pharmaceutical industry, application for a CMA includes the possibility of earlier market access as competitors and the prospect of a good reputation and financial profits. However, the main motivations to apply for a CMA should include a strong focus on the pharmaceutical enterprise's responsibility versus the public out of ethical considerations. Opposed to the mentioned advantages, also certain disadvantages exists in connection with a CMA for a pharmaceutical company. They include extra workload when the annual renewal is due, large numbers of variation applications to be submitted, and possible additional risk management requirements to be fulfilled. Furthermore, a certain danger can not be excluded that the company may not be able to present the comprehensive data agreed upon as specific obligations by granting of CMA. This includes possible serious negative financial consequences and a negative reputation.

The clinical development of MPs for serious and life-threatening diseases, especially in orphan indications, requires innovative methodological approaches. It is important to recognise that new biomarkers may have the potential to speed up the availability of MPs if they are not only used for development decisions in companies, but also for regulatory decision making. In order to be used as the clinical basis for CMA they should be sufficiently widely accepted for trials with the same intention.

An important issue for CMA at a relatively early stage in clinical development for innovative new medicines is the generation of an adequate safety profile. Improvements in risk management processes, including pharmacovigilance measures, could contribute to encourage applicants to envisage more readily the approach of CMA.

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Annex I

Table 4

List of Medicinal Products granted Marketing Authorisation under Exceptional Circumstances and Conditional Marketing Authorisation [17,71]

Product / active Substance	MAH	Indication	Orphan designation under 141/2000/EC / date	MA type	Granted under validity of relevant parts of Regulation	Date of MA	Full MA/date
Taxotere® / docetaxel trihydrate	Aventis Pharma	breast cancer non-small cell lung cancer prostate cancer gastric adenocarcinoma	n. a.	Exceptional circumstances	2309/93/EEC	27 November 1995	7 July 1998
Viramune® 200 mg tablets Viramune 50 mg/5 ml oral suspension / nevirapine	Boehringer Ingelheim International GmbH	combination therapy for the antiviral treatment of HIV-1 infected patients with advanced or progressive immunodeficiency	n. a.	Exceptional circumstances	2309/93/EEC	5 February 1998	25 April 2002
Mab Campath® / alemtuzumab	Genzyme Europe BV	treatment of lymphocytic leukaemia after failure of alkylating agents	n. a.	Exceptional circumstances	2309/93/EEC	6 July 2001	
Foscan® / temoporfin	Biolitec pharma ltd.	palliative treatment of advanced head and neck squamous cell carcinoma after failure of prior therapies	n. a.	Exceptional circumstances	2309/93/EEC	24 October 2001	
Glivec® / imatinib mesilate	Novartis Europharm Ltd	treatment of adult and paediatric patients with - newly diagnosed Philadelphia chromosome associated chronic myeloid leukaemia adult patients with - Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST). - unresectable dermatofibrosarcoma protuberans (DFSP) - recurrent and/or metastatic DFSP not eligible for surgery	14 February 2001 (chronic myeloid leukaemia indication) 20 February 2001 (GIST indication)	Exceptional circumstances	2309/93/EEC	7 November 2001	

Trisenox® / arsenic trioxide	Cephalon UK Ltd	relapsed acute promyelocytic leukemia (APL),	18 October 2000	Exceptional circumstances	2309/93/EEC	5 March 2002	
Onsenal® / celecoxib	Pharmacia - Pfizer EEIG	reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis	20 November 2001	Exceptional circumstances	2309/93/EEC	17 October 2003	
Zevalin® / ibritumomab tiuxetan	Schering AG	the [90Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell non-Hodgkin's lymphoma	n. a.	Exceptional circumstances	2309/93/EEC	16 January 2004	
Reyataz®/ atazanavir sulphate	Bristol Myers Squibb	combination therapy for the antiviral treatment of HIV-1 infected treatment experienced adults	n.a.	Exceptional circumstances	2309/93/EEC	2 March 2004	
Velcade® / bortezomib	Janssen-Cilag	treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation	n. a.	Exceptional circumstances	2309/93/EEC	26 April 2004	
Prialt®/ ziconotide	Eisai Limited	treatment of severe chronic pain in patients who require intrathecal analgesia	9 July 2001	Exceptional circumstances	2309/93/EEC	21 February 2005	
Aptivus® / tipranavir	Boehringer Ingelheim International GmbH	in combination with other antiretroviral medicinal products for the treatment of HIV 1 infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor	n. a.	Exceptional circumstances	2309/93/EEC	25 October 2005	
Revatio® / sildenafil (as citrate)	Pfizer Limited	treatment of pulmonary arterial hypertension exercise capacity	12 December 2003	Exceptional circumstances	2309/93/EEC	28 October 2005	
Naglazyme® / galsulfase	Biomarin Europe Ltd.	long-term enzyme replacement therapy in patients with Mucopolysaccharidosis VI; initiation of early treatment of young patients (aged <5 years) suffering from a severe form of the disease	14 February 2001	Exceptional circumstances	726/2004/EC	24 January 2006	
Evoltra® / clofarabine	Bioenvision Limited	treatment of acute lymphoblastic leukemia in pediatric patients	5 February 2002	Exceptional circumstances	726/2004/EC	29 May 2006	

