Strategic evaluation of the regulatory instruments for obtaining early market access in the EEA, Canada and USA of a novel anticancer drug

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List of abbreviations

ADME	Absorption-Distribution-Metabolism-Excretion
AIDS	Acquired Immune Deficiency Syndrome
ALS	Amyotrophic Lateral Sclerosis
ATU	Autorisation Temporaire d'utilisation (Temporary Authorisation for Use)
BLA	Biologic Licence Application (US term for an MAA for a new biologic product)
BSC	Best Supportive Care
CAP	Clinical Assessment Package (Canadian term for the clinical documentation to be submitted as part of a request for priority review)
CBER	Center for Biologics Evaluation and Research (at FDA)
CDER	Center for Drug Evaluation and Research (at FDA)
CFR	Code of Federal Regulation (US legislation)
CHMP	Committee of Human Medicinal Products
CLIN	Clinical
CMA	Continuous Marketing Application
CMC	Chemistry Manufacture Control (synonymous for quality part of MAA)
COMP	Committee for Orphan Medicinal Products
CP	Centralised Procedure
CPMP	Committee of Proprietary Medicinal Products (now CHMP)
CTD	Common Technical Document
DCP	Decentralised Procedure
DGRA	Deutsche Gesellschaft für Regulatory Affairs
DFS	Disease Free Survival
DR	Draft
EC	European Community
EEA	European Economic Area (EU + EFTA)
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association (currently: Iceland, Liechtenstein, Norway)
e.g.	Example given
EMEA	European Medicines Agency
EOP1	End-of-Phase 1 (clinical development phase)
EOP2	End-of-Phase 2 (clinical development phase)
EU	European Union
EWP	Efficacy Working Party
FD&C	Federal Food, Drug, and Cosmetic (Act) (US legislation)
FDA	Food and Drug Administration (US federal authority that regulates foods, pharmaceutical drugs and medical devices for human use)

FDAMA	Food and Drug Administration Modernization Act
GIST	Gastrointestinal stromal tumour
HIV	Humane Immunodeficiency Virus
ICD-O	International Classification of Diseases for Oncology
IND	Investigational New Drug Application
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MRCC	Metastatic renal cell carcinoma
MRP	Mutual Recognition Procedure
MS	Member State (of EEA)
NAS	New Active Substance
NDA	New Drug Application (US term for an MAA for a new drug product)
NDS	New Drug Submission (Canadian term for an MAA for a new drug product)
NME	New Molecular Entity
NML	New Medicines Legislation (new legislation in the EEA as of entry into force of the amended Directive 2001/83/EC and the Regulation (EC) No 726/2004)
NOC	Notice of Compliance (Canadian term for MA)
NOC/c	Notice of Compliance with Conditions (Canadian type of MA)
NOC/c-QN	Notice of Compliance with Conditions – Qualifying notice
NOD	Notice of Deficiency
NON	Notice of Non-compliance
NP	National Procedure
OMP	Orphan Medicinal Product
ORR	Objective Response Rate
PDUFA	Prescription Drug User Fee Act
PFS	Progression Free Survival
Ph 1	Phase 1 (clinical development phase)
Ph 2	Phase 2 (clinical development phase)
PSUR	Periodic Safety Update Report
QoL	Quality of Life
RCC	Renal cell carcinoma
RU	Reviewable Units (US/FDA terminology)
SAP	Special Access Programme
SmPC	Summary of Product Characteristics
S/NDS	Supplemental New Drug Submission
TTP	Time to Progression
WHO	World Health Organisation

1. Introduction and scope

Already in the very early development phase of a new medicinal product the pharmaceutical, pre-clinical and clinical studies necessary for a submission are being planned with respect to design, duration, budgeting etc. Therefore, it may be crucial already in this planning phase to gain knowledge on whether e.g. a conditional marketing authorisation, a marketing authorisation under exceptional circumstances in the EEA and/or an accelerated approval or fast track procedure in the US and/or a notice of compliance with conditions in Canada can be a possibility for the medicinal product under development. Also the regulatory requirements especially with respect to the clinical studies for such specialised submissions may differ significantly to those for standard submissions. Moreover, as differences do exist in the regulatory requirements in case of both standard submissions and submissions for early marketing authorisations between the EEA and other regions, it is advantageous at an early stage to develop regulatory strategies for the drug development in order to make a submission obtaining an early market access in one or more of these three regions possible.

This master's thesis addresses the various options for obtaining a marketing authorisation early in the development phase with special regard to the development of a novel anticancer drug. Main focus is on the new legal provisions for obtaining a conditional marketing authorisation in the EEA as compared to the already existing provisions for making use of a marketing authorisation under exceptional circumstances, compassionate use programmes, orphan drug regulations and obtaining an accelerated assessment. As similarities do exists to regulations in other regions, parallels to the US and Canadian legal systems are drawn.

1.1 Clinical relevance for early market access of new anticancer therapies

According to the International Agency of Research for Cancer within the next 20 years a 50 % increase in the cancer rate is to be expected and the prevalence of malignant cancers and cancer mortality are also increasing. According to the World Cancer report approximately 22 million people worldwide are momentarily living with a cancer disease, annually 10 million new cases of cancer are diagnosed and 12.6 % of the global mortality rate correlate to deaths from oncological diseases[i,ii]. Of the global burden of cancer incidence more than 25 % occurs in Europe although Europe only makes up about 12 % of the world's population and the annual cancer incidence has been growing steadily in Europe over the last 20 years[iii].

As it is estimated that approximately 80 % of cancers are caused by environment and lifestyle and i.e. potentially preventable, a strong focus is being directed towards cancer prevention activities, e.g. campaigns in support of cessation of tobacco consumption and highly caloric and fatty diets. Despite these activities and the fact that many significant advances have already been introduced, people will continue to develop cancer diseases and there does not exist a cure or unequivocal preventive measures for the development of cancer. Hence, the need for improving cancer therapy remains in order to cause a reduction in the cancer incidence world wide and the associated morbidity and mortality as well as to improve the lives of the patients suffering from cancer. The strategy for cancer control shall ideally not only include the treatment of cancer but also prevention, early detection and screening, supportive care, rehabilitation, and palliative care for optimal results[iii].

Cancer which is a collective term of more than 100 individual diseases that arise when malignant forms of abnormal cell growth emerge in one or more locations of the body. Cancer

diseases usually occur after a series of genetic mutations remove the normal cell growth mechanisms resulting in uncontrollable cell division and growth and with time the development of a tumour. Cancer diseases may have both genetic and environmental causes and possess extreme biological diversity as no two cancer diseases act exactly the same and as opposed to many other diseases, cancer may develop at any location in the body and at any stage in life. Cancer treatment will therefore be decided dependent on type, stage, location in the body, standard medical practice in the country where the patient is treated as well as whether the patient may be able to pay for the treatment in the case no insurance or reimbursement system will cover the costs. Moreover, for some cancer diseases the biological mechanism is well-known whereas for others it is not. The biological diversity of cancers as well as the ageing of the population present the largest hurdles for the development of new anticancer therapies[iii].

A recent paradigm shift has occurred in cancer research and development of new therapies, which is caused by advances in the fields of molecular biology and genetics resulting in a greater understanding of the biological mechanism behind many cancer diseases. This paradigm shift has resulted in the development of new anticancer therapies that target the genes causing the specific disease. The advantage of this therapy concept as opposed to the classical chemotherapy is that these agents are designed to detect and destroy specific cancer cells and simultaneously leaving the healthy cells unaffected. However, huge hurdles still exist in anticancer therapy, in that[iii]:

1. tumours grow via multiple mechanisms and thus knowledge of each of these mechanisms is necessary for the development of an optimal therapy
2. cancer cells are typically subject to rapid mutation
3. tumours often turn resistant
4. adjacent cancer cells in a tumour may behave different and therefore not susceptible to the same drug

Patients suffering from such a disease often have a short estimated survival. Thus, the patient is dependent on effective treatment as early as possible after the diagnose is given in order for his survival time to be extended and/or his quality of life to be improved.

Hence, it is obvious that there are still many unmet medical needs in cancer treatment and a need for innovative therapies for many cancer diseases continues to exist.

2. Background

2.1 Need and reasons for introduction of regulatory instruments for obtaining early market access for new and efficacious anticancer therapies

The licensing process of new drugs for serious or life-threatening diseases and conditions for which there is an unmet medical need should enable an early market access to new therapies that significantly improve length and/or quality of life of the patients. Patients suffering from a life-threatening cancer disease usually only survive for a short period of time after they have been diagnosed and these patients are therefore dependent on efficacious treatment as soon as possible. In Europe the regulatory procedures available prior to coming into force of the review of the European pharmaceutical legislation (hereafter referred to as new medicines legislation; NML)[iv] have needed improvement for a long time as the processes were either restrictive in scope, retrospective and unpredictable for applicants or very rarely applied such as accelerated evaluation. Before November 2005 no European equivalents to the regulatory mechanisms in the US (e.g. “priority review”, “ accelerated approval”, “rolling submissions”, see chapter 4.1) which have shown effective in enabling early market access of important new drugs e.g. for

cancer treatment were practically applied[v]. Prior to the implementation of the NML it would typically take about 10 years to develop and register a new medicinal product – from the discovery of the active principle to the introduction of the formulated product on the market. For patients suffering from a serious and/or a life-threatening disease in the EEA this could be too long and there has been a need to review the European pharmaceutical legislation for a long time in order to be able to shorten development times for serious, life-threatening or emergency-use medicines[vi]. With the introduction of the NML the legal provision allowing for the grant of a conditional MA has been introduced, enabling market access prior to the clinical phase III of new and very efficacious anticancer drugs for which a positive risk-benefit balance of the medicinal product can be demonstrated and an unmet medical need is fulfilled. In this case, a new and promising anticancer drug could be made available to the patients approximately 2-3 years earlier due to fact that the confirmatory phase III trials can be performed after grant of the MA.

In the USA the situation over the last 10-15 years on the introduction of innovative drugs has also faced problems as despite the fact that the yearly US spending for pharmaceutical research and development has more than doubled, it has come to a steady decrease in the submissions of product applications (see figure 1 below). The reasons for this seem the increased costs of the development of a new medicinal product as the product development has become more complex and unpredictable and simultaneously the rate of products "failing" to succeed the clinical development phase remains high (approx. 80 %)[vii,viii].

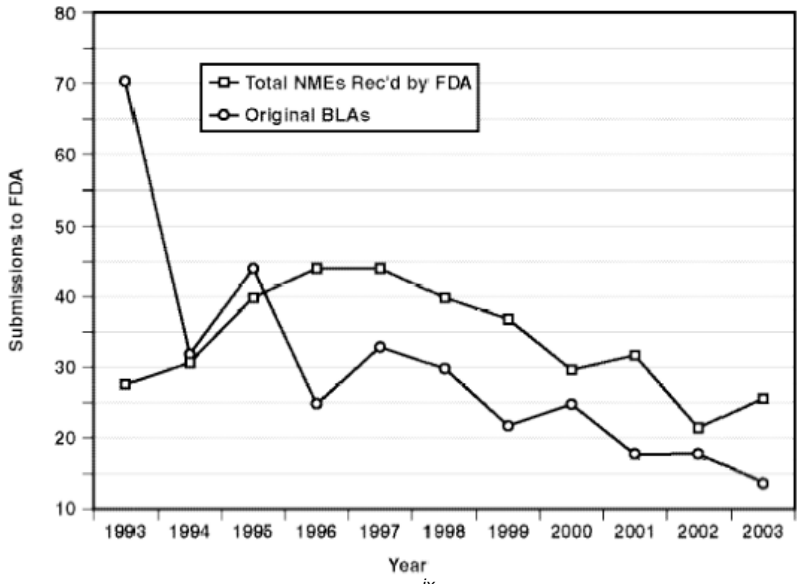

Figure 1: 10-year trend in drug submissions to the FDA[ix]

A report addressing this slowdown in innovative medical therapies submitted to the FDA for approval was released by the FDA in March 2004. In the report the urgent need to modernise the medical product development process to make product development more predictable and efficient was described, and i.e. the so-called "Critical Path Initiative" was established. The primary purpose of the FDA Critical Path Initiative is to ensure that basic scientific discoveries translate more rapidly into new and better medical treatments by creating new tools to demonstrate the safety and effectiveness of new medicinal products in faster timeframes with more certainty and at lower costs. In March 2006 a Critical Path Opportunities List and Report was released by the FDA based on feedback from stakeholders and the special insights of the FDA product reviewers in which it was described how new scientific discoveries in fields such as genomics and proteomics, imaging, and bioinformatics could be applied to improve the accuracy

of the tests used to predict the safety and efficacy of investigational medicinal products and outlines an initial 76 "science projects" divided into the following six key areas :

- Better evaluation tools: Biomarkers and disease models
- Streamlining clinical trials
- Harnessing bioinformatics
- Moving manufacturing into the 21st century
- Products to address urgent public health needs
- At-risk populations

In regard to the current availability of therapies for cancer diseases there is worldwide an urgent need for better treatment alternatives for the most types of cancer as for most cancers the therapeutic options are insufficient in that they do not target specific cancer cells. In enabling the development of new and better cancer drugs, the improvement of regulatory processes, introduction of comprehensive drug development programs as well as the advancement of cooperation between the regulatory agencies (e.g. via scientific advice) worldwide play immense roles.

2.2 Historical aspects of the conditional MA, MA under exceptional circumstances and accelerated evaluation in the EEA

With the introduction of Council Directive 75/318/EEC[x] in May 1975 a legal provision enabling the use of an application for MA under exceptional circumstances became part of the EU pharmaceutical legislation:

*"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 authorisation 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 introduced the first possibility at Community level applicable for anticancer drugs of filing an application for MA in the EEA in situations where complete clinical data – as defined in the respective guidelines valid at the given point of time - would not be available for the justified reasons as stated above (this legal provision as applicable today is described in more detail in chapter 3.3).

Furthermore, in the year 1994 a legal provision allowing for making medicinal products for rare or severe diseases under special circumstances available to patients at an early stage prior to grant of an MA was introduced in France[xi], the so-called "Autorisation Temporaire d'utilisation"

(Temporary Authorisation for Use, ATU). The aim of the ATU is to provide early access to new promising treatments where a genuine public health need exists, i.e. in the treatment of patients suffering from serious disease and having reached a situation where no therapy exists[xii].

With a view to stimulate research and development of medicinal products for rare diseases the European legislation on orphan medicinal products (OMP) comprising Regulation (EC) No 141/2000[xiii] on orphan medicinal products and Commission Regulation (EC) No 847/2000[xiv] laying down the provisions for implementation of the criteria for designation of a medicinal product as an OMP and definitions of the concepts 'similar medicinal product' and 'clinical superiority' were introduced in the year 2000. Approximately 36 % of all OMPs in the EEA are anticancer drugs.

In the US, the FDA began with the appearance of AIDS, and concurrently with the formation of patient activist groups in the 1980's a series of regulatory initiatives intended to expand on the definition and administrative practice of priority review of certain medicinal products. These initiatives included expanded early access to promising products under certain conditions as well as assistance from FDA to companies during the development of such products[xv].

The European Commission proposed in 2001 to follow the US by introducing a fast track registration procedure for products of major therapeutic interest, allowing them to be assessed and authorised quickly and efficiently. The Commission also recommended the possibility of a conditional MA in particular cases when there is a specific patient need. Additionally, the Commission proposed to introduce a Europe-wide system to make medicines available before an MA would be granted, on grounds of compassionate use. This would ensure that patients are not discriminated with respect to e.g. the location of clinical trials performed by a particular company[xvi]. In his speech July 2001[xvii], member of the European Commission Mr. Erkki Liikanen spoke of the need for increasing the availability of new and innovative medicines in Europe: *"We want to increase the availability of new and innovative medicines on the European market, while at the same time ensuring that the basic criteria of safety, quality and efficacy are met. This will also ensure that EU scientific assessments for major new medicines are as fast, if not faster than those performed by the US FDA.(..)"*

Data from 2002 have shown that the European average approval time for cancer drugs was 458 days (range 301–812 days), whereas the average US approval time for cancer drugs was 273 days. Moreover, since 1997, FDA has subjected 18 cancer drugs to its priority review process, and its priority cancer drug approval average was an impressive 186.5 days (range 72–414 days)[xviii].

As part of the EMEA Road Map to 2010[xix], the EMEA identifies the improvement of the centralised procedure - which is now obligatory for all new anticancer drugs - and timely access to innovative medicinal products for patients suffering from severe or life-threatening conditions as priority objectives that need to be achieved before the end of this decade.

3. Current regulatory framework for obtaining early market access in the EEA

3.1 Introduction

The overall aim of the pharmaceutical legislation of the European Community, which has validity in all Member States of the EEA, is the protection of public health and the free movement of medicinal products. A medicinal product may only be placed on the market in the EEA when an MA has been granted either by the competent authority of a Member State of the EEA (national

authorisation) or by the European Commission in accordance with Regulation (EC) No 726/2004 (a Community authorisation). A national MA may be granted for a medicinal product for human or veterinary use which has undergone either a purely national procedure (NP) in one EEA Member State, a decentralised procedure (DCP) where a MA in more than one Member State is strived for and no MA in the EEA exists or a so-called mutual recognition procedure (MRP) where an MA in more than one Member State is strived for and one or more MAs already exist in the EEA. A Community authorisation may be granted for a medicinal product for human or veterinary use which has undergone a centralised procedure[xx].

The Commission will grant a Community authorisation for the following medicinal products for which an MAA was submitted and found acceptable:

- medicinal products referred to in the Annex to Regulation (EC) No 726/2004[xxi] (mandatory scope), which may only be authorised via the centralised procedure and medicinal products for which the therapeutic indication is the treatment of AIDS, cancer, neurodegenerative disorder or diabetes[1] as well as medicinal products with orphan drug designation;
- medicinal products referred to in Article 3(2) of Regulation (EC) No 726/2004, relating to products containing new active substances, products which constitute a significant therapeutic, scientific or technical innovation or products for which the granting of a Community authorisation would be in the interest of patients or animal health at Community level. The applicant has to request confirmation that the product is eligible for evaluation through the CP (optional scope) and the EMEA will decide on the matter; and
- generic medicinal products of a centrally authorised medicinal product if not using the option in Article 3(3) of Regulation (EC) No 726/2004

In the context of Regulation (EC) No 726/2004 cancer shall mean all malignant and borderline malignant neoplasms, following the current International Classification of Diseases for Oncology[xxii] (ICD-O). This includes primary or secondary malignant neoplasms, carcinoma in situ, and neoplasms classified as uncertain whether benign or malignant (behaviour codes /1, /2, /3, /6, /9), but benign neoplasms (behaviour code /0) are not defined as cancer. The mandatory scope of the CP therefore includes following medicinal products for cancer treatment: anti-neoplastic agents and adjuvant treatments as defined in Annex I of the EMEA guideline EMEA/296293/2005 and not e.g. agents developed for the prevention of side-effects of cancer treatment, chemopreventive or diagnostic agents[xxiii].

An application for MA shall - irrespective of the type of MA application procedure (NP, DCP, MRP or CP) - include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to Directive 2001/83/EC as amended[xxiv], and this documentation is to be presented in the CTD format, which is commonly accepted throughout the ICH regions.

The fundamental requirement for authorising medicinal products for marketing in the EEA is an overall favourable risk-benefit balance estimated upon the data presented in the MAA with respect to the product quality as well as efficacy and safety in the proposed therapeutic indications. This is legally provided for in Directive 2001/83/EC as amended in which the risk-benefit balance is defined as an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, where the risks relate to the quality, safety or efficacy of the medicinal product regarding patients' health or public health, as well as to undesirable effects on the environment.

[1] with effect from 20 November 2005 and with effect from 20 May 2008, the CP is made mandatory for medicinal products for human use with an NAS for which the indication is for treatment of auto-immune diseases and other immune dysfunctions and viral diseases.

The MA for a medicinal product is associated with an evidence of efficacy based on data which demonstrate a clinical superiority as compared to placebo or another active therapy, or equivalence or non-inferiority as compared to the current standard therapy.

Article 116 of Directive 2001/83 as amended[xxiv] states the legal grounds for which an MA cannot be granted:

*„The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the **product is harmful** under normal conditions of use, or that it **lacks therapeutic efficacy**, or that **the risk-benefit balance is not positive** under the normal conditions of use, or that its **qualitative and quantitative composition is not as declared**. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product."*

Hence, an MA cannot be denied solely due to the fact that the establishment of therapeutic efficacy is based on a limited amount of clinical data which is inevitable in the development of new the therapies for certain cancer diseases (e.g. due to small patient population of the therapeutic indication).

Generally, in the clinical development of a new drug the first use in humans is conducted in a small number of healthy volunteers in order to study the tolerability as well as the pharmacokinetic and pharmacodynamic characteristics of the drug following the administration of selected doses which are chosen based on the results from the pre-clinical development. However, for anticancer drugs such as cytotoxic compounds, it is generally accepted that patients instead of healthy volunteers are included in Phase I trials for ethical reasons: the healthy volunteers should not be exposed to a drug with known high toxicity and patients suffering from a severe or life-threatening disease should be offered the best possible treatment. Placebo is, however, increasingly used as add-on comparator to standard therapy or to "best-supportive-care" (BSC) in pivotal trials. If BSC or the selected active background therapy is appropriate, placebo as add-on comparator offers the possibility to reduce bias in general and to assess e.g. symptom control[xxv].

In the past, a large number of anticancer drugs have been authorised for marketing without having completed clinical development and i.e. the efficacy and safety was not been confirmed prior to grant of the MA. This situation will most likely not change for future anticancer drugs until suitable non-clinical models with adequate predictive properties have been established[xxv].

The NML provides for two different types of MAs deviating from the "normal" MA. Article 14(7) of Regulation (EC) No 726/2004[xxi] lays down the legal provision for the so-called conditional MA and Article 14(8) of the same Regulation enables the granting of an MA under exceptional circumstances. Both types of MAs are described individually, and similarities and differences between these two possibilities in the EEA to apply for an MA for a medicinal product early in the development phase with a limited amount of clinical data are evaluated in the following.

3.2 Conditional marketing authorisation

Along with the NML which entered into force in November 2005, the possibility of applying for a so-called conditional MA was introduced in the EU pharmaceutical legislation. The conditional MA is one regulatory instrument allowing for giving certain important medicinal products the possibility of obtaining an MA at an early stage in the clinical development phase provided that a positive risk-benefit profile can be demonstrated. Since at the point of time of which such an MA

is granted, only limited clinical data are available (and in cases where a public health emergency situation exists also pre-clinical and/or quality data may be limited), the conditional MA will be subject to specific post-approval obligations such as conducting further studies in order to enable the submission of confirmatory data post-approval. In this way, the patients will be given access to a new and efficacious anticancer drug as early as possible based on the earliest evidence of a positive benefit-risk ratio in humans in the given therapeutic indication. With time the conditional MA will be switched to a "normal" MA as full data become available.

The new procedure for obtaining a conditional MA is exclusively applicable to new therapies for which unmet medical needs in life-threatening and rare diseases such as cancer and orphan conditions exist, where it may be difficult to obtain enough clinical data as generally required for a full application, and in public health emergency situations such as in the case of a flu pandemic.

3.2.1 Legal background

The legal provision allowing for the use of a conditional MA is laid down in Article 14(7) of Regulation (EC) No 726/2004[xxi] which entered into force on 20 November 2005:

*"Following consultation with the applicant, an **authorisation may be granted subject to certain specific obligations**, to be reviewed annually by the Agency[2]. The list of these obligations shall be made publicly accessible.*
*By way of derogation from paragraph 1, 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)."[3]

With the Regulation (EC) No 507/2006 of 29 March 2006[xxvi] the legal provisions for granting a conditional MA were laid down. Article 2 of this regulation legally defines which types of medicinal products that may make use of a conditional MA:

This Regulation shall apply to medicinal products for human use that fall under Article 3(1)[4] and (2)[5] of Regulation (EC) No 726/2004 and belong to one of the following categories:
*1. medicinal products which aim at the **treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases**;*
2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC;
*3. medicinal products designated as **orphan medicinal products** in accordance with Article 3 of Regulation (EC) No 141/2000.*

Of these three categories, number 1 and 3, respectively, may apply to new anticancer drugs.

Decision 2119/98/EC[xxvii] aims to improve the prevention and control in the EC of a series of communicable diseases which are categorised in the Annex of the Decision; such as diseases preventable by vaccination, sexually-transmitted and food- and water-borne diseases and

[2] In this context Agency means the European Medicines Agency EMEA
[3] Where Article 87(2) states: "Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof". Decision 1999/468/EC lays down the roles of the European Commission, Council and Parliament, respectively
[4] refers to the mandatory scope of the centralised procedure (CP)
[5] refers to the optional scope of the CP, except for generic medicinal products of medicinal products authorised via the CP as these are covered by Article 3(3)

diseases of environmental origin. Hence, category number 2 does normally not apply to anticancer drugs.

Since OMPs are often used in the treatment of oncological diseases, the criteria for obtaining an orphan drug designation are listed in the following and discussed in chapter 3.4.1.

Article 3 of Regulation (EC) No 141/2000[xiii] lists the criteria for designation of a medicinal product as an orphan drug:

- *the medicinal product 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*
- *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.*

Article 4 of Regulation (EC) No 507/2006[xxvi] lists the requirements to be met in order for a medicinal product to make use of an application for conditional MA:

"1. A ***conditional marketing authorisation may be granted*** *where the Committee[6] finds that,* ***although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied****, all the following requirements are met:*
(a) the ***risk-benefit balance of the medicinal product****, as defined in Article 1(28a) of Directive 2001/83/EC,* ***is positive****;*
(b) it is ***likely that the applicant*** *will be in a position to* ***provide the comprehensive clinical data****;*
(c) ***unmet medical needs will be fulfilled****;*
(d) the ***benefit to public health of the immediate availability*** *on the market of the medicinal product concerned* ***outweighs the risk inherent i****n the fact that additional data are still required.*

In ***emergency situations*** *as referred to in Article 2(2),* ***a conditional marketing authorisation may be granted****, subject to the requirements set out in points (a) to (d) of this paragraph,* ***also where comprehensive pre-clinical or pharmaceutical data have not been supplied****.*

2. For the purposes of paragraph 1(c), 'unmet medical needs' means a 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 those affected."

An application for a conditional MA shall make use of the CP and applies exclusively to medicinal products which may or must go through a CP in accordance with the provisions of Regulation (EC) No 726/2004. Where an applicant wishes to apply for a conditional MA in accordance with Article 14(7) of Regulation (EC) No 726/2004, a justification covering the following aspects should be included in an official request prior to or together with the submission of the application for conditional MA[xxviii]:

- Evidence that the product falls under Article 3(1) or 3(2) of Regulation (EC) No 726/2004 (i.e. mandatory or optional scope of the CP, except for generics of medicinal products authorised via the CP) and belongs to one of the categories listed in Article 2 of Commission Regulation (EC) No 507/2006;

[6] In this context Committee means the CHMP

- Evidence that the product complies with the requirements laid down in Article 4 of Commission Regulation (EC) No 507/2006;
- A proposal for completion of ongoing studies, conduct of new studies and/or collection of pharmacovigilance data where appropriate.

Not only the applicant can propose the use of the conditional MA procedure for a medicinal product which is likely to fulfil the legal requirement as listed above, also the CHMP may recommend the use of a conditional MA procedure and the granting of a conditional MA during an ongoing MA procedure after consultation with the applicant. The possibility for the CHMP to recommend the granting of a conditional MA will apply to new MAAs for which a CHMP opinion will be adopted as of the April 2006 CHMP meeting[xxix].

3.2.2 Regulatory requirements

Once a conditional MA has been granted, the MAH is required to complete ongoing studies or to conduct such new studies as agreed as specific obligations to the conditional MA. Moreover, the MAH is obligated to submit a periodic safety update report (PSUR) to the EMEA and to the Member States immediately upon request or at least every 6 months after grant or renewal of the conditional MA, respectively. The aim of these special obligations is to confirm the favourable risk-benefit balance as demonstrated at the point of time of the application for conditional MA as laid down in Article 4(1)(a) of Commission Regulation (EC) 507/2006. A medicinal product for which a conditional MA has been granted must include in its product information (SPC and package leaflet) a clear statement on the fact that the MA granted for the product is of conditional nature.

The conditional MA has a validity of one year and hence is subject to an annual renewal in which the special obligations and their timeframes are assessed. Analogously to a “normal” MA granted in the EEA, the application for renewal of the conditional MA must be submitted at least 6 months prior to expiry. Along with the application for renewal of the conditional MA, an interim report is to be submitted addressing the fulfilment of the specific obligations to which the conditional MA is subject. Based on the assessment of the renewal application the CHMP will express its opinion on the specific obligations and their respective timeframes and as to whether these shall be retained or possibly modified.

The objective of the conditional MA is that the MA will with time become a “normal” full MA no longer subject to the specific obligations of the conditional MA, when complete data become available and hence the specific obligations have been completed. In such a situation the CHMP will adopt a positive opinion in favour of granting an MA in accordance with Article 14(1) of Regulation (EC) 726/2004 (i.e. a Community authorisation). Such an MA will be valid for 5 years and be subject to the “normal” post-approval obligations such as submitting safety data in form of PSURs in the predetermined time intervals.

An EMEA guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No. 507/2006 on the conditional MA for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 is currently in the preparation. It is being expected that key aspects of this guideline will include the early notification from the applicant about the intention to request a conditional MA and demonstrating a clear justification that the medicinal product falls within the scope of a conditional MA[xxx].

3.2.3 First experiences with the conditional marketing authorisation procedure

In April 2006 the first conditional MA was granted in the EU, for the medicinal product Sutent (active ingredient: sutinib malate) which was designated as an OMP in March 2005, for the following indications[xxxi]:

- treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
- treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon alfa or interleukin-2 therapy.

The effectiveness of Sutent in GIST has been demonstrated in 312 patients who could not receive the authorised medicinal product containing imatinib, or who had failed on treatment with imatinib, where it was compared to placebo in a double-blind study with time to tumour progression as primary clinical endpoint. In this study it was demonstrated that Sutent was more effective than placebo in GIST: the time taken before progression of the disease was 27.3 weeks in patients who received the medicine, against 6.4 weeks in patients who received placebo. The interim results were sufficiently good for the study to be discontinued early and for the patients who were receiving placebo to be switched to Sutent. In renal cell carcinoma, Sutent has been studied in an open study with 106 patients who had failed on treatment with interleukin and/or interferon with overall response rate being the primary clinical endpoint. In renal cell carcinoma, just over 25% of the patients treated responded to treatment with Sutent.

The CHMP concluded that Sutent has shown its effectiveness in patients with GIST when treatment with imatinib is not an option. In renal cell carcinoma, they concluded that the results seen were sufficiently high for Sutent to have shown its effectiveness but that comprehensive information was not yet available. Therefore, the CHMP decided to grant a conditional MA for Sutent in both indications. The MAH is further obliged to provide to the CHMP the results of a currently ongoing study in patients with renal cell carcinoma who have not been treated with interleukin or interferon and to carry out studies of the use of the medicine in patients who have liver or kidney problems.

The advantage of the conditional MA is that the patients gain early market access to new anticancer medicines where an early evidence can be demonstrated based on a small amount of clinical data. Due to the severity of the diseases even an access only a few months earlier than would be the case with a “normal” MA may save the lives of many cancer patients. This is the main argument for allowing a conditional MA of a new medicinal product where the safety profile is not completely known and the efficacy not confirmed in a large patient population.

3.3 Marketing authorisation under exceptional circumstances

As already mentioned in chapter 2, the legal provision for granting an MA under exceptional circumstances was introduced in the EU pharmaceutical legislation with Directive 75/318/EEC[x].

Since the year 2000 40 medicinal products have been granted an MA under exceptional circumstances[xxxii]. 14 of these have already fulfilled their specific obligations and have thus become “normal” MAs. Of the 40 MAs granted under exceptional circumstances 6 are medicinal products for the treatment of a cancer disease:

- Foscan (temoporfin)
- Glivec (imatinib mesilate)

- MabCampath (alemtuzumab)
- Trisenox (arsenic trioxide)
- Velcade (bortezomib)
- Zevalin (ibritumomab tiuxetan)

All of these 6 MAs under exceptional circumstances are still under this status.

Since the conditional MA as possibility of obtaining an MA early in the development phase has only recently been introduced in the EU pharmaceutical legislation, it is likely to assume that several of those medicinal products which have in the past gained an MA under exceptional circumstances, if they would be assessed today they might be granted a conditional MA instead of an MA under exceptional circumstances. The legal definitions of these two types of MAs are to some extend overlapping making the distinction difficult in many cases. An evaluation of the similarities and the differences between the two types of MAs is given in chapter 3.4.

3.3.1 Legal background

Article 14 (8) of Regulation (EC) No. 726/2004 makes the granting of an MA under exceptional circumstances possible; the legal provision reads:

*"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. This authorisation may be granted only for objective, verifiable reasons and must be **based on one of the grounds set out in Annex I to Directive 2001/83/EC**. Continuation of the authorisation shall be linked to the **annual reassessment** of these conditions."*

In analogy with Article 14 (8) of Regulation (EC) No. 726/2004 which refers to medicinal products making use of the CP, Article 22 of Directive 2001/83/EC which covers the legal provision for medicinal products that undergo national procedures (MRP, DCP or NP) reads:

In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, 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. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I. Continuation of the authorisation shall be linked to the annual reassessment of these conditions. The list of these conditions shall be made publicly accessible without delay, together with deadlines and dates of fulfilment.

whereas Annex I, Part II of Directive 2001/83/EC[xxxiii] states:

*When, as provided for in Article 22, the **applicant can show that he is unable to provide comprehensive data on the 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 authorisation may be granted subject to certain specific obligations.*

  These obligations may include the following:

  a) the applicant shall complete 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 in the case of a radio-pharmaceutical, by an authorised 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.

3.3.2 Regulatory requirements

The use of an MA under exceptional circumstances may be proposed either by the applicant or by the CHMP:

Proposal by applicant

Where an applicant considers that the grounds for approval under exceptional circumstances apply, a justification provided in Module 1.5.4 of the documentation should be submitted to the competent authority, covering the following aspects[xxviii]:

- A claim that the applicant is unable to provide comprehensive non-clinical or clinical data on the efficacy and safety under normal conditions of use
- A listing of the non-clinical or clinical efficacy or safety data that cannot be comprehensively provided
- Justification on the grounds for approval under exceptional circumstances
- Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information)

The justification on the grounds for applying for an MA under exceptional circumstances should be based on objective and verifiable reasons[xxxiv]:

1) Inability to provide comprehensive data on efficacy and safety due to rarity of the indication
   Such justification should preferably take all relevant epidemiological evidence into account in order to estimate the rarity of the condition worldwide, and further to quantify the size of the population that would be available for such studies. The justification should also describe previous studies conducted in similar populations and it should be stated whether the medicinal product has obtained an orphan designation in the EEA although orphan status alone is not sufficient to justify the inability to provide comprehensive efficacy and safety data. Furthermore, the justification must contain an evaluation and discussion of the feasibility of conducting the required studies, including a detailed description of issues relating to the study design and statistical considerations (e.g. error probabilities, hypotheses, assumptions for recruitment and follow-up, sample size calculation and methodology). In addition, the feasibility of conducting other studies that would yield more informative data on the efficacy or safety of the product should be evaluated and discussed.

2) Inability to provide comprehensive information due to the present state of scientific knowledge
   In such a justification the applicant should describe what scientific knowledge would be required to conduct such trials and justify the lack of such knowledge. An example could be that certain diagnostic tools have not yet been developed in order to specifically study the defined patient population. Again, the feasibility of conducting other studies that could yield more information should be evaluated and discussed.

3) Inability to collect the required information because it would be contrary to medical ethics
The applicant should in such justification describe the relevant principles of medical ethics with precise reference to internationally accepted standards or other guidelines on ethics and justify the general acceptance of such principles and their applicability in this specific case. Where available, statements by ethics committees or relevant health authorities on the ethics of collecting such information should also be provided. The applicant should give proposals for detailed information on the specific procedures/obligations to be conducted as described below.

Proposal by the CHMP

Even if the applicant has not proposed the use of the procedure for granting an MA under exceptional circumstances, the CHMP may propose for adopting an opinion under exceptional circumstances based on the criteria fixed in the legislation as described above. This will occur when comprehensive data on the efficacy and safety of the medicinal product is not available. In this case the CHMP will communicate the proposal including any specific obligations to the applicant and an agreement with the applicant must be settled before adoption of the opinion. The CHMP assessment report should address the same aspects as described in the above for the proposal by the applicant[xxxiv].

Annual review

An MA under exceptional circumstances is reviewed annually in order to reassess the risk-benefit balance. The fulfilment of any specific procedures/obligations imposed as part of the MA under exceptional circumstances is aimed at the provision of further information on the safe and effective use of the product and will normally not lead to the completion of a full dossier and i.e. a “normal” MA. In those cases where the applicant has finally been able to provide comprehensive data on the efficacy and safety under normal conditions of use (a “full dossier”) and no specific procedures/obligations remain, a “normal” MA could be granted, as was the case for the above mentioned 14 of the 40 MAs granted under exceptional circumstances since 2000. An MA under exceptional circumstances may be varied e.g. by addition of new indications, however, in such cases, the MA will remain under exceptional circumstances. The renewal of the MA of a medicinal product under exceptional circumstances follows the same rules as a “normal” MA, hence, in accordance with Article 14 (1-3) of Regulation (EC) No. 726/2004 and the MA will be valid for five years. Once renewed, the MA shall be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal[xxxiv].

3.4 MA under exceptional circumstances versus conditional MA

A conditional MA as described in chapter 3.2 may be granted to medicinal products for which the applicant can demonstrate a positive risk-benefit balance, based on e.g. an early evidence of effects that are expected to predict the clinical outcome from an ultimately comprehensive development. Such a conditional MA is only a temporary authorisation and is not intended to remain conditional. A conditional MA is subject to a renewal procedure once a year. Once the data required for confirming the positive risk-benefit relationship are provided and thereby a “full dossier” is obtained, the conditional MA can be converted into a “normal” MA.

As opposed to a conditional MA, an MA under exceptional circumstances is not expected to become a “normal” MA based on comprehensive data on efficacy and safety. Often, however,

as this may be difficult to predict, a distinction is problematic and in general an MA under exceptional circumstances should not be granted when a conditional MA is more appropriate. A conditional MA is e.g. granted in the absence of comprehensive clinical data when it is likely that the applicant will be in the position to provide such data in a short timeframe, whereas the fulfilment of any specific procedures/obligations imposed as part of an MA under exceptional circumstances is aimed at providing information on the safe and effective use of the product and will normally not lead to the completion of a full dossier[xxxiv].

Type of MA	Conditional MA	MA under Exceptional Circumstances
Data available at grant of MA	Positive risk-benefit balance based on scientific data is demonstrated, confirmation is pending	Comprehensive data on efficacy and safety is not expected to be provided
Validity of MA	MA valid for one year, on a renewable basis	MA valid for 5 years and after renewal unlimited unless a further renewal must be processed due to safety matters. MA reviewed annually to reassess the risk-benefit balance
Change of MA status	Once pending studies are provided, conditional MA can become a "normal" MA	MA will normally not lead to the completion of a full dossier and become a "normal" MA
Advantage to patients	Early access of efficacious treatment -> longer survival/improved quality of life	Access to treatment: yes/no, depending on grant or refusal of MA

Table 1: Comparison of the main principles of conditional MA vs. MA under exceptional circumstances

3.4.1 Orphan medicinal products

Developing new therapies for rare diseases is under normal market conditions often impossible due to the fact that the cost of development and bringing them to market may usually not be compensated by the expected sales. It is estimated that rare diseases comprise an amount of 5000-8000 conditions and that about 30 millions Europeans in the 25 EU member states suffer from a rare disease[xxxv]. OMPs are often anticancer drugs and therefore the legal provisions on OMPs are discussed in the following.

With a view to give financial incentives to stimulate research and development of medicinal products for rare diseases the European legislation on OMPs comprising Regulation (EC) No 141/2000[xiii] and Commission Regulation (EC) No 847/2000[xiv] were introduced. The legislation on OMPs provides the following incentives to sponsors in order to ensure that patients suffering from rare diseases are given access to treatment:

- 10-year period of market exclusivity once an orphan medicinal product is authorised,
- protocol assistance,
- eligibility for Community and Member State initiatives which support research and development of orphan medicinal products,
- unreserved access to the centralised procedure
- the possibility to request fee reductions from the EMEA.

As stated in Article 3 of Regulation (EC) No 141/2000[xiii] a medicinal product shall be designated as orphan where it can be established:

*„(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,* ("prevalence criterion")
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**;* ("insufficient return-on-investment criterion")
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."*

A medicinal product which has been designated as orphan must fulfil the same requirements for establishing the quality, safety and efficacy prior to placing it on the market as apply to all other medicinal products. With the adoption of Regulation (EC) No 726/2004, from 20 November 2005 all MAs for products designated as orphans will have to be granted in accordance with the CP which is the main change of the OMP legislation as result of the NML. Prior to the granting of an MA for an OMP, the COMP may review the designation as an OMP to establish if the criteria for the designation are still met. In case it is established before the MA is granted that the designation criteria are no longer met, the OMP will be removed from the Community register of OMPs in accordance with Article 5(12) of Regulation (EC) No 141/2000[xx].

The 10-year market exclusivity for the OMP begins as of the date of the granting of the Community MA. This means that similar medicinal products[7] will not be granted an MA for the same therapeutic indication unless the MAH of the OMP gives consent, is unable to supply sufficient quantity of the medicinal product, or the second applicant demonstrates that although similar, the medicinal product is safer, more effective or otherwise clinically superior[8] to the originator[xx].

In accordance with Annex I of Directive 2001/83/EC as amended[xxiv]:
*"In the case of an **orphan medicinal product** in the meaning of Regulation (EC) No 141/2000, general **provisions of Part II-6 (exceptional circumstances) can be applied**. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned."*

Since an OMP can be subject to an MA under exceptional circumstances as well as a conditional MA dependent on whether it can be expected that the applicant will be able with time to provide comprehensive data, it may be difficult to select the right procedure for the OMP. In this case the choice of registration procedure should be discussed with the EMEA.

The European Commission has recently published a working document on the experience gained with Regulation (EC) No 141/2000 on OMPs[xxxvi]: During the first five years of implementation of the Regulation on OMPs (April 2000-April 2005), the predominant therapeutic areas corresponding to the designated orphan medicinal products were cancer (36%), metabolic disorders (21%), immunology (11%), and cardiovascular and respiratory disorders (12%).

[7] The definition of a 'similar medicinal product' is laid down in Article 3 of Commission Regulation (EC) No 847/2000
[8] The definition of 'clinically superior' is laid down in Article 3 of Commission Regulation (EC) No 847/2000

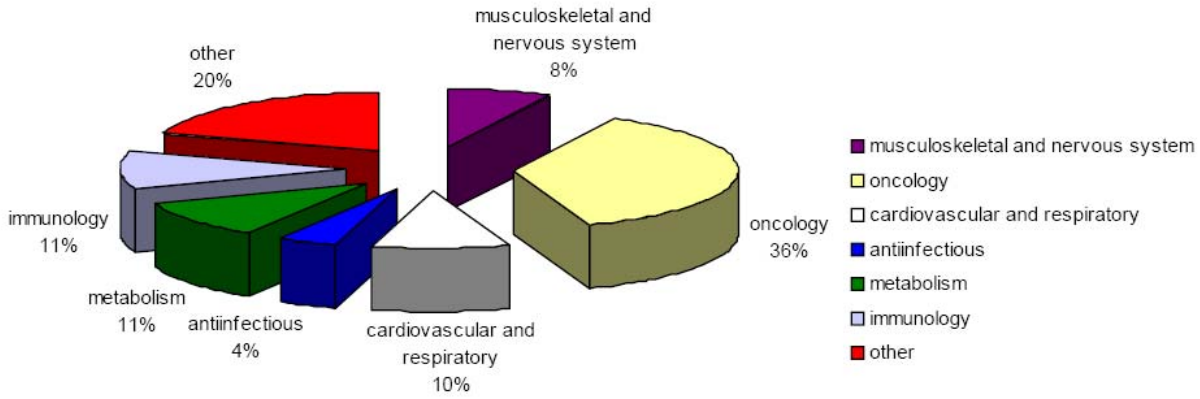

Figure 2: Corresponding therapeutic areas of the OMPs designated between April 2000 and April 2005

Of the 268 designated OMPs between April 2000 and April 2005, 49 (19%) have applied for an MA. Of these, 44 have filed through the centralised route and 5 via national procedures. During the same period, 22 OMPs have received an MA. Of those, 20 have been authorised via the CP and 2 through NP. Of the 22 OMPs for which an MA has been granted in the period between April 2000 and April 2005, 13 of these MAs were granted under exceptional circumstances[xxxvii] implying that often OMPs also fulfil the criteria for obtaining an MA under exceptional circumstances.

3.4.2 EMEA advice

The mechanism of seeking a scientific advice from the EMEA is applicable for all types of medicinal products for which the centralised procedure is possible or obligatory. For OMPs the scientific advice (protocol assistance) is facilitated in that this advice is subject to a fee exemption.

Prior to initiation of the clinical development programme of a medicinal product intended to make use of an application for either a conditional MA or an MA under exceptional circumstances it is highly recommended that the applicant seeks advice from the EMEA.

First of all, EMEA may through discussions with the applicant assist in selecting the most appropriate type of MA for the medicinal product in concern. Such discussions should preferably take place in the context of a pre-submission meeting 4-6 months prior to submission of the application.

Secondly, with respect to the clinical endpoints, compliance with the categories of medicinal products set out in Article 2 and requirements laid down in Article 4(1) of Regulation (EC) No 507/2006[xxvi], where the conditional MA is the MA type of choice, it is of immense importance that an agreement is reached between the applicant and EMEA at an early stage in the development phase. Where an MA under exceptional circumstances is the more appropriate choice, the applicant should seek advice from the EMEA concerning the justification for applying for an MA under exceptional circumstances. Moreover, inability to provide comprehensive data as well as the limitations imposed by the rarity of the disease, or scientific knowledge to collecting comprehensive information on safety and efficacy should be discussed with the EMEA as early as possible during drug development. Scientific advice cannot be requested on the ethical aspects of such collection of information.

The aim of the scientific advice from EMEA is that the applicant and EMEA discuss and agree on a clinical trial programme and thereby accelerate the development phase of the medicinal product by avoiding misinterpretation of current guidelines etc.

3.5 Accelerated assessment

With the introduction of the NML in November 2005 it has become mandatory for all new anticancer medicinal products to use the CP for obtaining an MA. In principle, this results in a maximum duration from start of the procedure until CHMP opinion of 210 days excluding possible clock-stops for oral or written explanations from the applicant.

When the medicinal product for which an MAA is submitted is of major interest to the public health, the applicant can further request for accelerated assessment in accordance with Article 14(9) of Regulation (EC) No 726/2004[xxi]:
*"When an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of **major interest from the point of view of public health** and in particular from the viewpoint of **therapeutic innovation**, the **applicant may request an accelerated assessment** procedure. The request shall be duly substantiated.*
*If the Committee for Medicinal Products for Human Use accepts the request, the time-limit laid down in Article 6(3), first subparagraph, shall be **reduced to 150 days**."*

Hence, accelerated assessment is applicable to new anticancer drugs for which promising efficacy is demonstrated.

The applicant can submit his request for accelerated assessment at any time prior to the submission of the MAA, however, preferably no later than 10 working days in advance of the CHMP plenary meeting preceding the intended start of the evaluation procedure[xxxviii].

The accelerated assessment procedure is applicable to MAAs for medicinal products for human use falling within the mandatory and optional scope of the CP as stated in the articles 3(1) and 3(2) of Regulation (EC) No 726/2004. The applicant's request for accelerated assessment shall include a justification presenting the arguments to support the expectation that the medicinal product introduces new methods of therapy or improves existing methods that addresses the greater unmet needs (such as serious, chronically debilitating, or life-threatening conditions when available methods are absent or insufficient) for maintaining and improving the health of the Community. The following list of key items would normally be addressed in a justification for a request for accelerated assessment:

- The unmet needs and the available methods of prevention, diagnosis or treatment.
- The extent to which the medicinal product is expected to have major impact on medical practice, its major added value, and/or how it addresses the greater unmet needs.
- A brief outline of the main available evidence (e.g., number of clinical trials, key results) on which the applicant bases its claim of major public health interest[xxxix].

Until the introduction of the NML the possibility of gaining an accelerated evaluation of an MAA was exclusively provided for in a guideline[xl] and it has been very rare for an MAA undergoing the CP to be given accelerated evaluation[xli].

As for the use of an application for conditional MA or MA under exceptional circumstances, it is highly recommended prior to making a request for accelerated assessment that the applicant seeks advice from the EMEA. The possibility of combining the use of accelerated assessment

with the application for a conditional MA or MA under exceptional circumstances exist where the CHMP decides the MAA may be eligible to both.

3.6 Compassionate use

Legal provisions for the compassionate use of medicinal products have been introduced in the EEA pharmaceutical legislation with the NML. The aim of compassionate use is to offer a treatment alternative to patients suffering from a life-threatening disease (e.g. a cancer disease) who cannot be adequately treated with authorised medicinal products or who may not be enrolled in clinical study programmes in order to receive the best possible treatment. A compassionate use of a medicinal product enables the availability of an unauthorised medicinal product to a group of patients not enrolled in a clinical study programme. In order to grant a compassionate use, the medicinal product, the group of patients as well as the sponsor must comply with certain requirements. These requirements are described in the following:

The legal requirements of the compassionate use of medicinal products subject to an MAA via the CP or undergoing clinical trials are laid down in Article 83 of the Regulation (EC) 726/2004 :

"1. By way of exemption from Article 6 of Directive 2001/83/EC Member States may make a medicinal product for human use belonging to the categories referred to in Article 3(1) and (2) of this Regulation available for compassionate use.
2. For the purposes of this Article, 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) ***available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease*** *or whose disease is considered to be* ***life-threatening****, and* ***who can not be treated satisfactorily by an authorised medicinal product****. The medicinal product concerned must either be the* ***subject of an application for a marketing authorisation*** *in accordance with Article 6 of this Regulation* ***or must be undergoing clinical trials****.*
3. When a Member State makes use of the possibility provided for in paragraph 1 it shall notify the Agency.
4. When compassionate use is envisaged, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted. The opinions shall be updated on a regular basis.
5. Member States shall take account of any available opinions.
6. The Agency shall keep an up-to-date list of the opinions adopted in accordance with paragraph 4, which shall be published on its website. Article 24(1) and Article 25 shall apply mutatis mutandis[9].
7. The opinions referred to in paragraph 4 shall not affect the civil or criminal liability of the manufacturer or of the applicant for marketing authorisation.
8. Where a compassionate use programme has been set up, the applicant shall ensure that patients taking part also have access to the new medicinal product during the period between authorisation and placing on the market.
9. This Article shall be without prejudice to Directive 2001/20/EC and to Article 5 of Directive 2001/83/EC."

Although compassionate use is now provided for in the EU pharmaceutical legislation, compassionate use implementation remains a national issue. Article 83 of Regulation (EC) No 726/2004 on compassionate use should be interpreted as complementary to national legislations and provides an option to the Member State who wish to receive a CHMP opinion regarding the conditions for compassionate use of a specific medicinal product which falls within the scope of Article 83(1) and 83(2)[xlii].

[9] Latin term meaning "things being changed which are to be changed"

4. Early market access outside the EEA

4.1 USA

By having a look at the history of the regulations for enabling early market access of drugs for the treatment of serious or life-threatening diseases, it is obvious that the US has been the pathfinder of these regulatory instruments providing incentives for the pharmaceutical industry to put resources into the research and development of new treatments for e.g. rare conditions and cancer diseases for which the hard clinical endpoints are difficult to study in a normal clinical setting.

The Orphan Drug Act was introduced already in 1983, the regulation on Treatment Use of Investigational Drugs and the rule on Accelerated Approval in 1987, procedures for the so-called Subpart E drugs encouraging an early cooperation between the FDA and the manufacturers in the development of new drugs for life-threatening and severely debilitating illnesses were introduced in 1988 and the so-called Parallel Track Mechanism made promising drugs for AIDS and HIV-related diseases more widely available during the processing of controlled clinical trials as of 1992[xliii].

In this way, the US has provided for introducing similar regulatory instruments in the EU and other regions of the world.

The various US regulatory mechanisms for enabling an early market access are elucidated in the following chapters of this thesis.

4.1.1 Orphan drugs

In the US the Orphan Drug Act was introduced in 1983 providing incentives for the pharmaceutical industry for the development of OMPs such as financial benefit, market exclusivity and priority review. The aim of this legal provision was to provide incentives for therapies that were not likely to generate revenue significant enough to justify development costs. The Orphan Drug Act has been amended by the US Congress 3 times - in 1984 where the term orphan drug was redefined, in 1985 where the marketing exclusivity was extended to patentable as well as un-patentable drugs and in 1988 where sponsors were required to apply for orphan designation before submitting an application for marketing approval[xliv].

The prerequisite for obtaining an orphan designation in the US is that the medicinal product which can be a chemical drug or a biologic is intended to treat a condition affecting fewer than 200,000 Americans or when the sponsor is not expected to recover development costs plus reasonable profit within seven years following FDA approval. The orphan designation can be requested anytime before filing an application for an MA (in the US this is called a New Drug Application (NDA) or in case of a biologic drug a Biologic Licence Application (BLA))[xlv].

Once a designation as an orphan drug in the US is obtained the following benefits are gained:

- financing to support development
- a 7 year period of exclusive marketing
- treatment use of the investigational orphan drug
- faster reviews of submissions may be provided if the treatment is for a life-threatening disease (priority review / accelerated approval, see also the chapters 4.1.3-4.1.5)
- a tax credit for clinical research-related spending (50% of qualified clinical costs as well as additional provisions)

- research grants for clinical testing
- user fee waivers

Marketing exclusivity is granted for a period of 7 years following FDA approval. During this period the FDA cannot approve a drug for the same indication unless it receives the consent of the MAH of the first OMP or if the drug cannot be manufactured in adequate amounts. In 1992, the FDA issued a further criteria which requires that a sponsor must demonstrate clinical superiority .

At the FDA the Office of Orphan Products Development is responsible for the administration of the Orphan Drug Act as well as the assessment of the applications for orphan drug designation. Section 316.20 of the 21 CFR 316 lays down the requirements for the content and format of a request for orphan-drug designation which shall contain information on the disease and its prevalence, the specific indication sought, as well as the regulatory and marketing status of the product[xlv].

4.1.2 Treatment Investigational New Drug

In the US, the FDA has for many years taken a more active part and still does play an important role in the development phase of new medicinal products as compared to regulatory agencies in other countries and the EU.

Already in 1938, the legal requirement that pharmaceuticals intended for use in humans had to be pre-cleared with FDA for safety was introduced in the US legislation, in the Federal Food, Drug, and Cosmetic (FD&C) Act[xlvi]. Hence, to use an investigational medicinal product in humans an Investigational New Drug Application (IND) would have to be submitted and the FDA would have to grant a permission for a study to proceed. An IND approval is also required for the initiation of studies with approved medicinal products in new populations or new dosage regimens as the risks here are unknown. The current US legislation lays down the following provision in Section 505 [21 U.S.C. 355] of the FD&C Act[xlvii]:

"(i)(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—
(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, or preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;
(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; (…)."

A similar provision was introduced in the EEA legislation as recent as in 2001 with the Directive 2001/20/EC of 4 April 2001[xlviii].

In the treatment of serious or life-threatening diseases an investigational new drug may be the only possible therapy with significant therapeutic effect. Under such circumstances, the FDA can

grant a temporary use of the investigational agent for compassionate purposes through a treatment IND[10] in accordance with 21 CFR 312.34[xlix].

A sponsor may apply for a treatment IND should the criteria in 21 CFR 312.34 be fulfilled[xlix]:

"(1) FDA shall permit an investigational drug to be used for a treatment use under a treatment protocol or treatment IND if:
(i) The drug is ***intended to treat a serious or immediately life-threatening disease****;*
(ii) There is ***no comparable or satisfactory alternative drug or other therapy available*** *to treat that stage of the disease in the intended patient population;*
(iii) The drug is ***under investigation in a controlled clinical trial*** *under an IND in effect for the trial,* ***or all clinical trials have been completed****; and*
(iv) The ***sponsor of the controlled clinical trial is actively pursuing marketing approval*** *of the investigational drug with due diligence.*
(2) Serious disease. For a drug intended to treat a serious disease, the Commissioner may deny a request for treatment use under a treatment protocol or treatment IND if there is insufficient evidence of safety and effectiveness to support such use.
(3) Immediately life-threatening disease. (i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for treatment use of an investigational drug under a treatment protocol or treatment IND if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug:
(A) May be effective for its intended use in its intended patient population; or
(B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.
(ii) For the purpose of this section, an "immediately life-threatening" disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment."

The FDA has 30 days to assess a treatment IND. A treatment IND protocol should include[l]:

- The intended use of the drug
- An explanation of the rationale for the use of the drug, including either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments, as appropriate
- A brief description of the criteria for patient selection
- The method of administration of the drug and the dosages
- A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimise risk.

4.1.3 Accelerated approval

The US legislation further allows for accelerated approval of new drugs for serious or life-threatening illnesses (e.g. cancer diseases) where the clinical study design is based upon a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity[xv]. The US accelerated approval is the US equivalent to the EEA conditional MA.

The legal provision for accelerated approval of chemical drugs[11] is laid down in 21 CFR Part 314, Subpart H[li]:

[10] Another possibility is the so-called emergency use IND according to 21 CFR 312.36 which is not described further in this thesis
[11] The legal provision for accelerated approval of biologics is laid down in 21 CFR Part 601, Subpart E

*"This subpart applies to certain new drug products that have been studied for their safety and effectiveness in **treating serious or life-threatening illnesses** and that **provide meaningful therapeutic benefit to patients over existing treatments** (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy). (…)*

***FDA may grant marketing approval** for a new drug product on the basis of **adequate and well-controlled clinical trials** establishing that the drug product has an **effect on a surrogate endpoint that is reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, **to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity**. Approval under this section will be subject to the **requirement that the applicant study the drug furthe**r, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence. (…)*

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:
(1) Distribution restricted to certain facilities or physicians with special training or experience; or
(2) Distribution conditioned on the performance of specified medical procedures.
(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product. (…)"
An accelerated approval is not a full approval for which the review process has been shortened (see also chapter 4.1.5 priority review). Accelerated approval is a conditional approval for which post-approval obligations in form of further clinical studies must be fulfilled and/or the approval may be subject to restrictions in order to assure a safe use. As opposed to the EEA conditional MA the US accelerated approval is granted for an unlimited period of time and does not cease to be valid unless the FDA actively withdraws the approval.

The FDA may withdraw the approval in the cases where[xv]:

- A post-marketing clinical study fails to verify clinical benefit
- The applicant fails to perform the required post-marketing study with due diligence
- Use after marketing demonstrates that post-marketing restrictions are inadequate to assure safe use of the drug product
- The applicant fails to adhere to the post-marketing restrictions agreed upon
- The promotional materials are false or misleading
- Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

22 cancer drug applications have been approved by the FDA under the accelerated approval regulations between December 1992 and June 2004. In most cases, the FDA has recommended at least two well-controlled clinical trials to be conducted in order to provide sufficient clinical evidence. In some cases, however, the FDA has found that evidence from one single trial was sufficient, but generally only in cases in which a single multi-centre study provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and in which confirmation of the result in a second trial would be practically or ethically impossible. For drugs approved for treatment of patients with a specific stage of a particular malignancy, evidence from one trial may be sufficient to support an efficacy supplement for treatment of a different stage of the same cancer. Medicinal products which are approved under accelerated approval regulations must demonstrate a benefit over available therapies. It is recommended that sponsors meet with the FDA prior to submission of study protocols intended to support NDA or BLA applications eligible for accelerated approval in order to obtain FDA advice on e.g. the clinical study programme. These meetings usually include a

multidisciplinary FDA team of oncologists, statisticians, clinical pharmacologists, and often external expert consultants. After such meetings sponsors may submit protocols and request a special protocol assessment (see also chapter 4.1.7) that provides the acceptability of endpoints and protocol design to support an NDA or BLA[lii].

4.1.4 Fast track programmes

The FDA fast track policy comprise all programmes which are established to facilitate the drug development during the IND stage and expedite the review of new drugs intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. A drug can be said to address an unmet medical need if the only available treatments for the condition are approved under the accelerated approval regulations, either on the basis of an effect on a surrogate endpoint or with restrictions on distribution. Hence, a medicinal product which is developed under fast track may also qualify for approval under subpart H (accelerated approval, see also chapter 4.1.3).

The legal provision for the fast track procedure is laid down in the Food and Drug Administration Modernization Act (FDAMA) of 1997 which establishes the scope of fast track products and defines the designation as first requested by a sponsor. After a request is made to the FDA, the FDA must respond within 60 days as to whether a fast track designation may be assigned and i.e. whether the medicinal product may follow the fast track process.

Section 506(a)(1) of the FDAMA states that a drug designated as a fast track product[liii]:

- *"is intended for the treatment of a serious or life-threatening condition"*:
  high probability of death unless disease course will be interrupted and/or increased incidence of potentially fatal outcomes (primary clinical endpoint: survival); serious conditions with causal association with morbidity/mortality: e.g. HIV, AIDS, cancer
- *"demonstrates the potential to address unmet medical needs for the condition"*:
  no existing therapy available or the new drug possesses a therapeutic advantage to existing therapies (e.g. improved compliance, less toxic, for patients unresponsive to existing therapy)

The fast track classification thus does not apply to a product alone, but applies to a combination of the product and specific indication for which it is being studied. The indication includes both the condition for which the drug is intended (e.g., heart failure) and the anticipated or established benefits of use (e.g., improved exercise tolerance, decreased hospitalisation, increased survival). It is therefore the development programme for a specific drug for a specific indication that will receive fast track designation.

In order to allow for a facilitated drug development phase and expedited approval procedure, early communication between the FDA and the sponsor is essential enabling an early agreement on the design of the major clinical efficacy studies. A fast track designation allows for the so-called "rolling submission" in which an early review of portions of a marketing application is made possible in advance of the complete NDA or BLA by submission of selected parts of the documentation to the moment of finalisation in order to enable a better distribution of the workload at the FDA. Fast track products may also be eligible to participate in the FDA pilot 1 and pilot 2 programs for Continuous Marketing Applications (CMA) which allow an expanded rolling review as well as an intensified interaction between FDA and sponsor in the drug development phase, respectively. The overall goal of these pilot programmes is to shorten review times and to provide opportunity for interaction between the FDA and sponsors[liv].

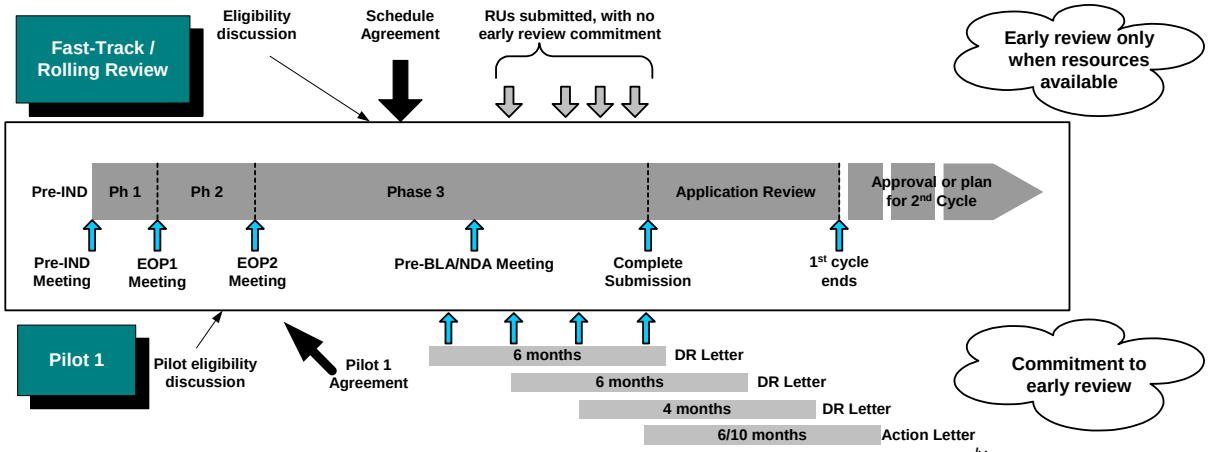

Figure 3: Comparison of the Fast-Track/Rolling Review and CMA Pilot 1 Programs[lv]

This figure shows that the interaction between the applicant and the FDA is strengthened in the Pilot 1 programme as compared to the fast-track development programme. Furthermore, in the Pilot 1 programme as opposed to the fast-track development programme the FDA is obligated to review the reviewable units (RUs) within a fixed time frame upon submission.

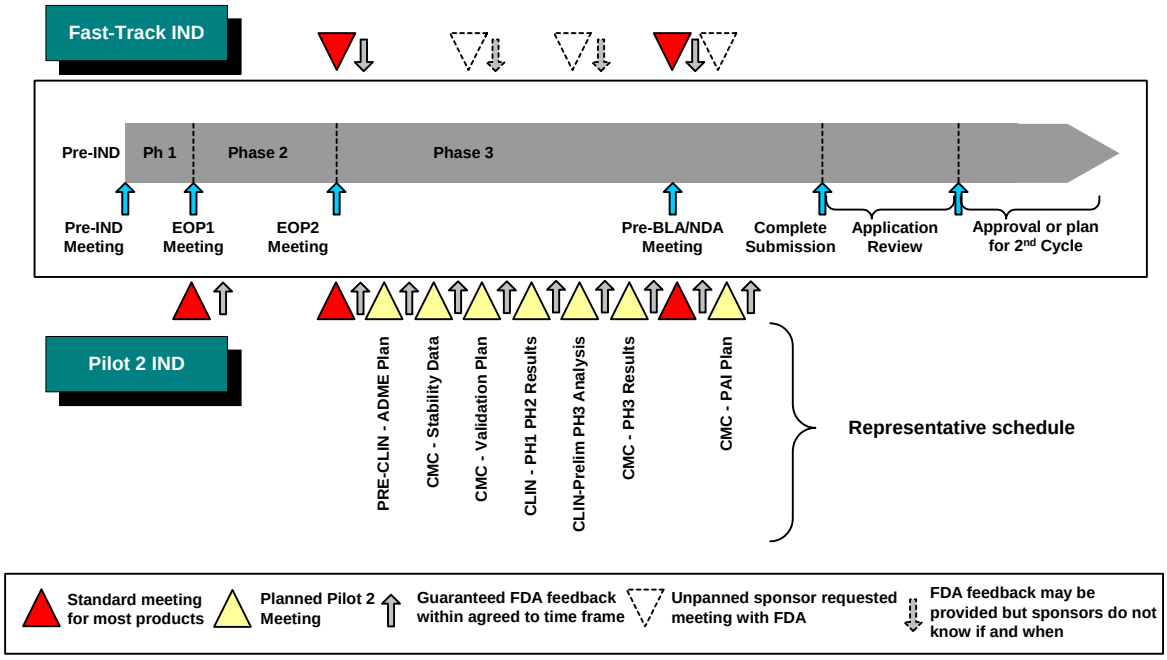

Figure 4: Illustrative Differences between a Fast-Track IND and a CMA Pilot 2 Product

Figure 4 demonstrates that in the IND process the interaction between the FDA and the sponsor is intensified in that continuously meetings take place in order to discuss the individual steps of the product development. In addition, the FDA is obligated to give feedback to the sponsor on the issues raised within an agreed time frame.

4.1.5 Priority review

Priority review is an FDA review classification in which the drug product, if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or

prevention of a disease. Priority review is a time frame used by the FDA to target a review of a completed application (as opposed to an accelerated approval, see also chapter 4.1.3). The target date of approval under the priority review designation is 6 months as compared to 10 months for non-priority or standard drugs. Fast track designation is not a prerequisite in order for an NDA/BLA to be eligible for priority review[xv].

4.1.6 Parallel track mechanism

The FDA parallel track policy permits wider access to promising new drugs for AIDS/HIV related diseases under a separate expanded access protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV[lvi].

4.1.7 Special protocol assessment

As part of the review of the PDUFA of 1992 in November 1997, the FDA decided to set specific performance goals for special protocol assessment and agreement. These PDUFA goals fix the time frame of the FDA evaluation of certain protocols to 45 days. This also includes the evaluation of issues relating to the protocols to assess whether they are adequate to meet scientific and regulatory requirements identified by the sponsor. Three types of protocols related to PDUFA products are eligible for this special protocol assessment under the PDUFA goals[lvii]:

- animal carcinogenicity protocols
- final product stability protocols, and
- clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim, if the trials had been the subject of discussion at an end-of-phase 2/pre-phase 3 meeting with the review division, or in some cases, if the division agrees to such a review because the division is aware of the developmental context in which the protocol is being reviewed and the questions are being answered. The clinical protocols for phase 3 trials can relate to efficacy claims that will be part of an original NDA or BLA or that will be part of an efficacy supplement to an approved NDA or BLA.

4.2 Canada

Analogously, Health Canada acknowledged in the mid 1990s that new regulatory instruments were needed in order to give the pharmaceutical industry incentives to focus on research and development of certain serious, life-threatening or severely debilitating diseases or conditions for which no known cures exist (e.g. HIV, ALS and some cancers). Support for an accelerated approval mechanism had been expressed from federal, provincial and territorial governments, and numerous stakeholder groups, including patient groups and industry, with a goal to facilitate patient access to potential therapeutic breakthroughs[lviii]. As a result the regulatory instruments of the conditional approval, the so-called “Notice of compliance with conditions”, and the priority review of submissions were established in Canada in the late 1990s.

4.2.1 Notice of compliance with conditions

In May 1998 a policy statement concerning the Notice of Compliance[12] with Conditions (NOC/c) was published. The aim of the new NOC/c policy was to provide patients suffering from serious,

[12] Notice of Compliance is the Canadian term for a marketing authorisation which is required for a medicinal product to be placed on the market

life-threatening or severely debilitating illnesses or conditions, accelerated access to promising new therapies[lviii].

An approval under the NOC/c policy may be granted for a drug product with promising evidence of clinical effectiveness providing it possesses an acceptable safety profile based on a risk-benefit assessment, and is found to be of high quality.

To be eligible for consideration of an approval under the NOC/c policy, a drug submission must first meet the Health Canada criteria as defined as follows:

The NOC/c policy applies to a New Drug Submission[13] (NDS) or Supplemental New Drug Submission[14] (S/NDS) for a serious, life-threatening or severely debilitating disease or condition for which there is promising evidence of clinical effectiveness based on the available data that the drug has the potential to provide

- effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or
- a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

Health Canada generally understands "promising clinical evidence" as evidence based on well-controlled and well-conducted clinical trials establishing that the drug product has an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit. The use of the term "promising" does not suggest the application of a standard lesser than "substantial" evidence of clinical effectiveness (see 4.2.2 Priority review) and Health Canada acknowledges the importance of flexibility in assessing whether promising evidence presented, in the context of such diseases and current scientific knowledge, is viewed as substantial.

In all cases, a prerequisite for issuance of an NOC, qualifying under the NOC/c policy, will be the sponsor's written commitment to pursue confirmatory studies acceptable to Health Canada.

The designation for eligibility under the NOC/c policy applies to a medicinal product for a specific indication for which it is being studied and not the product alone. Applicants seeking advice with respect to eligibility for consideration of an approval of the medicinal product under the NOC/c policy are required to give a pre-submission presentation to Health Canada review staff in order to discuss the details of the submission.

For the purpose of understanding in order to enable an evaluation of the various regulatory instruments, the key terms applied in the criteria for eligibility for consideration of an approval under the NOC/c policy are defined in the following:

- *"Serious" / "Life-threatening"*

By means of definition all life-threatening conditions are per se "serious". In defining whether a condition is "serious", Health Canada believes that factors such as survival, day-to-day functioning or the likelihood that the disease if left untreated, will progress from a less severe condition to a more serious one all should be taken into account. The latter includes, but is not limited to:

[13] An NDS is the Canadian equivalent of the EU MAA or US NDA, an application for an NOC of a new drug
[14] An S/NDS the Canadian equivalent of the EU extension application, defined as the introduction of significant manufacturing changes or modifications of the recommendations for use (labelling) of a previously approved drug

- AIDS
- All other stages of HIV infection
- Alzheimer's dementia
- ALS
- Angina pectoris
- Heart failure
- Cancer and
- other diseases that are clearly serious in their full manifestations.

In general, "serious" conditions are associated with morbidity with a substantial impact on the daily functioning. Reversible persistent or recurrent morbidity outcomes may also be sufficient to qualify for consideration under the NOC/c policy should all additional criteria be met.

- *"Severely debilitating"*

NOC/c eligibility also applies to drug submissions indicated for the treatment of a severely debilitating illness or condition wherein there exists an unmet medical need or for which a substantial improvement in the risk-benefit profile of the therapy is demonstrated. Many chronic illnesses that may be generally well-managed by available therapy may have severely debilitating outcomes. Examples of such conditions include inflammatory bowel disease, asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, depression, psychoses.

- *"Effective treatment, prevention or diagnosis of a disease in risk..."*

Serious, life-threatening or severely debilitating illnesses or conditions, for which no therapy is presently marketed in Canada, represent an obvious medical need. A new therapy effective in the treatment, prevention or diagnosis of that condition would therefore meet this criterion for eligibility under the NOC/c policy.

- "*Significant increase in efficacy and/or significant decrease"*

For the above NOC/c criterion to be met, the applicant should be able to demonstrate that the therapy has the potential to provide a statistically significant and clinically relevant improvement in risk-benefit profile, over existing therapies on the Canadian market. The potential of the therapy can be construed from:

- Studies with surrogate markers that require validation;
- Phase II trials that would require confirmation with Phase III trials consistent with the normal course of development of a therapeutic entity; or
- Phase III trials where a single small to moderately sized study would require confirmation of either the efficacy or safety of the given medicinal product.

The risk-benefit evaluation may include any of the following aspects:

- Improvement in one or more of the serious outcomes of the condition on which the effect is claimed;
- A favourable effect on a serious symptom or manifestation of the condition for which no therapy exists;
- A benefit in individuals unable to tolerate, or unresponsive to, existing therapies;
- Demonstration of effectiveness in combination with other critical drugs, where no information is available or where combined use with existing therapies is not feasible due to safety or efficacy considerations;

- Demonstration that the new drug is able to provide benefits that are similar to existing therapies while a) avoiding serious toxicity present in existing therapies and/or b) avoiding less serious toxicity, common to the therapy, which results in the discontinuation of treatment of a serious disease; and
- The ability to provide similar benefit to existing therapies while demonstrating improvement in some factors, such as compliance or convenience, shown to lead to improved effects on serious outcomes.

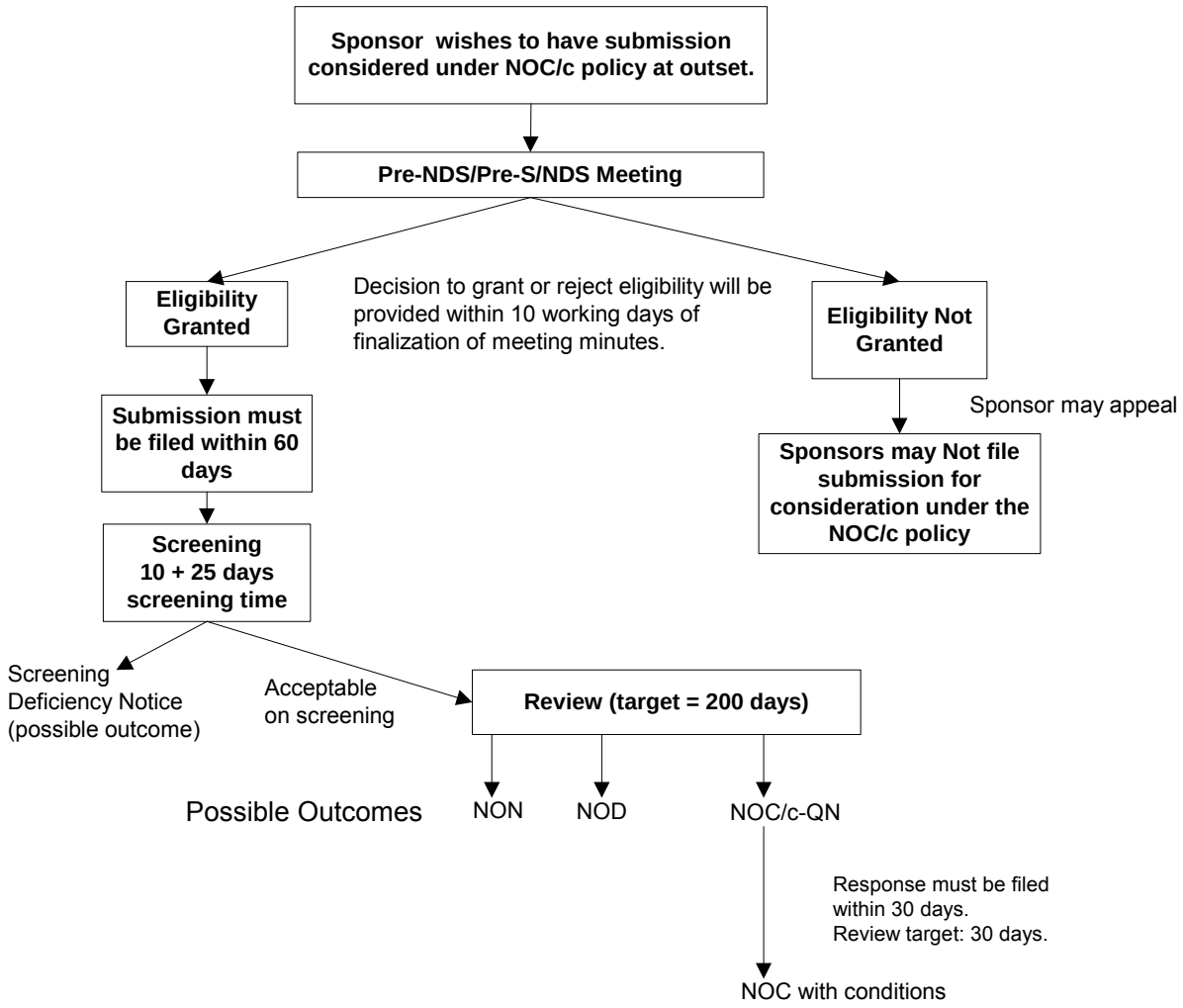

Figure 5: Procedure for granting a NOC/c in Canada

Upon submission of a data package for eligibility for NOC/c, the data are reviewed and when it is determined that the application qualify under the NOC/c policy, the appropriate Directorate of Health Canada will contact the sponsor to discuss particulars of the submission, confirmatory trials and potential consideration under the NOC/c policy. Thereafter and in the case where the outcomes of the discussions between Health Canada and the sponsor are positive, Health Canada will issue a Notice of Compliance with Conditions Qualifying Notice (NOC/c-QN) indicating that the submission qualifies for an NOC under the NOC/c policy. Furthermore, the NOC/c-QN will outline the additional clinical evidence to be provided in confirmatory studies, post-market surveillance responsibilities and any requirements related to advertising, labelling or distribution of the medicinal product.

The sponsor must submit the following documentation to Health Canada within 30 calendar days of NOC/c-QN receipt :

a) Any additional information requested by Health Canada (Dear Health Care Professional Letters, Product Specific Fact Sheets and Product Monographs consistent with requirements outlined in the Guidance for Industry on NOC/c)
b) An initial outline of proposed confirmatory trials, a rationale bridging the "Promising Clinical Evidence" with the proposed confirmatory studies and an initial outline of any agreed-upon safety monitoring studies
c) A letter signed by the Chief Executive Officer, or designated signing authority, indicating if the sponsor agrees to have the submission considered under the NOC/c policy
d) A draft letter of undertaking signed by the Chief Executive Officer, or designated signing authority, of the sponsor having a form and content satisfactory to Health Canada. This shall include an outline of confirmatory studies intended to verify the clinical benefit of the product including
    i. an indication of timeframes,
    ii. the post-market surveillance commitments made,
    iii. a paragraph outlining agreed-upon advertising, labelling or distribution requirements imposed on the product,
    iv. a commitment to notify and report specific issues of concern,
    v. a complete listing of ongoing additional clinical trials related to the product and
    vi. copies of any marketing approvals for the product under review from any other drug regulatory authority.

The sponsor's response to the NOC/c-QN will upon submission be subject to a 30 day review by Health Canada. In the case where the response is considered acceptable, Health Canada will together with the sponsor finalise the conditions associated with issuance of the NOC and the Letter of Undertaking. For medicinal products which are granted an NOC/c, the NOC will be issued with the notation:

"You have undertaken to conduct timely, well designed studies to verify the clinical benefit of this drug. You have also undertaken to provide appropriate educational material and comply with any post-market surveillance commitments and advertising, labeling and distribution requirements placed on the drug. Failure to comply with any one or all of these undertakings may be interpreted as suggesting, inter alia, the possibility of insufficient evidence, at that time, to establish the effectiveness of the drug for the purposes recommended. Accordingly, consideration will be given to regulatory action, removing the product from the market under the authority of the Food and Drugs Act and Regulations."

The conditions which are associated with approval of a medicinal product for a particular indication will remain until these conditions have been fulfilled and approved by Health Canada. Prior to the removal of conditions from the NOC, subsequent submissions will be processed as follows :

- supplemental (Level 1) changes that rely on the safety and efficacy of the original submission (e.g. new strength or formulation of the drug product), for which approval was granted under the NOC/c policy, will be processed as supplemental NDSs (S/NDSs) and if approved, these will receive NOC/c status;
- administrative changes in product and/or manufacturer name which therefore rely on the safety and efficacy of the original submission, will receive NOC/c status if approved; and
- subsequent submissions for a new indication must demonstrate efficacy, safety and clinical pharmacology independent of the original submission. As such, upon outcome of a review of the data provided, such submissions may qualify for an

NOC, with or without conditions. Submissions should be filed as S/NDSs cross-referencing the chemistry and manufacturing, pre-clinical and clinical pharmacology (if appropriate) data in the original submission.

In the event that all conditions associated with approval of the original drug submission have been fulfilled and are removed by Health Canada, the approval status (i.e., NOC/c status) of all subsequent submissions which rely on efficacy and safety information provided in the original application, will be revisited and amended accordingly where justified. Similarly, upon revocation or suspension of the original NOC, appropriate action will be taken for all subsequent submissions.
In the event that the outcome of subsequent reviews of the medicinal product determine that the conditions have not been satisfied, the responsible Directorate will contact the sponsor to discuss next steps. For products approved under the NOC/c policy, failure to comply with any of the undertakings contained within the Letter of Undertaking, may result in issuance of a stop-sale letter by Health Canada or Health Canada advising that the drug be recalled from the market.

A reassessment of the NOC/c policy and an evaluation of the linkages with Health Canada's Priority Review policy has been initiated in order to enhance the level of consistency in applying the policy, and to address the need for guidance documents to facilitate consistent interpretation .

4.2.2 Priority review

In December 1996 a policy statement on the Priority Review of Drug Submissions was published in Canada. This policy has continuously been revised over the years to clarify the eligibility criteria and review process. The policy as valid today provides for the accelerated review of eligible NDSs and S/NDSs intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses or conditions for which there is substantial evidence of clinical effectiveness that the drug provides[lix]:

- effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or
- a significant increase in efficacy and/or significant decrease in risk such that the overall risk-benefit profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

Health Canada generally views "substantial evidence of clinical effectiveness" as evidence consisting of at least two adequate and well controlled clinical studies, each convincing on its own to establish effectiveness of the drug involved. The effectiveness of the therapy would be assessed by experts qualified by scientific training and experience to evaluate the effect of the drug in treating the represented indication under the conditions of use prescribed, recommended or suggested in the labelling or proposed labelling thereof. In some instances, clinical evidence consisting of a single, large-scale, adequate and well controlled study or one pivotal trial and additional clinical evidence may be deemed "substantial". "Promising" clinical evidence including the use of non-validated surrogate markers, or Phase II studies is further addressed within the scope of the NOC/c policy (see 4.2.1 Notice of compliance with conditions)[lix].

The priority review status in Canada allows for a shortened review target of 180 calendar days as compared to the standard review target of 300 days. Therefore, the review of a priority submission will commence before the review of other pending submissions of the same

therapeutic area, which have not gained a priority review status. Once priority review status has been granted, the submission is expected to:

1) be filed within 60 calendar days;
2) contain the information and material for the purposes of a new medicinal product as provided for in the Division 8, Part C of the Food and Drug Regulations[lx]; and
3) be in accordance with Management of Drug Submissions Guidance[lxi].

Sponsors seeking priority review status in Canada are recommended to give a brief presentation to the Health Canada review staff prior to submitting a written request for priority review status in order to discuss the details of the submission as well as the potential eligibility of the submission for priority review status[lix].

Prior to submitting the application for NOC, the sponsor is required to submit a written request for priority review status to Health Canada together with a completed Clinical Assessment Package (CAP). In case the written request or CAP is incomplete, the submission will not be accepted. Upon receipt of the CAP as part of a request for priority review, the data package is forwarded to the appropriate review division for assignment to a clinical assessor. The clinical assessor may request additional supporting information to support and clarify the information provided in the written request for priority review. The sponsor must submit any requested supplementary information within two working days and if the supplementary information is not received within these two working days, the decision to accept or reject priority review status will be based on the information provided in the original request exclusively. Within 30 calendar days after the receipt of the written request, Health Canada will notify the sponsor of the decision to accept or reject the request. If the request is accepted, the sponsor will submit the full application for NOC to Health Canada within 60 calendar days after the date of issuance of the acceptance letter[lix].

4.2.3 Orphan drugs

There is no legal framework for OMPs in Canada. In April 1993, possible Canadian policies for regulating OMPs were reviewed and it was concluded that there were already a number of programs in place to ensure that Canadians have access to medicines which have not been approved (including the Special Access Programme, the use of INDs and importation of drugs for personal use). OMPs usually qualify for NOC/c as well as for priority review in Canada, which means that the target review time is 6 months. In addition, an application for a fee reduction for an OMP would likely be granted by Health Canada. The US, EU and Japanese OMP programs are intended to support the development and co-ordination of research in rare diseases. These countries/regions have significantly larger populations than Canada and the Canadian population may not be large enough to support significant research and development of OMPs[lxii].

4.2.4 Special access programme

The Canadian Special Access Programme (SAP) provides access to non-marketed drugs for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed or where they are unsuitable or unavailable.

The SAP enables a manufacturer to sell a medicinal product that cannot otherwise be sold or distributed in Canada. SAP may be applicable for medicinal products such as pharmaceutical, biologic, and radio-pharmaceutical products not approved for sale in Canada. Most of these drugs treat patients with life-threatening diseases or serious conditions such as intractable depression, epilepsy, transplant rejection, haemophilia and other blood disorders, terminal

cancer, and AIDS. The SAP can also respond to specific health crises, such as an outbreak of a communicable disease, by providing access to non-marketed drugs.

The idea behind SAP is not to promote or encourage the early use of drugs or to circumvent the clinical trials review and approval process or the new drug approval process, but to provide compassionate access to drugs on a patient by patient basis[lxiii].

5. Regulatory strategies for enabling early market access of a novel anticancer drug

Clinical development - considerations on the study design and selection of study endpoints

Irrespective of whether an application for a conditional MA, for an MA under exceptional circumstances or for a "normal" full MA is made, it should be clear that every effort should be made to conduct a randomised trial, even in very small target patient populations[xli].

The selection of the clinical trial endpoint is probably the most crucial factor in the design of a clinical study for a new anticancer drug in order to make the generation of meaningful clinical data possible. The endpoints selection is further influenced by the choice of target population and the type of drug (conventional cytotoxic vs. targeted therapy). Moreover, is this selection complicated due to the somewhat different view points of the regulatory agencies of the different regions of the world. The ideal endpoint of oncology clinical trials is the overall survival as the advantages of this endpoint would assure an unequivocal and unbiased interpretation of the study results. However, this endpoint is rarely selected as this would require a very large amount of patients as well as a very long duration of the study.

In the **EEA** overall survival and progression free survival (PFS) or disease-free survival (DFS) are generally the preferred primary endpoints for confirmatory clinical studies (Phase III). PFS as well as time to progression (TTP) measure the disease free survival, the difference between PFS and TTP being that death is included in the measurement of PFS. These endpoints are not always directly associated with clinical benefit and, hence, not always true surrogate parameters for overall survival. TTP is, however, recommended as primary endpoint for exploratory Phase II trials where it is not certain what the anti-tumour effects of a drug will be. In particular, where the submission of an application for a conditional MA or for an MA under exceptional circumstances is planned the level of evidence provided by the surrogate endpoints must be extensively evaluated[, lxiv]. In general, in order to obtain an MA a favourable risk-benefit relationship should be established with confirmatory Phase III studies designed with the aim to establish the risk-benefit profile of the experimental medicinal product, including supportive measures, in a well-characterised target population of relevance for clinical practice. These studies should be randomised and reference controlled in nature. The target population as well as the reference regimen (e.g. BSC) of these studies are normally defined by disease, stage and prior lines of therapy. For approval of an MA under exceptional circumstances, it is acknowledged that in some of these cases, comprehensive data on safety and efficacy cannot be provided prior to grant of the MA and in these cases approval may be associated with certain specific conditions. Moreover, for a conditional MA in which there is a situation of an unmet medical need, a preliminary benefit–risk evaluation based on early data must be demonstrated compatible with a favourable profile at the time of approval. However, there is a need to confirm that benefit–risk is indeed favourable in the target population post-approval. This means that finalisation of confirmatory trials in no way should be jeopardised by early licensing. Furthermore, and in case

the product proves harmful in the normal condition of use, or if therapeutic efficacy is lacking, revocation of marketing authorisation (or a revision of labelling) is foreseen as a viable option[xxv].

The **US** FD&C Act requires that substantial evidence of effectiveness must be derived from adequate and well-controlled clinical investigations which must allow a valid comparison to a control and must provide a quantitative assessment of the effect of the drug. In general, the FDA recommends that at least two well-controlled clinical studies are conducted. However, in some cases, evidence from a single multi-centre trial providing highly reliable and statistically strong evidence of the clinical benefit has been accepted by the FDA. Anticancer drugs approved under accelerated approval must provide a clinical benefit over available therapy. In order to satisfy this criterion typically single-arm studies in patients with refractory tumours, where no available therapy exist, are designed. The accelerated approval regulations (21 CFR Part 314, subpart H, 21 CFR Part 601, subpart E) allows for use of additional endpoints for approval of drugs intended to treat a serious or life-threatening disease and that either demonstrate an improvement over available therapy or provide therapy where none exists. In this case the FDA may grant approval based on a clinical effect on a surrogate endpoint when this is reasonably likely to predict clinical effect. In oncology trials, survival is the preferred clinical endpoint, but the FDA has accepted other endpoints such as:

- objective response rate (ORR),
- improvement in survival,
- quality of life (QoL),
- PFS,
- DFS,
- improved functioning or improved tumour-related symptoms

for the approval of anticancer drugs, whereas ORR has been the primary surrogate endpoint used to support anticancer accelerated drug approvals in the last decade. The use of biomarkers has not yet been accepted as further research is still needed to establish the validity of the available tests and to determine whether improvements in such biomarkers are reasonably likely to predict clinical benefit or are established surrogates for clinical benefit[lii].

In **Canada** in general, Health Canada views substantial evidence of clinical effectiveness as evidence consisting of at least two adequate and well controlled clinical studies, each convincing on its own to establish effectiveness of the drug involved. However, in some instances clinical evidence consisting of a single, large-scale, adequate and well controlled study or one pivotal trial and additional clinical evidence may be considered “substantial”. It is acknowledged that when approval under the NOC/c policy is granted, confirmatory studies may not yet be available, however, ongoing. In some instances, sufficient cumulative testing has been done to substantiate that an effect on a surrogate marker is predictive of clinical benefit. However, until surrogate markers have been validated, evidence of the effect of a drug on non-validated surrogate markers cannot replace data that demonstrate an effect on recognised clinical endpoints which are reasonably likely to predict the clinical benefit of the drug. In such instances, Health Canada may request additional confirmatory studies to further verify the clinical benefit of the drug[lviii, lix].

In the EEA, US and Canada, the selection of primary and secondary clinical endpoints as well as the use of surrogate endpoints (e.g. biomarkers) should clearly be justified based on the characteristics of the test drug, the proposed therapeutic indication and the target population to be included in the study, including the size of the population. Since this selection is crucial it is recommended to discuss the design of the clinical study programme including the proposed endpoints with the regulatory agencies during the planning phase of the clinical study in order to

agree on the particulars of the development programme as early as possible and, where possible, avoid doubling of clinical studies to be performed due to different views of the different agencies.

Preparation of regulatory submission

Where an application for conditional MA, MA under exceptional circumstances or accelerated assessment in the EEA, an accelerated approval, fast track or priority review in the US or a NOC/c or priority review in Canada is planned, it is appropriate that the applicant already early in the development phase of the medicinal product makes strategic considerations based on the regulatory environment in the three regions.

The various regulatory instruments for obtaining early market access in the EEA were presented and evaluated in chapter 3 and those for enabling early market access in the US and Canada in chapter 4, respectively. In summary, the following possibilities for obtaining an authorisation to market a new medicinal product at an early stage in the product development in the three regions are presented in Figure 6 below.

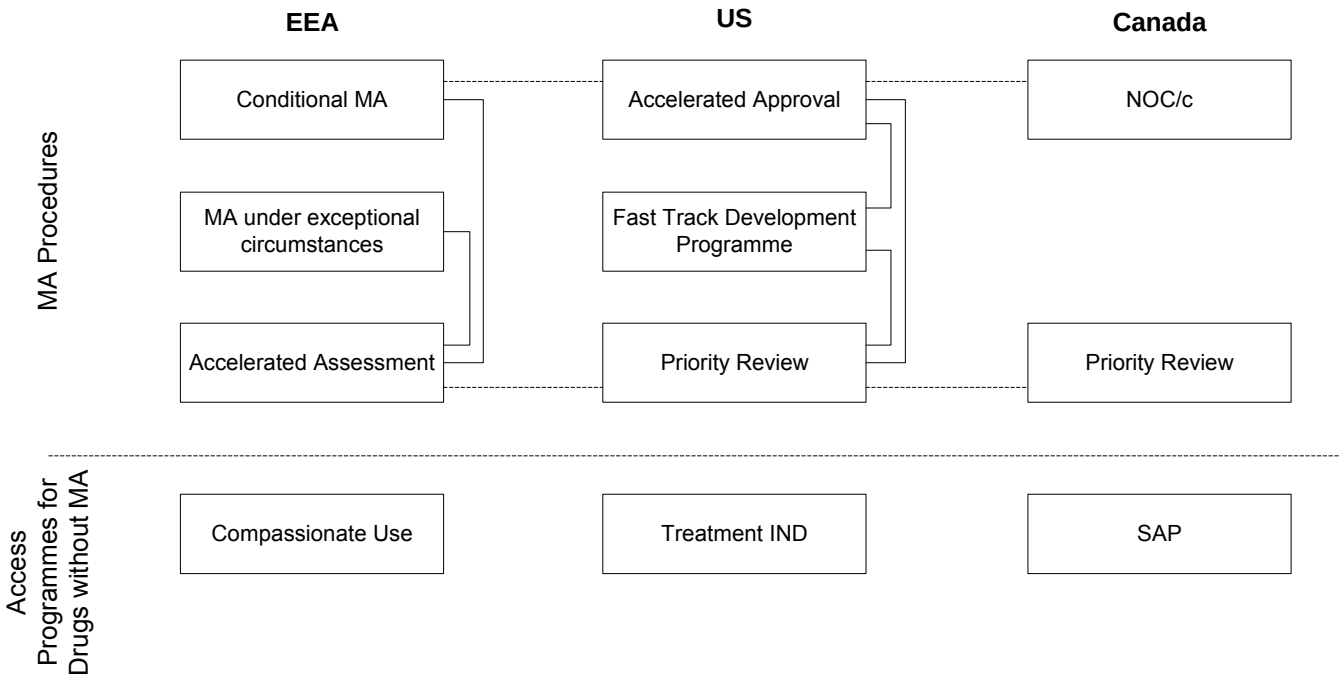

Figure 6: Overview of the regulatory instruments for obtaining early market access in the EEA, US and Canada

As figure 6 demonstrates, there are many parallels in the regulatory measures for enabling early market access to new important therapies - such as novel anticancer drugs – between the EEA, US and Canada. The differences between the regulatory particulars in the different regions are less clear and these are probably mostly due to the different interpretations of the various terms such as “unmet medical need” at the different regulatory agencies.

In the following a comparison of the regulatory particulars and approval procedures of four important anticancer medicinal products which have recently been authorised in the EEA, USA and Canada, respectively, is given in order to provide information on the extend to which the three authorities differ in their assessment of the available data provided with the application. In

this comparison it is assumed that the same clinical data have been submitted in the three regions.

1) Sutent (sutinib malate; protein tyrosine kinase inhibitor/anti-angionetic agent)[lxv, lxvi, lxvii]

	EEA	USA	Canada
Date of 1st approval	24.07.2006	26.01.2006	31.05.2006
Therapeutic indications	- Treatment of unresectable and/or metastatic malignant GIST after failure of imatinib mesylate treatment due to resistance or intolerance. - Treatment of advanced and/or MRCC after failure of interferon alfa or interleukin-2 therapy	- Treatment of GIST after disease progression on or intolerance to imatinib mesylate - Treatment of advanced RCC	Treatment GIST after failure of imatinib mesylate treatment due to resistance or intolerance
Status of approval	GIST+MRCC: Conditional MA	GIST: Full approval RCC: Accelerated approval	Full approval
Priority review given	No	Yes, approved in less than 6 months	Yes
Primary clinical endpoint	GIST: TTP MRCC: ORR	GIST: TTP RCC: ORR	TTP

2) Nexavar (sorafenib tosylate; protein tyrosine kinase inhibitor/anti-angionetic agent)[lxviii, lxix, lxx]

	EEA	USA	Canada
Date of 1st approval	19.07.2006	20.12.2005	28.07.2006
Therapeutic indications	Treatment of patients with advanced and RCC who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy	Treatment of advanced and RCC	Treatment of locally advanced / metastatic RCC in patients who failed prior cytokine therapy or are considered unsuitable for such therapy
Status of approval	Full MA	Full approval	NOC/c
Priority review given	No	No	Yes
Primary clinical endpoint	PFS	PFS	PFS

3) Velcade (bortezomib mannitol boronic ester; inhibitor of the proteolytic activity of the proteasome)[lxxi, lxxii, lxxiii]

	EEA	USA	Canada
Date of 1st approval	26.04.2004	25.03.2005	24.04.2006
Therapeutic indications	Mono-therapy for the 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	Treatment of multiple myeloma patients who have received as least one prior therapy	Treatment of multiple myeloma patients who have relapsed following front-line therapy and are refractory to their most recent therapy
Status of approval	MA under exceptional circumstances	Accelerated approval of sNDA	NOC/c
Priority review given	No	No	No
Primary clinical endpoint	ORR	ORR	ORR

4) Glivec/Gleevec (imatinib mesilate; protein tyrosine kinase inhibitor)[lxxiv, lxxv, lxxvi]

	EEA	USA	Canada
Date of 1st approval	07.11.2001	05.10.2001	09.2001
Therapeutic indications	- Treatment of patients with newly diagnosed Philadelphia chromosome CML for whom bone marrow transplantation is not considered as the first line of treatment - Treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis - Treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant GIST	- Treatment of patients with newly diagnosed Philadelphia chromosome CML - Treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis - Treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant GIST	Treatment of patients with CML in blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy
Status of approval	MA under exceptional circumstances	Accelerated approval	NOC/c
Priority review given	Accelerated evaluation	No	No
Primary clinical endpoint	CML: overall haematologic and cytogenetic response rates GIST: ORR	CML: overall haematologic and cytogenetic response rates GIST: ORR	CML: overall haematologic and cytogenetic response rates

From the four cases summarised in the above it is clear that the regulatory authorities in the three regions are of a similar opinion when it comes to the clinical development programme as in all cases the same clinical endpoints in the pivotal studies have been accepted indicating that the same clinical studies were accepted in the three regions. However, when it comes to granting a full or conditional approval and/or priority review, the three authorities seem to differ greatly in their opinion on which data must be available in order for a full or conditional MA to be granted as well as on which drugs are of "priority" although the criteria as described in the chapters 3 and 4 seem quite alike. In this matter, naturally, also the different legal fundaments in the different regions and the different empowerment of the EMEA, the FDA and the Health Canada, respectively, play important roles. In order to critically evaluate these differences an immense work would have to be done which could not be completed within the scope of this thesis and moreover, such a research work would unlikely provide appropriate information as the individual interpretation of the cornerstones of the drug development is influenced by manifold parameters such as current guidelines, as well as the individual opinions and knowledge of the assessor/reviewer. In conclusion, it must be highlighted that in order to plan a regulatory submission in the EEA, US and Canada of a novel anticancer drug, active communication with the individual authorities should be sought at as early a point of time in the drug development as possible.

Recently, a bilateral meeting with the EMEA and the FDA was held and at this meeting the existing confidentiality agreement has been extended. With this agreement the two parties may exchange information with respect to legal and regulatory issues, orphan drug designation, MA procedures and parallel scientific advice as part of their regulatory processes. The parallel scientific advice allows for an applicant as a pilot project to seek advice by both authorities simultaneously on the same questions regarding the product development. The parallel scientific advice is not a joint advice as the two authorities have the right to give different advice. However, it is a measure that facilitates an agreement process between the two parties in a certain question although no guarantee is given[lxxvii].

Although there is no guarantee that the EEA, the US and the Canadian authorities will issue the same or a similar advice to a certain question to the development programme of a new medicinal product, it is appropriate early in the development phase to discuss issues such as study design of the clinical studies, the possibility of applying adaptive clinical trial design and statistical methods to perform interim analysis of early results (e.g. Bayesian approach), the amount of clinical studies, the point of time for submission of the MAA as well as the possibility of a conditional MA, MA under exceptional circumstances and/or accelerated assessment/priority review with the competent authorities. This would lead to an overall better planning of the drug development phase, would likely avoid duplication of studies and allow for an accelerated preparation of the regulatory submission.

6. Conclusion and outlook

The new EU regulation introducing the conditional MA in the EEA pharmaceutical legislation will give patients suffering from cancer diseases early market access to new anticancer medicines where an early evidence on efficacy and safety can be demonstrated based on a small amount of clinical data. Due to the severity of the diseases even an access only a few months earlier than would be the case with a "normal" MA may save the lives of many cancer patients. This is the main argument for allowing a conditional MA of a new medicinal product where the safety profile is not completely known and the efficacy not confirmed in a large patient population. With time, however, the conditional MA will become a "normal" MA as comprehensive data have

been gained. This is the main difference to the MA under exceptional circumstances for which it cannot be expected that comprehensive data will ever become available, e.g. due to the rarity of the indication. Therefore, the MA under exceptional circumstances does not enable early market access of new and promising therapies, it is a possibility for obtaining an MA where data that will never become available are missing. The MA under exceptional circumstances is an instrument enabling market access to therapies for which an MA would otherwise not be granted.

In the US the accelerated approval is the equivalent to the EEA conditional MA. The US accelerated approval can be granted to new drugs for serious or life-threatening illnesses where the clinical study design is based upon a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. Analogously, in Canada an approval under the NOC/c policy may be granted for a drug product with promising evidence of clinical effectiveness providing it possesses an acceptable safety profile and is found to be of high quality. The EEA conditional MA, the US accelerated approval and the Canadian NOC/c all have in common that the MA is granted earlier than a "normal" MA based on promising evidence on efficacy and safety at an early stage, where confirmatory data are still outstanding which are to be provided post-approval.

From the four cases of anticancer drugs authorised in the EEA, US and Canada which are summarised in chapter 5 it is clear that the regulatory authorities in the three regions are of a similar opinion when it comes to the clinical development programme. However, when it comes to granting a full or conditional approval and/or priority review, the three authorities seem to differ greatly in their opinion on which data must be available in order for a full or conditional MA to be granted as well as on which drugs are of "priority" although the criteria as described in the chapters 3 and 4 seem quite alike. Therefore, it is of utmost importance that active communication with the individual authorities is sought at as early a point of time in the drug development as possible in order to agree on a clinical study programme and discuss the possibilities for applying regulatory instruments for obtaining early market access.

Having a look at the orphan regulations it can be seen that up until today, more than 1 million patients suffering from orphan diseases in the EEA alone may potentially benefit from the orphan medicines authorised during the first five years of application of Regulation (EC) No 141/2000 . Despite the success of the orphan regulations in the different regions, the implementation into practice has been criticised. One critic point is the unequal access for patients in the EEA to the registered OMPs in the Community due to the individual reimbursement systems in the different Member States. Due to the different procedures for pricing and reimbursement, the different public health priorities and the different budget allocation decisions with different time frames, access is not similar within the EEA. This is a problem also affecting those drugs which are granted MAs under exceptional circumstances and conditional MAs. In general, the costs of OMPs are high and the EEA Members States have a weak position to negotiate the prices in the absence of competition. Canada has anticipated the access problems and did not develop an orphan regulation itself but introduced a special programme to facilitate the access of drug products for rare diseases. Another critic point is that the FDA and the EMEA do not always come to the same conclusion concerning the safety and efficacy of the same OMP. Another point for improvement is that an OMP that has an MA in one region has to go through all phases of an MA procedure again in another region. Consequently, approximately half of the FDA approved OMPs are not available to the patients in the EEA[lxxviii].

A further disadvantage of the EU system for authorising medicinal products as compared to the US counterpart is the delayed access to the most advanced drug treatments. The average delay from initial drug launch to market in Europe is 33% longer than in the US (the UK is shortest – 0 days, while Greece is longest – 415 days). One reason for this slow uptake of new medicines as

compared to the US is the lengthy reimbursement negotiations that follow government approval in Europe of any new medicinal product[ix].

Despite the disadvantages and problems seen with the various systems as described above, appropriate regulatory mechanisms for enabling early market access of novel anticancer drugs have now been established in the EEA, US and Canada. Surely, improvements are needed but since the fundaments now exist in all of these three regions, an important step has already been taken improving the regulatory environment for the development of new and better cancer therapies.

In addition, a further boost in accelerating the drug development can be expected as new technologies such as biomarkers, PET scanning and microdosing gain acceptance. Also the pharmaceutical industry may accelerate the development times by applying new biostatistic techniques as part of the clinical study design. In this way, Phase II/III studies combining dose selection and clinical confirmation by optimal use of interim analyses and Bayesian adaptive designs may lead to faster development times[lxxix].

Summary

As of November 2005 legal provisions for enabling an early market access to new and promising anticancer drugs exist in the EEA, US and Canada. The legal provisions in the three regions enable the grant of an early marketing authorisation where promising evidence on efficacy and safety is available and confirmatory data are still lacking. Due to these regulatory mechanisms patients suffering from cancer diseases will gain early market access to new anticancer medicines where an early evidence can be demonstrated based on a small amount of clinical data. Due to the severity of the diseases even an access only a few months earlier than would be the case with a "normal" marketing authorisation may save or ameliorate the lives of many cancer patients. This is the main argument for allowing a conditional marketing authorisation of a new medicinal product where the safety profile is not completely known and the efficacy not confirmed in a large patient population. At the same time an early return of investment is of interest for the pharmaceutical industry.

In the present thesis the various options of obtaining a marketing authorisation early in the development phase are addressed with special regard to the development of a novel anticancer drug. Main focus is on the new legal provisions for obtaining a conditional marketing authorisation in the EEA as compared to the already existing provisions for making use of a marketing authorisation under exceptional circumstances, compassionate use programmes, orphan drug regulations and obtaining an accelerated assessment. As similarities do exists to regulations in other regions, parallels to the US and Canadian legal systems are drawn.

With time the EEA conditional marketing authorisation will become a "normal" marketing authorisation as comprehensive data have been gained which is the main difference to the marketing authorisation under exceptional circumstances for which it cannot be expected that comprehensive data will ever become available, e.g. due to the rarity of the indication. Therefore, the marketing authorisation under exceptional circumstances does not enable early market access of new and promising therapies, it is a possibility for obtaining a marketing authorisation where data that will never become available are missing. The marketing authorisation under exceptional circumstances is an instrument enabling market access to therapies for which a marketing authorisation would otherwise not be granted.

In the US the accelerated approval is the equivalent to the EEA conditional marketing authorisation. The US accelerated approval can be granted to new drugs for serious or life-threatening illnesses where the clinical study design is based upon a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. Analogously, in Canada an approval under the notice of compliance with conditions policy may be granted for a drug product with promising evidence of clinical effectiveness providing it possesses an acceptable safety profile and is found to be of high quality. The EEA conditional marketing authorisation, the US accelerated approval and the Canadian notice of compliance with conditions all have in common that the marketing authorisation is granted earlier than a "normal" marketing authorisation based on promising evidence on efficacy and safety, where confirmatory data are still outstanding which are to be provided as a post-approval obligation.

There are many parallels in the regulatory mechanisms for enabling early market access to new important therapies - such as novel anticancer drugs – between the EEA, US and Canada. The differences between the regulatory particulars in the different regions are less clear and these are probably mostly existent in the interpretation of the various terms at the different regulatory agencies. When looking at some of the most recent approvals of novel anticancer drugs in the three regions, it is clear that the regulatory authorities in the three regions are of a similar

opinion when it comes to the clinical development programme as in all cases the same clinical endpoints in the pivotal studies have been accepted indicating that the same clinical studies were accepted in the three regions. However, when it comes to granting a full or conditional approval and/or priority review, the three authorities seem to differ greatly in their opinion on which data must be available in order for a full or conditional marketing authorisation to be granted as well as on which drugs are of “priority”. In this matter, naturally, also the different legal fundaments in the different regions and the different empowerment of the EMEA, the FDA and the Health Canada, respectively, play important roles. Although there is no guarantee that the EEA, the US and the Canadian authorities will issue the same or a similar advice to a certain question to the development programme of a new medicinal product, it is appropriate early in the development phase to discuss issues such as study design of the clinical studies, the possibility of applying adaptive clinical trial design and statistical methods to perform interim analysis of early results (e.g. Bayesian approach), the amount of clinical studies, the moment for submission of the marketing authorisation application as well as the possibility of a conditional marketing authorisation, marketing authorisation under exceptional circumstances and/or accelerated assessment/priority review with the competent authorities. This would lead to an overall better planning of the drug development phase, would likely avoid duplication of studies and allow for an accelerated preparation of the regulatory submission.

Despite disadvantages and problems seen with the various systems in the EEA, US and Canada, appropriate regulatory mechanisms for enabling early market access of novel anticancer drugs have now been established in the EEA, US and Canada. Surely, improvements are needed but since the fundaments now exist in all of these three regions, an important step has already been taken improving the regulatory environment for the development of new and better cancer therapies.

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

Hamburg, den