Sutent® / sunitinib malate	Pfizer Limited	treatment of GIST, treatment of MRCC	10 March 2005 (not applicable early September 2007)	Conditional approval	726/2004/EC 507/2006/EC	19 July 2006	11 January 2007
Diacomit® / stiripentol	Biocodex	use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy	5 December 2001	Conditional approval	726/2004/EC 507/2006/EC	4 January 2007	
Prezista® / darunavir	Janssen-Cilag International NV	in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV 1) infection in highly pre treated adult patients who failed more than one regimen containing a protease inhibitor	n.a.	Conditional approval	726/2004/EC 507/2006/EC	12 February 2007	
Daronrix®/ A/Vietnam/ 1194/2004 (H5N1) whole virus inactivated antigen	Glaxo SmithKline Biologicals S.A.	prophylaxis of influenza in an officially declared pandemic situation	n.a.	Exceptional circumstances	726/2004/EC	21 March 2007	
Advagraf® / tacrolimus	Astellas	prophylaxis of transplant rejection in adult kidney or liver allograft recipients, treatment of allograft rejection	n. a.	Exceptional circumstances	726/2004/EC	23 April 2007	
Focetria ®/ A/Vietnam/ 1194/2004 (H5N1) virus surface inactivated antigen	Novartis Vaccines and Diagnostics S.r.l.	prophylaxis of influenza in an officially declared pandemic situation	n. a.	Exceptional circumstances	726/2004/EC	2 May 2007	
Increlex®/ mecasermin	Tercica Europa Ltd.	long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor 1 deficiency	26 August 2005	Exceptional circumstances	726/2004/EC	3 August 2007	
Atriance®/ neralabine	Glaxo Group Limited	T-cell acute lymphoblastic leukemia and T-cell lymphoblastic leukemia after non-response or relapse following treatment with ≥ 2 chemotherapeutic regimen	16 June 2005	Exceptional circumstances	726/2004/EC	Positive CHMP opinion 21 June 2007	
Yondelis® / trabectedin	Pharma Mar S.A.	treatment of soft tissue sarcoma by binding to DNA and prevention of multiplying of tumour cells	30 May 2001	Exceptional circumstances	726//2004/EC	Positive CHMP opinion 19 July 2007	

Annex II

General overview over the phases of clinical development of medicinal products

Clinical trials are defined according to Article 2(a) of Directive 2001/20/EC[38] as "Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy".

The clinical development of medicinal products is generally described as consisting of four temporal phases (Phases I-IV). Usually, the conduct of successful studies of Phases I-III is a precondition for marketing authorisation. Although these phases may provide an inadequate basis for classification of clinical trials because one type of trial may occur in several phases, the types of studies are commonly related to the phase for which they present the most typical kind of study.

An overview of study phases and their aims is presented in the following according to ICH Guideline E8[23].

Phase I trials (human pharmacology)

These tests, representing the first administration of a new medicinal product in humans, are designed to assess pharmacokinetic and pharmacodynamic characteristics of a therapy, including initial estimation of the drug's safety profile, tolerability, and dose ranging. Usually, small groups of healthy subjects are included into Phase I trials, which are always conducted in clinics under strict observation of the subjects by experienced staff.

Under specific circumstances, i. e. for the test of new oncological or HIV drugs, only patients are included into Phase I trials. Because of ethical reasons healthy subjects should not be exposed to drugs for which a certain toxicity is known or expected. On the other hand, patients suffering from such a severe disease should not be denied a possible treatment in observance that the benefit/risk balance for them is somewhat shifted in comparison to that for healthy subjects.

Phase II trials (therapeutic exploratory)

Once the safety of the therapy has been confirmed as far as possible in initial Phase I trials, Phase II trials are performed. These may at first be uncontrolled and proof of concept Phase IIa trials to assess dosing requirements and tolerability. Afterwards randomised and controlled Phase IIb trials to further study safety and in addition demonstrate efficacy in the targeted indication are performed on a larger group of patients (usually 100-300 subjects suffering from the respective disease).

One important goal of Phase II studies is determination of the doses, dose-response relationships, and regimen as a basis for Phase III trials. Studies in Phase II are typically conducted in a group of patients selected by relatively narrow criteria, therefore presenting a rather homogenous population. The treatment phase of these trials takes approximately only up to two months.

Phase III trials (therapeutic confirmatory)

These trials are the most expensive and time consuming (6-12 months of treatment) trials. Their aim is to gain an informative statistical comparison of the treatment groups in order to assess/confirm tolerability, safety and efficacy as well as dose-response relationship in short-term and long-term treatment in the intended indication and target population.

Preferentially, Phase III clinical trials should be randomised and double-blinded in order to demonstrate the therapeutic benefit and to answer to questions on adverse effects, including rare ones, and on influences of specific factors (i. e. age, reduced organ functions, etc.). They are intended to explore the medicinal product's use in wider populations, in different stages of the disease, or in combination with other medicinal products. Also, they shall provide a basis for risk/benefit and benefit/cost evaluations.

Several 100 to several 1000 patients may be included in Phase III multicenter trials and should be statistically representative for conditions in hospitals and doctor's practices. Phase III trials are difficult to design and perform, especially in therapies for serious, life-threatening and chronic conditions.

Typically, it is expected by regulatory agencies as FDA and EMEA that at least results from two successful Phase III trials are submitted in order to obtain "full" marketing authorisation. However, it is common practice that certain Phase III trials are continued while application for marketing authorisation has already been submitted and approval is still pending.

Phase IV trials (therapeutic use)

They begin usually after marketing authorisation of medicinal products and are important for optimisation of the drug's use "in daily life" in relation to the approved indication(s). Phase IV trials include studies on drug-drug interactions, dose-response or safety studies as well as studies on mortality, morbidity, and epidemiological studies.

The aim is to refine understanding of benefit/risk relationships in general or in special populations and environments. Another focus lies on identification of less common or long-term adverse reactions over a larger patient population and timescale than was possible during the initial clinical trials. Furthermore, results of Phase IV trials serve to refine recommendations.

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

Ingelheim, 11. September 2007

Unterschrift: