# Regulatory strategies for life-cycle management of chemical defined cytostatic drugs with regard to the new pharmaceutical legislation – two case studies

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# 1. List of Abbreviations

| | |
|---|---|
| AC | Accession Country |
| ADR | Adverse Drug Reaction |
| ATC | Anatomical Therapeutic Chemical Classification System |
| CAP | Centralised Authorised Product |
| CG | Co-ordination Group |
| CHMP | Committee for Medicinal Products for Human Use |
| CP | Centralised Procedure |
| CTD | Common Technical Document |
| DCP | Decentralised procedure |
| EBD | European Birthday |
| eCTD | Electronic Common Technical Document |
| EMEA | European Medicines Agency |
| EPC | European Patent Convention |
| EPO | European Patent Office |
| EU | The European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HoA | Heads of Agencies |
| IBD | International Birthday |
| ICH | International Conference on Harmonisation |
| IMP | Investigational Medicinal Product |
| IMPD | Investigational Medicinal Product Dossier |
| MA | Marketing Authorisation |
| MAH | Marketing Authorisation Holder |
| MR | Mutual Recognition |
| MRFG | Mutual Recognition Facilitation Group |
| MRP | Mutual Recognition Procedure |
| NCA | National Competent Authority |
| NCE | New Chemical Entity |
| NMS | New Member State |
| NTA | Notice To Applicants |
| OTC | Over the Counter Drugs |
| pdf | Portable Document Format |
| PIL | Package information leaflet |
| PSUR | Period Safety Update Report |
| QOS | Quality Overall Summary |
| R&D | Research and Development Department |
| rtf | Rich Text Format |
| SmPC | Summary of Product Characteristic |
| SOP | Standard Operating Procedure |
| SPC | Supplementary Protection Certificate |
| SAE / SADR | Serious Adverse Event / Serious Adverse Drug Reaction |

# 2. Introduction

## 2.1. Why it is important to develop regulatory strategies for product life-cycle management?

Within the last three years a number of new regulations, directives and corresponding guidelines have been issued and a lot more will be following in the near future. Consequently, the regulatory environment is getting more and more stringent. In addition, with increasing generic competition or competition within the same product class the companies face growing pressure to maximise the value of their drugs throughout their life-cycles and improve the return on investment for their product. Even established products are under compulsion to be first on the market with new strengths or enhanced products. As a result, the product's life-cycle has to be optimize in order to achieve peak product sales rapidly, and to sustain peak sales for as long as possible.

Against this background developing regulatory strategies for product life-cycle management becoming more and more essential and a competent regulatory strategy can shorten to time to market. In order to achieve these goals the pharmaceutical company might establish an effective life-cycle management team. In addition to regulatory affairs, key personnel from the following departments should be considered for inclusion in the team: e.g. R&D, patent counsel, manufacturing, marketing, licensing, and perhaps someone in upper management.

### 2.1.1. *Late and early stages of a product's life*

Life-cycle management traditionally refers to either expanding or prolonging the life of an already approved drug. And even the most successful products face a ticking clock to patent expiration and generic competition. However, from the regulatory point of view, the regulatory strategy differs, depending on the stage on a product's life. Given the long development process life-cycle management should start long before application for the product is filed. At this early stage development of life-cycle strategies can prolong data and market exclusivity, and as a result improves the return on investment for the product. Whereas, in the late stage of a product when the product is established, regulatory strategies emphasise on enhancement of the product in order to prolong the product's life-cycle or to gain market place advantages. The term "established products" subsumed all products either at the end of their market exclusivity or data protection period and products, which are marketed more than 10 years including generics.

In an early stage the regulatory strategies for a NCE focus predominately on getting marketing authorisation as quick as possible in order to have the marketed product protected by a basic patent in force as long as possible and to obtain market exclusivity as long as possible. To achieve this, a detailed development plan should be compiled encompassing the future strategies for an extension of the period exclusivity, e.g. approval of a new indication, application for a SPC. This also includes the decision of an adequate application procedure, which should be selected in consideration of the future regulatory environment, the business as well as the life-cycle management strategies. Although the periods of exclusivity are still at their beginning, as soon as the product is approved, the development of further improvement of the product should be directly adjoined. Ideally, patents should protect such developments of further improvement. Later on, this stage will carry over to the late life-cycle management strategies

Late life-cycle management of established products mainly focuses on:

1. The improvement of the product in order to
   - expand and extend the usage of the product and/or (e.g. OTS switch, new strengths or package sizes)
   - increase their differentiation versus the first-generation product, other competitive products, and generics (i.e. new pharmaceutical formulations, new routes of administration, combination with drug delivery systems).
2. Reduction of the regulatory workload through harmonization, i.e. quality part of the dossier or renewal dates.

### 2.1.2. *The new pharmaceutical legislation*

During the last three years the European Council adopted a package of Community legislation on pharmaceuticals, updating the existing rules with the aim of responding to technical and scientific innovations whilst maintaining a high level of health protection and continuing to ensure the proper functioning of the EU's internal market in the pharmaceuticals sector.

With regard to the subject of this Master Thesis, the following legislation have been adopted:

- Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004 on authorisation and supervision of medicinal products for human and veterinary use and on the European Medicines Agency [replacing Regulation (EC) No 2309/03])[1]
- Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (referred in this master thesis as consolidated Directive 2001/83/EC)[2]
- Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use
- Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State
- Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

## 2.2. Framework of this master thesis

With regard to the new pharmaceutical environment this master thesis is intended to illustrate the manifold regulatory strategies for the life-cycle management of cytostatic drugs in a multinational operating company within the life-cycle management team. The main focus is directed at the review of Directive 2001/83/EC and Regulation (EC) No 2309/03; in the following the 'new legislation'.

In this framework, the assets and drawbacks of the respective strategies are assessed (i.e. selection of the application procedure; application for a new indication or a new pharmaceutical form). Moreover, for some strategies a proposed project plan or a brief overview of the documentation as required by the current regulatory legislation and guidelines is attached in order to facilitate the decision-making process by the life-cycle management team and the internal proceeding. As already outlined in section 2.1.1, for the different stages within the product's life the potential strategies have discriminative features. Hence, this master thesis is divided into two main parts: Early stage life-cycle management for NCE and late stage life-cycle management for an established product. The potential strategies are exemplified with case studies; of which one case study is used for a NCE and one for an established product, respectively.

The cytostatic drugs have unique features, which have to be considered when developing regulatory strategies (see following section 2.2.1). Under this terminology chemically defined drugs as well as 'biologics' e.g. antibodies are incorporated. However, for regulatory work different guidelines have to be applied. Due to that reason the framework of this master thesis is limited to chemically defined cytostatic drugs. Beside, the impact of forthcoming legislation is also evaluated briefly.

In this context it should be noted that all explanatory documents i.e. guidelines, position papers etc. regarding the new legislation which have been published until the 20-Feb-2005 are taken into consideration.

### 2.2.1. *Unique features of cytostatic drugs and their impact on regulatory strategy*

From regulatory point of view cytostatic drugs posses some unique features, which may have an impact on life-cycle management:

1. The indication 'cancer' and the severe side effects of cytostatic drugs require a close medical monitoring[3]. Due to medical reasons an OTC-switch as laid down in Art 74 (a) of the consolidated Directive 2001/83/EC is not possible.
2. Some tumours are quite rare so that a designation for an orphan medicinal drug might be granted[4]. However, once the product is designated marketing in more frequent therapeutic indication will be subsided the orphan medicinal drug status.
3. Due to ethic reasons the efficacy is not tested against placebo in cancer clinical trails[5]. Instead of placebo the efficacy and safety are measured against standard therapy consisting of other cystostatic drugs. The selection of the right standard therapies is often problematical because of the various standard therapies and treatment schedules. In addition, most cystostatic drugs are given in combination chemotherapy. Against this background the design of the clinical studies is quite complex. With lack of a standard therapy open controlled clinical trails might be acceptable by the authorities.

4. On average cystostatic drugs are given as injection or infusion. Current only a few oral cytostatic drugs are available. In contrast to the most parenteral forms, which have to be reconstituted or diluted in common solutions for infusion (like NaCl-solution or Ringer solution), oral formulations are "ready-to-use". This aspect has to be taken into consideration, because of the toxicity of the drugs the preparation of the ready-to-use solution has to be done in specialized pharmacies. Notwithstanding that patients and pharmacists would prefer oral preparations, the development of oral formulations is a challenge. In view of problems with drug uptake, suitable coating, toxicity to skin and mucous membrane or first pass metabolism in case of a pro-drug.
5. In the development of new oral pharmaceutical formulations it should be considered that bioequivalence has to be shown in patients. Like in other clinical trials with cytostatic drugs it is not ethically justifiable to run bioequivalence studies in healthy volunteers due to their extreme toxicity. Therefore, longer study duration should be planned.
6. In the paediatric patient population very few controlled clinical trails have been done so far. Thus, mainly due to liability reasons and the age-related differences as pointed out in the guidance “Clinical Investigation of Medicinal Products in Children”[6]. Consequently, very few data are available in this patient group and the off-label-use of cystostatic drugs in children is almost 100 %. However, data on paediatric use might be mandatory for the future. The impact on the forthcoming legislation is discussed in chapter 3.3.2.

# 3. Early stage life-cycle management for new chemical entity

In the following sections of this chapter possible regulatory strategies for early life-cycle management of NCE are based on a case study.

The scenario for a NCE in the treatment of cancer is given below:

The patent for a new chemical defined substance was filed at the EPO and the patent was granted in October 1994. Pharmaceutical and clinical development were carried out in accordance with GLP/GCP. The pharmaceutical form is powder for solution for injection. For both, drug substance and finished product, the manufacturer and the site of batch release are located in the EU.

The results of phase III studies are showing that the new drug is at least very efficient in the two common types of solid tumours in comparison to standard therapy. The drug was given in combination with other cytostatic drugs used in the indications breast cancer and non-small cell lung cancer in first line treatment. Scientific advice had been given by two NCAs and as well by the CHMP. The marketing strategy is to market the product initially in 10 member states including Norway, Poland and Hungary.

The company is a multinational operating company with subsidiaries or contacts in all MS. There is no intention for co-marketing and co-promotion. Within the next years the MA will be likely expanded to other countries of the community depending on each market's demand.

The product's trade name was already registered as ‘Mitoxin’. This trade name could be used in all European Member States. Submission of the dossier in CTD- is scheduled for the fourth quarter of 2005.

## 3.1. Planning for submission - Selection for application procedure

### 3.1.1. *Mutual recognition or centralised procedure?*

Concerning this NCE scientific advice had been given by the CHMP as well as by two NCAs. In any case these NCAs are foreseen as RMS or rapporteur/co-rapporteur depending on which application procedure will be implemented.

On 20-Nov-2005 the new Regulation (EC) 726/2004 comes into effect. In the annex of this regulation is laid down which medicinal product has to be authorised by the community. Among others, NCE for the treatment of cancer will fall in the category of drugs for which the CP will become mandatory. Until 20-Nov-2005 the company will still have the opportunity to select between the following application procedures depending on the submission date:

- MRP according the old legislation (until 30-Oct-2005)
- DCP according to the consolidated Directive 2001/83/EC (from 30-Oct-2005 to 20-Nov-2005
- CP according to Regulation (EC) No 2309/93 (until 20-Nov-2005)

With the new legislation the status of the EMEA will be strengthened. Therefore, it would be interesting how concerned national authorities will handle an application for MA after 30-Oct-2005 for NCEs falling under the scope of the new centralised procedure. In the respective Directive 2004/27/EC it is clearly states that:

> *"Wherever it is proposed to change the scope of the centralised procedure, it should be no longer be possible to opt for the mutual –recognition procedure or the decentralised procedure with respect of (...) new active substances and for which the therapeutic indication is the treatment of (...) cancer (...)".*

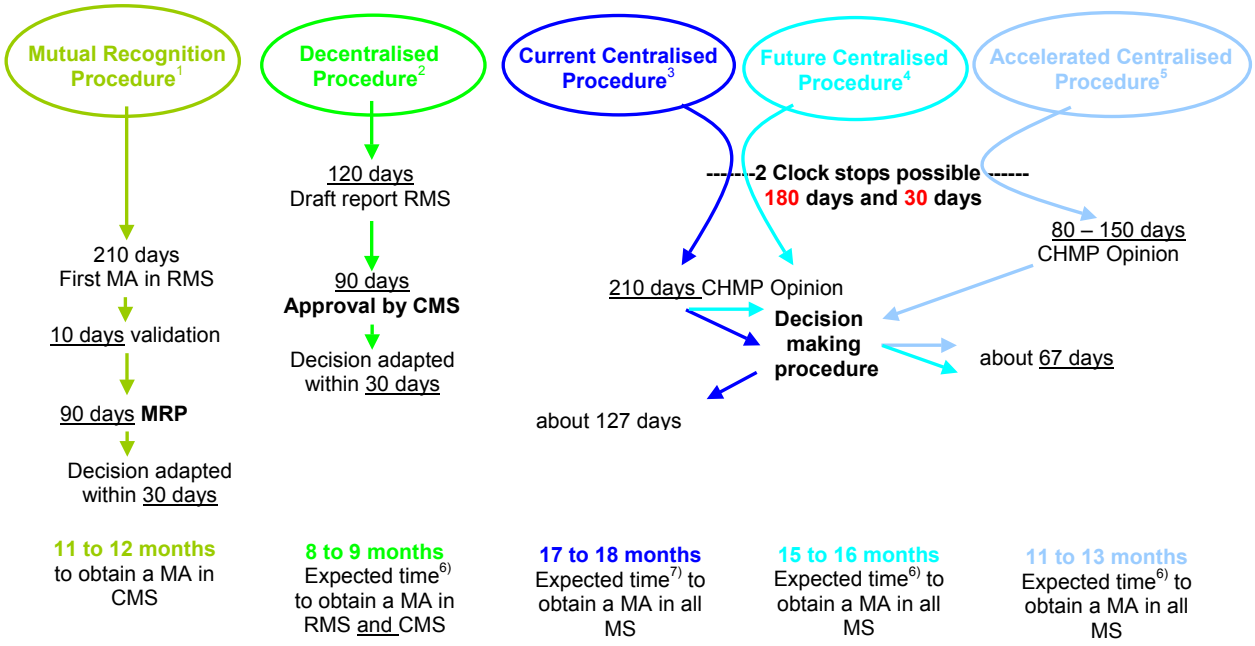
Legally, the submission has to be accepted by all NCAs, because the old Regulation (EC) No 2309/93 is still in effect, because NCE listed in Annex B of this Regulation the CP is optional. However, it is likely that some NCA will ask the applicant to switch to the CP, especially smaller NCAs. In the present case with Germany or Sweden as RMS, it seems more likely that those authorities are willing to accept the application for a decentralised procedure.

Nevertheless, the disadvantages and advantages between these procedures have to be measured up against one and another carefully. Because of the fact that the procedure has an impact on e.g.:

- Time to market
- Number of countries in where a MA is designated
- Period of data and market exclusivity
- Parallel import
- Fees and handling of regulatory procedures

*Time to market*

One of the key points is time to market. From the economical point of view it is essential to place the product on the market as soon as possible in order to obtain the longest possible market exclusivity. In case of cystostatic drugs, which are at the upper end of price scale the prolongation of the exclusivity by months up to even a year has great impact on the annual turn over. Particular attention should be paid to the time to first approval and the time to obtain an MA in all countries planned for. After the new pharmaceutical legislation is entered into force, the new application procedures are implemented.




**Flow Chart 1:** Comparison of time to approval of the different application procedures

According to Art. 28 (1) of Directive 2001/83/EC; [2)] according to Art. 28 (3) of consolidated Directive 2001/83/EC [3)] under Regulation 2309/93; [4)] under Regulation 726/2004; [5)] according to Art. 14 (9) of Regulation 726/2004; [6)] At present guidelines regarding the exact proceeding of the new procedures, like Decentralised Procedure (DCP) and accelerated Centralised Procedure (CP), have not been published yet. Due to that reason the calculation of the expected time to approval is made under the assumption that the time frames of clock stops and of validation remain unchanged. [7)] For the 'old' CP the expected time to approval includes all clock stops and does not reflect the accelerated evaluation ('day-70 assessment report'). For the new DCP no clock stop is assumed. The average time frames of the decision-making procedure were based on an article written by Clayton[8]. For more details see text.

Based on the time frames laid down in the legislation the expected average approval times of the current and future application procedures are calculated. As shown in flow chart 1, comparing the time to approval of the first MA the decentralised procedures i.e. MRP and DCP are much shorter than the centralised procedures. For products, which have not been authorised in the Community the new DCP proposed an MA within 8 to 9 months (without clock stop) after a valid application has been filed, and all parties have agreed on the assessment report. If agreement is not reached within 90 days the matter will then be referred to the new co-ordination group. Within 60 days the problem should be sorted out there[7]. Otherwise, a referral will be initiated (for more details see next paragraph 'Number of countries in where a marketing authorisation is designated'). In contrast to the old MRP a clock stop of a maximum of six months might be foreseen for the DCP as proposed by some industrial associations. Thus to allow the MAH enough time for preparing the answers on questions risen from the concerned authorities. However, this point is still under discussion. But keep in mind, if all parties agreed on this

proposal, time to approval could be prolonged by another 6 months. In that case the times to approval of the DCP in comparison to the future CP are quite similar, even longer than the proposed accelerated CP.

In general the DCP (without clock stop) will ensure the rapidest market access and thus will increase the return of investment. In this aspect it is important to note that an MA will be issued approximately at the same time in all MS involved. Whereas, in the 'old' MRP the first MA is granted in almost the same period of time but in RMS only. This has a great impact on the period covered by SPC, which is discussed in detail in section 3.2.1 (see also flow chart 2 for overview and comparison).

In relation to the CP, the DCP without clock stop is twice as fast as the CP without considering the measures to accelerate approval time. Comparing the time to approval of the current CP with the future CP the reduction will be between 2 and 3 months due to a shortened decision-making process. This process will be generally reduced from 127 days to 67 days on the average[8]. In contrast to the old Regulation within the new one a time limit of 15 days is set for the Commission to finalise the decision after consulting the standing committee. However, under the new Regulation 726/2004 there are new measures to accelerate time to approval (see section 3.1.2. for discussion). If choosing MRP or DCP it should be taken into consideration how many countries and which are involved. There are some uncertainties explained in detail the next paragraph.

*Number of countries in where a marketing authorisation is designated*

In the present case MAs in 10 countries are designated encompassing Norway and two NMS. However, choosing the MRP or DCP for so many countries at the same time is a huge enterprise. In case of disagreement i.e. with the assessment report, content of SPC, labelling it is difficult to reach an agreement. In this context it should be considered that:

- Although the new member states have been receiving training in the European regulatory procedures they might not be so familiar with these procedures.
- In contrary to CP there are no clock stops for the preparation of answers to questions raised from the NCAs. Sufficient time might allow additional investigations for solving outstanding issues. However, a 6-months clock stop for the DCP might be also foreseen, but this topic is still under discussion.
- When a MRP under the old Directive 2001/83/EC is started, in case of disagreement the MRFG has no legal status and can only act as a mediator between the MS. Moreover, in comparison to the CP no additional time is given for solving the problem. If the problem cannot be solved, a referral will then be initiated. Aside creating other nuisances a referral is a time-consuming procedure and will prolong the time to approval by months.
- At the time when the consolidated Directive comes into force the status of the MRFG is legalised[9]. Then this group will be renamed into Co-ordination group with new responsibilities as described in a report prepared by the Ad Hoc Working Group[10]. However, at present their exact working procedures and the corresponding time lines are still uncertain[11]. Moreover, if the new group cannot solve points of disagreement i.e. on SmPC or assessment report, within 60 days the matter has still to be referred to the CHMP.

Against this background, there is some probability that time to approval might be prolonged due to an arbitration procedure and/or leaded to withdrawal of the application in some countries.

Moreover, a separate application has to be filled in Norway. Whereas at the end of the CP a national MA is granted by Norway.

In a second step marketing is planning to distribute the product in other countries within the EU. Up to now the countries are unidentified but they will be chosen by marketing short term depending on the market's demand in the country. In order to avoid the risks and the time consuming procedure of a repeated-use MRP it might be wise to decide in favour for the CP. The initial procedure takes longer but allows in this case a more flexible marketing strategy. In addition, when in 2008 or later new countries will join the EU; the marketing authorisation along with the granted period of data protection should be extended to those countries. This could be gathered from a reflection paper published by the EMEA and PERF[12].

One question remains when choosing the CP whether a company can be forced by the Commission to distribute the product to all countries of the community. In the old as well as the new legislation nothing is mentioned regarding the requirements of the MAH to place the product on the market. So far, the company can choose independently whether to market the product and where. With regard to this practice, the ‘sun set clause’ might have been incorporated in the new legislation (see also section 3.1.5). This policy has also an impact on the parallel trade, which is discussed in the section 3.1.4 'Parallel Import'.

*Fees and handling of regulatory procedures*

Taking the economical point of view on case scenario, the number of countries involved and the expected the fees for procedure and for future variations the CP causes lower cost than the MRP or DCP. Moreover, for a designated CAP only one application form has to be filled in. In addition, all parts of the dossier shall be accepted in English with exception to the labelling. Whereas in case of the MRP additional data and translations of specific parts of the dossier are requested by some countries[13]. This is also true for variations and renewals. Thus, it will make the CP easier to operate.

One disadvantage of the CP should not be underestimated: The expanded workload for labelling, translation and linguistic checks in all 22 EU-languages. However, in a multinational operating company with subsidiaries or contractors in each MS this work should be done by local regulatory affairs departments. Therefore, this workload should not have such a great impact on the selection of the application procedure.

### 3.1.2. *The Centralised Procedure under the Regulation (EC) No 726/2004: New measures to shorten approval times*

As already mentioned in chapter 3.1.1 the decision-making process will be shortened through the review of the legislation. In the new Regulation reference is made to the decision-making procedures as laid down in the Council Decision 1999/468/EEC and its adopting regulation[14]. Within the new Regulation the decision in favour of MA usually will be made through the management procedure[15], which will reduce the decision-making process from 130 to expected 67 days on the average (for overview see publication from R. Clayton[16]). However the time frame for preparing the CHMP-opinion remains unchanged within 210 days after receipt of a valid application. Granting of MA could be expected within approximately 15 months instead of 18 months on the average (see flow chart 1 and section 3.1.1; paragraph 'Time to market').

In addition to the shortened decision-making process the new Regulation provides new measures to accelerate approval time. Up to now there are no equivalent legal measures in

comparison to the US system[17] to accelerate approval time of products for serious or life-threatening diseases and conditions with an unmet medical need. In order to facilitate the approval for such medicinal products the new Regulation offers two new measures for approval as laid down in Art. 14 (7) and (9): temporal marketing authorisation and accelerated assessment (for overview see publication from M. Ericson et al.; 2004[18]). However, before implementation of the 'accelerated CP' in the legislation, there was still a possibility to apply for an accelerated evaluation for products for serious diseases[19].

The new category of 'temporal marketing authorisation' grants an early market access especially for those products that fulfil an unmet medical need in an earlier development stage, e.g. after phase II studies with promising results. Such an authorisation is valid for one year, on a renewable basis. However, the obligations when the temporary MA will be converted into a full MA remain to be clarified.

In the present case the phase III studies for two indications are already completed, showing efficacy against the clinical end point 'survival rate'. The study design for both studies had been discussed and agreed on with the CHMP and two NCAs. Most sections of the dossier, i.e. non-clinical safety, clinical safety and efficacy, are completed or in process of finalisation. At this late development stage it is questionable whether an application for a temporal MA according to Art. 14 (7) is reasonable. Against this background a request should be rather made for the accelerated assessment procedure. In this new procedure the time frame for issuing the CHMP opinion is shortened from 210 to a maximum of 150 days (for comparison with the other application procedures see also flow chart 1). Although there is no reference to Art 6 (3), second subparagraph, of the new Regulation it might be possible that the evaluation time might be between 80 and 150 days, so that approval might be expected in around 11 to 13 months (including clock stops). Thus, in comparison with the CP under the Regulation 2309/93 the MA is granted about 6 months sooner (see flow chart 1). Flow chart 2 (section 3.1.3) illustrates the periods of data and market exclusivity in dependence of the application procedure. With regard to those periods this procedure will grant a monopoly position on the market for almost 13 years in all MS (for detailed information regarding the impact of the SPC see section 3.2.1).

The conditions for the accelerated assessment procedure are laid down in Art.14 (9) of Regulation 726/2004. Such request should be duly substantiated and should be reserved for those

> *'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'.*

More detailed definition can be found at the website of the EMEA. On this website the EMEA point out that an accelerated evaluation might be performed in exceptional cases when a medicinal product is intended to provide answers to major public health needs and is defined by three cumulative criteria[20]:

1. *Seriousness of the disease (e.g. heavy disabling or life-threatening diseases such as AIDS,...) to be treated*
2. *Absence or insufficiency of an appropriate alternative therapeutic approach*
3. *Anticipation of high therapeutic benefit.*

It is highly likely that these criteria used for the accelerated evaluation might also be applicable to the application for the accelerated assessment procedure as laid down in the new Regulation.

Without doubt cancer is a life-threatening disease and its treatment would meet the major criteria 'major interest from the point of view of public health' as laid down in Art.14 (9) of the new Regulation and as well as in the first of the EMEA criteria. But the second criteria as well as the mentioned ‘therapeutic innovation’ in the Regulation seem to be more crucial to be fulfilled. The drug concerned belongs neither to a new chemical class nor shows a new mechanism of action. For both indications therapeutic approaches exist although with different efficacy.

But from interpretation of the wording ‘cumulative’ in the definition of the EMEA it could be concluded that the neither fulfilment of the second criteria not the 'therapeutic innovation' might be mandatory.

But clinical efficacy could be demonstrated to be slightly superior to standard therapy. Moreover, cardiac side effects were observed less frequently and with lower severity in comparison to standard therapy. Although this observation could not be shown to be statistically significant due to the design of the study (and therefore the statistical analysis), but might be used as supportive data. Both findings combined might be anticipating a high therapeutic benefit as required by the third criteria. The possibility remains that at least 2 of 3 criteria will be met. However, it has to be taken into consideration that it is still uncertain whether the EMEA will decide in our favour. But there are good chances that the EMEA will do so, when looking at the US. The largest group that experienced benefits from one of the expedited review mechanism was the one tested for the treatment of various forms of cancer[21].

Under the present case scenario the future ‘accelerated CP’ seems to be the appropriate application procedure mainly due to shorter time to approval (see also sections 3.1.3 and 3.2.2 for discussion of other details).

In the pre-submission guidance[22] it is point out that:

> *‘Any request for accelerated review needs to be sent to the EMEA (CHMP Secretariat) with a copy to the Rapporteur and Co-Rapporteur accompanied by the appropriate justification which takes into account the above mentioned criteria. Such request should be sent at the latest one month before the anticipated date of submission of the application.’*

Filing the application one month before the planned submission in the fourth quarter of 2005 might be a too narrow time line. However, this request might also fall under the scope of a pre-submission meeting with the EMEA. The EMEA high-lightened the use of such meetings in order to clarify any regulatory issues or difficulties four to six months prior to the anticipated date of submission[23]. In case of refusal at that early time the company might still have the opportunity to go for the old CP due to the granted 10 years of data exclusivity. It might be worth the consideration of asking the two NCAs who will be acting as rapporteur/Co-rapporteur in advance if they might support such request.

The following documentation might be prepared in adaptation to the EMEA’s Pre-submission guidance and Guidance for companies requesting scientific advice and protocol assistance[24]:

- A justification of the product’s eligibility for accelerated assessment; the Annexes of the justification might include clinical results presented as tabulated summaries
- A product profile
- Proposed SmPC
- An indication of the number of strengths/pharmaceutical forms/pack sizes.

- A statement whether the application is full or abridged.
- Scientific advice received in the past in accordance with Article 51(j) of Council Regulation (EEC) No 2309/93, as amended.
- A proposed classification for the supply of the medicinal product.

It should be taken into consideration, if adding a new indication the additional one-year market exclusivity protection period will not apply to those products authorised under the 'old' legislation (see also section 3.2.2).

### 3.1.3. *Impact of the application procedure on period of data and market exclusivity*

Another important point is the diverse periods of exclusivity, which vary in dependence from the selected application procedure (see flow chart 2 for overview). In general those periods provide additional protection against generic competition after patent expiry in Oct 2014.

The period of data and market exclusivity for NCE will be harmonised in the community according to the '8 + 2 + 1 formular'. In general for NCEs a 8-year data protection and a 10-years marketing protection will be granted in the Community, regardless of MA-procedure. The market exclusivity will be extended to a period of 11 years if the MAH obtains a new indication within the conditions as laid down in the legislation[25] (see also section 3.2.2). So that in total a maximum of 11 years of market exclusivity could be obtain in comparison to the previous 10 years. However, generic companies can start with the development of generics even when the product is still covered by a valid patent. Moreover, the application can then be filed at the end of the data protection period but placing the product on the market will be only allowed after ten-years market exclusivity calculated from the date of the first MA. One should noted, that in the past the generic companies move out the development of generics outside the EU, where the data protection is not relevant. Therefore, the first generic product could appear on the market around eight months after the period of data exclusivity is expired because the generic application can only filed after it's expiration. However, with regard to the new legislation the company should expect the generic competition the day following the expiration of the market exclusivity.

This means, in case of the MRP under the old directive the clock starts after the first MA has been granted in the RMS. Regarding the periods of data and market protection the MRP according to the 'old' legislation contains some disadvantages. According to Art. 10 (1) iii of the Directive 2001/83/EG a six or ten years the period of protection is granted depending on each country. As already agreed on in two other areas the NMSs might be allowed to have a phasing-in period for the extension of data exclusivity for products from six to 10 years[26] after 20-Nov-2005. However, if an application for marketing authorisation is filed before 30-Oct-2005 the data protection period of the 'old' Directive applies. This arises from 'Deadlines for the transposition' of amending Directive 2004/27/EC, Art. 2:

> *"The periods of protection provided in Article 1, point 8, which amends Art. 10 (1) of Directive 2001/83/EC, shall not apply to reference medicinal products for which an application for authorisation has been submitted before the date of transposition to in Article 3, first paragraph."*

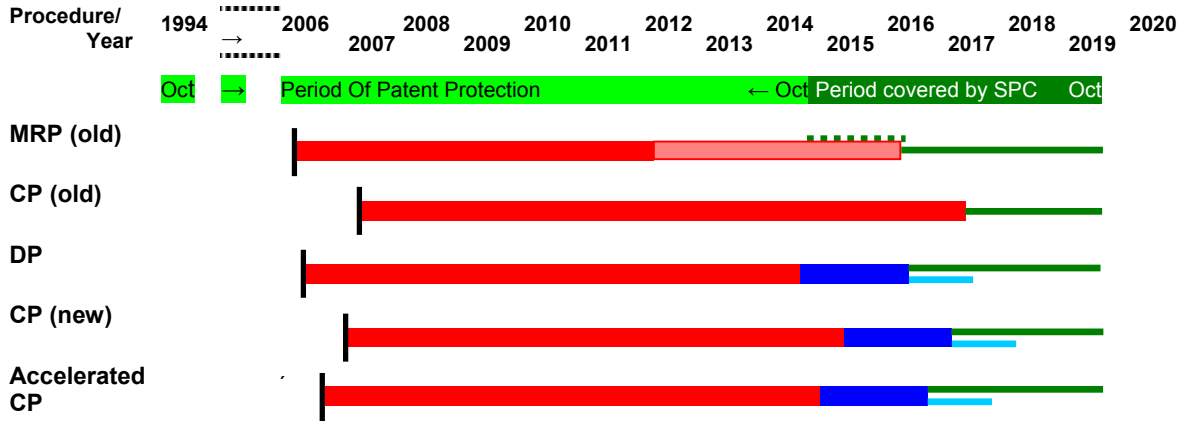
As consequence, at the end of the patent protection in Oct 2014, the company will be facing earlier generic competition in countries where the six-years data protection period applies (see

flow chart 2). Thus, this will subsequently lead to a decrease in return of investment. Whereas in other countries, like Germany or France, the 10-years data protection period still applies.

In contrary, applying for MA under the 'old' Regulation 2309/93/EC a 10-year period of data and market exclusivity are granted within the community[27]. In comparison with the new Regulation two more years of data protection are granted. Similar to the exclusions from the new periods of data and market exclusivity in the consolidated Directive 2001/83 in Art. 89 of Regulation 726/2004 it is laid down that:

> *' The periods of protection provided for in Articles 14 (11) and 39 (10) shall not apply to reference medicinal products for which an application for authorisation has been submitted before the date referred to in Article 90, second paragraph.'*

According to the above-mentioned paragraph developing and filing of a generic application in the MS should be prohibited within this 10-years period. Since the 'old' Regulation is still in force and community law takes precedence over national law, the10-year period of protection should be also applicable in the NMSs. In comparison to the other application procedures the DCP grants the longest period exclusivity with more than 13 years in all countries concerned. Followed by the accelerated CP with nearly 13 years. An early market access will maximise the use of SPC (which is illustrated in flow chart 2). Although the DCP grants the longest period monopoly market span from the regulatory point of view the company should decide in favour of the new 'accelerated CP' taking the discussion in other sections of this chapter into consideration (like fees, handling of future variations, time to market, 'sun set clause' etc.). Moreover, the company has the possibility for extension of the period of market exclusivity by one year, if the product is authorised by one of the new application procedures (see sections 3.1.3 and 3.2.2). A weak point of the new CP is that the generic products might be in the market as soon as the period of market exclusivity is expired. This circumstance has to be weighed up against the possibility of the extension of the period of market exclusivity.




***Flow chart 2**: Periods of exclusivities in dependence of the application procedure*

**Expected date of first MA** **Data and market exclusivity** **Market exclusivity** **SPC** **New indication**
SPC: Supplementary protection certificate; MRP: Mutual Recognition Procedure; CP: Centralised Procedure; DCP: Decentralised Procedure; MA: Marketing authorisation
Range of periods of exclusivity for each application procedure with regard to the expected time to approval when application is filled in the fourth quarter of 2005. For further details see text.

### 3.1.4. *A brief assessment of the risk level of the parallel trade*

Through the existing high price differences for medicinal products within the EU the parallel import from a MS with a low price environment into a MS with high price environment (like Germany, UK, and the Scandinavian countries) is made very attractive. This situation is increasingly getting worse after the EU-enlargement.

On the regulatory point of view the risk of parallel import is higher for CAP than for a product approved by MR or DCP. A CAP is by definition valid in all MS. Therefore, a product put on the market in one MS can be marketed in any other part of the Community by any distributor.

In the Act of Accession a specific mechanism is agreed upon by the EU and NMSs regarding a ban on parallel import of certain patented products from the NMS for a limited period after accession. Such caveats become effective for products, where the following requirement is applicable[28]:

> *'(...) of a patent or supplementary protection certificate for a pharmaceutical product filed in a Member States at a time when such protection could not be obtained in one of the above-mentioned new Member State for that product, may rely on the rights granted by that patent or supplementary protection certificate in order to prevent the import and marketing of that products in the Member State or States where the product in question enjoys patent protection or supplementary protection (...)'*

At present the EPO comprises 30 member states[29], most of them are members of the EU. However, up to now neither Malta nor Latvia have signed an extension agreement or are member of the EPO. Therefore, it might be possible that for both countries the caveat should become effective. However, with regard to the present case, at the time when the patent was granted, it should be checked together with a patent attorney if a patent could have been obtained in the NMS at that very time. In addition, a survey should be done whether an application was made for a patent extension at the EPO in those countries who are not party to the EPC but signed the Extension Agreements. In cases where no protection could be obtained, parallel import would be banned from those NMS.

A strategy for limiting parallel trade might be to develop a ‘stock management scheme’. Based on the distribution data, the company might decide to sell only limited amounts of the product to some wholesalers on a country-by country basis but assuring that there is sufficient national supply.

With regard to this, the European Court of Justice recently has confirmed the 'ADALAT'-judgement of the Court of First Instance;

> *"the right of a manufacturer faced, as in this case, with an event harmful to his interests, (.....)Accordingly, provided he does so without abusing a dominant position, and there is no concurrence of wills between him and his wholesalers, a manufacturer may adopt the supply policy which he considers necessary, even if, by the very nature of its aim, for example, to hinder parallel imports, the implementation of that policy may entail restrictions on competition and affect trade between Member States[30]".*

However, with the recent changes in the pharmaceutical law, namely Art. 81 (2) of the consolidated Directive 2001/83/EC and the new Regulation (EC) 1/2003, could worsen the legal position of the company. In a review prepared by Gassner (2004)[31] regarding the changes in the EU pharmaceutical law and it's impact on parallel trade, it was pointed out, that the applicable

parameter is the need of patients in the MS concerned. Moreover, the question still remains, whether it is legally permitted and economically legitimate in view of the national market fragmentation to accuse undertakings of restrictive practices. It seems highly likely, that further judgements will have been issued in order to clarify this question.

Recently, with regard to Art. 82 (abuse of a dominant position) of the Treaty, an opinion of the Advocate General Jacobs was published[32]. The opinion deals with the questions, whether a company in a dominant position refusing to provide a supply in full orders constitutes an abuse of that dominant position. And, what factors should be taken into account in assessing whether there has been an abuse dominant position. The answers to these questions are that

> *'A pharmaceutical undertaking holding a dominant position does not necessarily abuse that position by refusing to meet in full the orders sent to it by pharmaceutical wholesalers only by reason of the fact that it aims thereby to limit parallel trade. (…) the pervasive and diverse State intervention in the pricing of pharmaceutical products, which is responsible for price differentials between the Member States; (…) the fact that end consumers of pharmaceutical products may not in all cases benefit from parallel trade and that public authorities in the Member States, as the main purchasers of such products, cannot be assumed to benefit from lower prices, given that they are themselves responsible for fixing prices within their territories.'*

Parallel trade can not be completely prevented but within one possible understanding of the judgement and opinion above one can come to the conclusion, that the company must behave proportionately at all times and that an unreasonable supply would have negative consequences for the company. But on the other hand it seems possible to limit the supply to whole sales to some extent, even in a dominant position. This could be applicable in the present case because the product is a NCE used in the treatment of a life threatening disease where there are only few options for treatment.

The opinion from the Advocate General also emphasises the reasons for parallel trade. It should be noted, that this opinion has to be confirmed by the European Court of Justice.

However, an extensive discussion of the highly complex subject 'parallel trade' would go beyond the scope of this master thesis and therefore should be discussed elsewhere.

### 3.1.5. *Implications of the "sun set clause"*

Within the review of the pharmaceutical legislation a "sun set clause" is implemented respectively in Art. 14 paragraphs 3 and 4 of Regulation 726/2004 and as well as in Art. 24 paragraphs 4 and 5 of the consolidated Directive 2001/83. This clause is of overriding importance for the MA of those products, which are actually not marketed or never have been marketed. In the meaning of the afore mentioned Articles a MA will be ceased to be valid, if the product is

> *'no longer actually present on the market for a period of three consecutive years'* or is not placed on the market *'within three years of its granting'.*

The text of the new Regulation comes into force on 20-Nov-2005 whereas the text of the consolidated Directive has to be implemented into national law by the MS before 30-Oct-2005[33]. After gaining the experience of the timely implementation of previous directives it seems doubtful whether the implementation would have been completed in all MS until this date. Also, it is an unsolved issue how the MS take over the text of the Directive into their national law in its original wording. One could imagine that the clause is restricted only to products that have been

authorised according to one of the European procedures (DCP, MRP or CP), or else an exception for purely national authorised products is made. Furthermore, it seems also quite conceivable that some MS will provide transition periods for its implementation.

When evaluating the impact of the sun set clause on the present case scenario the exact meaning of 'placed on the market' is a moot point. Does this mean the product should be available on request only e.g. from hospitals or selling a few packages each year only to maintain the licence? At present there is neither an explanation from EMEA, HoAs nor from the European Parliament. In any case invoices of sold products could be citied as evidence that the product has been placed on the market. As consequence, the potential interpretation of legislation from the industrial point of view might be the one that selling a few packages each year in countries concerned should be enough to maintain the MA. Nevertheless, almost with certainty this matter will appear within short time before the European Court of Justice in order to get a clarification.

It should be taken into account that in the case a MRP or DCP the authorised product has to be *'placed on the market'* in each of the 10 authorising Member States[34]. In case a MA is declared as invalid in one of the MS and the product will be re-introduced in this MS a new MA has to be granted by the repeated-use of the MRP. This is a further drawback of the MRP (old) or DCP in comparison to CP. Contrary to the products authorised via MRP (old) or DCP, a MA for CAP is granted by Commission Decision and is valid within the Community. In Art. 14 (4) of the new Regulation it is said that:

> *'Any authorisation which is not followed by the actual placing of the medicinal product for human use on the Community market within three years after authorisation shall cease to be valid.'*

Taking the treaties the European Union is founded on into consideration, the European Community could be regarded as one market. The replacement of *'Community market'* with *'market'* in the following paragraph 5 of this Article should be understood in this context; Based on this definition, for maintenance it should be theoretically sufficient to sell a few packages of a CAP in one MS, because it's part of the *'Community market'*. Thus allowing a more flexible business strategy.

Against the setting of the concept of the one global MA (for details see section 3.2.3) it will be remain open whether this concept could also be applied to the 'sun set clause'. If applicable, only one of the pharmaceutical forms or strengths etc. needs to be placed on the market. With respect to the economy it should be regarded as legitimate to do so, because on the other hand the concept of one global MA entails deterioration of the protection of the intellectual property. The global MA might be defined by the core information on the product included in the first three sections of the procedure number (in bold); like for example ***DE/H/0268***/001/IA/075[35]**.**

## 3.2. Strategies for Prolongation of the periods of exclusivity

The strategies of how can the intellectual property prolongation be protected after patent expiry or expiry of market exclusivity should be developed by a life-cycle management team as early as possible in the product life-cycle. This is mainly due the long time for research, development and finally approval for i.e. new indications, new pharmaceutical form etc. Since Regulatory Affairs should be a part of the life-cycle management team, the following chapter gives a brief

overview about the regulatory environment in strategies in prolongation of or achieving of different periods of exclusivity in order to prevent generic competition as long as possible.

There are various mechanisms of protection:

*Patent protection*

Although no harmonisation of national patent laws has been taking place the EPC facilitates the interaction between European and national law[36]. Except Malta and Latvia, all MS have either signed the EPC or an extension agreement[37]. Each contracting or extension states:

> *'A European patent gives its proprietor the same rights as would be conferred by a national patent granted in that state. If its subject-matter is a process, protection is extended to products directly obtained by that process.'*[38]

In this context, it should be noted that the national law of the country concerned deals with any infringements of a European patent. The application for a European patent can be filed at the EPO.

*Supplementary Protection Certificate*

The SPC gives additional protection after patent expiry. The effect of this certificate is discussed in detail in section 3.2.1.

*Data and market exclusivity granted in the pharmaceutical legislation*

For products first authorised in the EU data and market exclusivity are granted according to Art. 10 (1) of the consolidated Directive 2001/83/EC and Art. 14 (11) of Regulation (EC) 726/2004 (for details see section 3.1.1). The market exclusivity can be prolonged by one year if the MAH obtains a new indication (for discussion see section 3.2.2.) or a change of classification of a medicinal product ('OTC-Switch'). The latter only applies for products authorised under the new legislation[39].

### 3.2.1. *Application for Supplementary Protection Certificate*

Since the patent protection expires in Oct 2014 an application for SPC might be useful in order to maintain market exclusivity for the NCE. Such a certificate prolongs the period of exclusivity covered by the marketing authorisation but does not prevent the development of generics. Moreover such a certificate could prevent parallel trade under certain conditions (for more details see section 3.1.4). The exclusivity in this certificate extends beyond the active ingredient mentioned in the marketing authorisation when the basic patent protects the active ingredient as such as well as the salts thereof. This arises from the judgement concerning 'Idarubicin'

> *' (....) where a product in the form referred to in the marketing authorisation is protected by a basic patent in force, the supplementary protection certificate is capable of covering the product, as a medicinal product, in any of the forms enjoying the protection of the basic patent.'*[40]

The certificate is valid in all MS[41] for a maximum duration of 5 years from the date on when it takes effect[42]. One should note this certificate grants not more than 15 years market exclusivity. According to Art 7 of Regulation 1768/92 the application should be lodged within 6 months after the first MA was granted either by one's MS or the European Commission when the following requirements are fulfilled[43]:

1. *Protection by a basic patent in force*
   Patent expiry is in Oct 2014. With regard to the present case, a survey should be done if the product is protected by basic patent in force in all MS.
2. *Valid marketing authorisation*
   The first MA is expected in 2006 or 2007 depending on the application procedure (for details see flow chart 1). At that specific time, the product is still protected by a basic patent in force.
1. *First application for SPC*
   The application for a certificate should be filed at the competent industrial property office of the MS. The addresses of those offices can be found on the web site of the European Patent Office[44].

In the present case the application shall contain:

- Request for a certificate with name and address of the applicant, the number of the European patent and the title of the invention
- Copy of the first MA and SmPC
- Proof that fees have been paid upon application in the MS concerned

The effect of the SPC on the period of market exclusivity is illustrated in flow chart 2. Depending on the date of first marketing authorisation and application procedure the additional benefit by SPC is between 5 years (MA granted via MRP in those countries which granted a six year data and market exclusivity) and approximately 3 years by the other application procedures.

It should be noted that the SPC is subject to the payment of annual fees in each MS, which increase annually. Due to that reason the applications should weigh the volume of sales versus the fees. Optionally, the SPC can be selectively withdrawn in each of the countries.

### 3.2.2. *Investigation for a new indication*

The majority of cystostatic drugs are subject to reimbursement. Nevertheless, there is still a high percentage of off-label use due to various individual treatment approaches by the physicians. It is a common practice in some MS, in case of off-label use, that the physicians have to justify the use; otherwise the reimbursement is still questionable. Therefore, using the drug in the approved indication would avoid much physician's paper work if the drug used in an indication, which is subject to reimbursement. Hence, adding a new indication after the first years on the market increase the market share.

Nearly two years ago, the Commission Regulations EC 541/95 and 542/95 were replaced by Regulations (EC) No 1084/2003 and (EC) No 1085/2003 for MR-products and CAPs, respectively. In these regulations two categories of minor types of variations have been introduced: Type IA and Type IB notification. In addition a clarification was specified of what kind of notification falls either under the scope of a variation or should be considered an extension of a marketing authorisation. A major variation of Type II is considered to be a not minor variation and thus does not fall under the scope of an extension to the marketing authorisation[45]. On the contrary, comparing to the old variation regulations in the new ones it is not distinguished whether the ATC code at the third level changes or not. Applying for a new indication is solely regarded as a Type II variation and shall be accompanied by the documentation as shown in flow chart 3.

Within the review of Directive 2001/83/EC and Regulation (EC) No 2309/93 an additional year of market exclusivity will be granted for a new indication under following conditions:

> *'To the ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years the marketing authorisation holder obtains an authorisation for one or more new indication which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies'*[46]

It should be noted that the additional year of market exclusivity only applies for products approved under the new legislation. In addition, a new concept of one 'global marketing authorisation' will be introduced (see also section 3.2.3). All variations and line extensions e.g. new indications, new routes of administration or pharmaceutical forms, shall be considered as belonging to the same MA[47]. In the interpretation of the new legislation and the concept of 'one global MA' should also apply for those medicinal products approved under the old legislation. With regard to all of these legal changes, even when a complete new drug application is made under new trade name and SmPC for the new therapeutic use and/or different posology; those variation/line extensions would be not regarded as new drug application and will not evoke a new period of data and market exclusivity[48, 61]. One possibility might be to protect the developed indication by a patent (for further details see section 3.2.3). But the requirements for granting the additional one-year protection are vague and need to be stipulated more clearly and precisely, especially for the criterion *'significant clinical benefit in comparison with existing therapies'*. A clarification what kind of data are expected for achievement would ensure the business strategy of the MAH and lowering the regulatory burden. One could imagine to support this criterion with statistical significant data only. This would increase excessively the regulatory and economical burden of pharmaceutical companies especially if the clinical benefit is the reduction of a specific type of side effects. Depending on the kind of question this would require studies with high case rates.

The old variation regulation imposes a massive burden for the pharmaceutical industry for obtaining a new indication for cytostatic drugs. In general, cytostatic drugs belong either to the chemical or therapeutic or pharmacological subgroup 86.1.1.B. 'chemical defined cytostatic drugs' or to 86.1.2.B.:'other anti-neoplastic drugs, chemical defined' and adding another indication in this treatment area does not lead to a change within the third ATC-level. However, the text of new legislation in connection with the new variation regulations could be pointed to the fact, that i.e. treatment of new patient groups or new treatment areas would be regarded a new indication[49]. This means for anti-neoplastic drugs that adding a treatment for another type of cancer i.e. some forms of leukaemia or other solid tumours, should be deemed as new indication.

However, the new variation regulations and corresponding guidelines are given only superficial details of what kind of data and documentation should accompany a type II variation for application of a new indication. With regard to those type II variations involving a complex change the competent authority should be contacted before submission[50].

Regarding the present case, previous study results have shown, that the drug is assumed to be effective in two other types of cancer: Soft tissue sarcoma and non-Hodgkin's lymphoma. At least one therapeutic exploratory study (phase II with a surrogate endpoint i.e. tumour response) should be conducted with the aim to investigate further the anti-tumour activity in both tumour types. Afterwards, the competent authority or the rapporteur should be liaised for scien-

tific advice regarding the study design of the following phase III study. In this context it might be also feasible to obtain a preliminary assessment of the 'clinical benefit'.

The therapeutic study should confirm the anti-neoplastic activity that has been previously in phase II study[51]. Normally the indication with the highest anti-neoplastic activity will be further investigated. But it should be noted, that further studies in a rare tumour will prolong the study because it will be difficult to include sufficient patients. As mentioned earlier in this master thesis the drug turn up to be having lesser cardio toxic side effects with reduced intensity in comparison to other drugs used in standard therapy. Therefore, the design of the studies should take this observation into account in order to improve or add to the scientific data status. Thus, showing a better risk-benefit-ratio against standard treatment due to lesser side effects might fulfil the criteria *'new indication including a significant clinical benefit in comparison with existing therapies'*.
Up to now further explanations regarding the course of this process are missing, e.g. if the MAH shall submit a separate request for the additional year of protection together with the application for a new indication. Or if the extension of the protection period will be issued automatically together with the authorisation of the new indication if this presented a clinical benefit. In addition, the question arises who will decide in favour of granting an additional year of protection. It might be proposed that for MR-products probably the RMS or in case of a CAP the CHMP will be responsible. In addition, it is still an open issue if the MAH could appeal against the decision. Moreover, it might be imaginable if one CMS will not recognise the RMS's decision that the matter will be referred to the CG. Under such circumstance the time to approval will be prolonged.

As set out in the paragraph above the MA-procedure could have an impact on the out come of respective variation and the time to approval. For the assessment process of this type II variation the 90-days time scale applies[52]. The entire time scale for completion of the process is shorter for MR-products than for CAPs. This is because within the time scale of MR-products only a clock stop of 90 days is foreseen whereas for CAP the clock stop can be extended up to 6 months[53].

According to the given time scales in the NTA, approval is expected approximately within 7 to 8 months for MR-products and 10 to 12 months for CAPs including clock stops. As shown in flow chart 3 one should calculate for the time to approval for a new indication six years on the average and require an extensive clinical development for the next four to five years. At the time when approval is expected in Q1/Q2 of 2012 there is only other two years of patent protection. With regard to one additional year of protection, the eighth year of MA is expected in 2014 (DCP, accelerated CP) or 2015 (CP under the 'new' and 'old' Regulation) pending on the application procedure. Therefore, in respect to the regulatory and economical conditions, it is important to obtain a new indication as early as possible in order to ensure a return of investment. Ideally, first preparations should start after receiving the preliminary assessment report of the RMS or CHMP opinion, which are expected in the second half of 2006.

With the implementation of Directive 2001/20/EC the principles of GMP must be applied for IMP[54]. In this context an IMPD has to be compiled providing information regarding quality, and data from non-clinical and previous clinical studies. This dossier together with other documents should be accompanying the request for authorisation of a clinical trial[55] and can be submitted in parallel to the Ethics Committees and NCAs. Reference is made to flow chart 3, which gives in overview what documentation has to be compiled at the respective developmental stage.

| Phase | Step | Activity | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|
| **Clinical Development** | | | | | | | | | |
| | 1 | Phase II trial: Compiling Study protocol and investigator's brochure | | | | | | | |
| | 2 | Conducting Phase II-study (surrogate endpoint tumour response) | | | | | | | |
| | 3 | Final Study report | | | | | | | |
| | 4 | Phase III trial: Compiling Study protocol and investigator's brochure | | | | | | | |
| | 5 | Conducting Phase III Study | | | | | | | |
| | 6 | Final Study report | | | | | | | |
| | 7 | New clinical overview and summary including expert report in CTD format | | | | | | | |
| **Regulatory Affairs** | | | | | | | | | |
| | 1 | Phase II trial: Preparing a simplified IMPD* | | | | | | | |
| | 2 | Submission request for authorisation of a clinical trial to the Ethics Committee and competent authority in relevant MS** | | | | | | | |
| | 3 | Phase III trial: Preparing scientific advise regarding Study design | | | | | | | |
| | 4 | Preparing a simplified IMPD* | | | | | | | |
| | 5 | Submission request for authorisation of a clinical trial | | | | | | | |
| | 6 | Preparing amendment to module 5, 2.4 and 2.6 of the dossier | | | | | | | |
| | 7 | Preparing SPC in all languages required | | | | | | | |
| | 8 | Submission of type II variation *** | | | | | | | |
| | 9 | Answering to question from authority | | | | | | | |
| **Expected Approval** | | | | | | | | | 1 1,2 |

*Flow chart 3: Project plan for a new indication*

The project plan facilitate the timely preparation of documents for commence of the clinical trial and as well as the necessary documentation for a type II variation. It should be noted, that due to the transposing of the clinical trial into national law the requirements might slightly vary from member state to member state. Therefore, aside the core information, the MAH shall prepare the necessary documentation according to the country-specific requirements.

After the approval of the Ethics Committee and national competent authority the phase II trials in the indications Soft tissue sarcoma and non-Hodgkin's lymphoma can commence. After the end of the phase II trials scientific advise should be requested for the phase III study design and endpoints in order to increase the success of this variation. Such meetings can reduce time to approval because at those meetings critical questions can be answers and concerns might be ceased due to adaptation of the protocol. The approval is expected in Q1 or Q2 of 2012 depending on the marketing authorisation procedure (1= MR-product; 2= CAP) and the different range of clock stops. It should be noted that the development of a treatment in the rare type of cancer like soft tissue sarcoma will extend time to approval.

*) For already approved products a simplified IMPD can be submitted according to the *'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial'*. Since the trial will be conducted outside the conditions of the summary of product characteristic (SmPC), the SmPC and information of the pilot studies in the indications should be sufficient.

**) The attached list of the afore-mentioned guideline indicates the core information and the member state specific to be submitted as part of a valid application and should include the following (without country-specific information): 1) application form; 2) EudraCT number; 3) Covering letter, 4) Investigator's Brochure; 5) Protocol; 6) simplified IMPD; 7) List of all member states concerned; 8) Opinion of the Ethics Committees; 9) Copy of the manufacturing authorisation

***) The documentation should include: 1) application form; 2) Providing evidence of payment of fees; 3) Update of clinical overview and summary; 4) expert report; 5) addendum of module 5 (supporting data); 6) Update of SmPC in all languages required; 7) Statement that clinical trials carried out outside the EU meet the ethical requirements of Directive 2001/20/EC; 8) List of all member states concerned (MRP only)

Furthermore, the clinical trials are subject to approval from the competent authority and the Ethics Committee in each MS before starting the trial independently from the MA-procedure. Regardless of the number of the Ethics Committees in the MS only one opinion shall be given in writing within a maximum of 60 days with a possible clock stop for providing additional information[56]. The competent authority in the MS in which the trial is to be conducted must approve the trial[57], but a written authorisation is not required in the present case[58].

If after 60 days the competent authority of the MS does not notify the sponsor of grounds for non-acceptance, the trial can commence[59].

In the present case a multi-centre trials will be conducted in two MS and as well as in Romania and Russia. Although, for the two latter countries the Directive 2001/20/EC is not applicable, approval shall be sought in the two MS. As soon as a positive opinion has been received in this MS the trials can commence[60]. However, the NCA and the Ethics Committee from the other MS should be informed about the opinion from the other's.

### 3.2.3. *Life-cycle management through patents*

Once the various periods of protection are expired, the original product will face a generic competition (for details see section 3.1.3. 'period of data and market exclusivity' and introduction of chapter 3.2). With the implementation of the concept of one ' global MA' in the new legislation it seems that further protection of the intellectual property of line extensions will not be granted i.e. neither an extension of data exclusivity nor market exclusivity. In Art. 6 (1) third subparagraph of the consolidated Directive 2001/83/EC it is states that:

> *'When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10 (1).'*

This might be supported by a judgement of the Court (Sixth Chamber) of 29th April 2004 (case RS C-106/01) in which line extensions, like adding a new route of administration or a new dose, were declared as further developments of the original product[61]. In this case a medicinal product (the immunosupressivum 'Neoral') was authorised under the hybrid-abridged procedure according to Art 10 (a)(i) of Directive 2001/83/EC. Furthermore, the new product has been shown to be suprabioavailable, therefore bio-equivalence was not given to the reference product 'Sandimmun'. Nevertheless, it should be still possible to submit a separate full independent application for a MA for a medicinal product, which has already been authorised with a different name and different SmPC[62].

However, in the meaning of the paragraph above, a new period of data and marketing exclusivity will not be initiated even if no reference is made to the previous MA and the application based on 'stand alone dossier'. Against this background one might raise the question how the pharmaceutical company can protect their intellectual property i.e. for the development new pharmaceutical form or another formulation. Therefore, other strategies have to be found in order to maintain or prolong the market exclusivity as long as possible. One strategy might be to protect further developments like new formulations or other modifications of the concerned

product through patents. Thus, protecting a development by a patent is becoming more and important in the current regulatory environment, for example:

- When developing a new indication as described in detail in section 3.2.2, the life-cycle management team should evaluate the possibilty to protect the intellectual property by a patent. In case of patent protection a generic company is not allowed to include this indication in their SmPC. As shown in other cases this procedure is succuessful in preventing generic competition, as previously shown by the product 'Novantrone' (INN mitoxantrone). For this medicinal product a new treatment regime for an auto-immune disorder was developed and the indication was protected by a patent. The product was placed on the market under another trade name, posology and SmPC, in order to separate the new indication from the already approved indications. This course of action allows the company advertisement for the new indication only without mentioning the original product 'Novantrone' and its indications. So that it is not obvious at the first glance that the original product can also be used in the treatment of an auto-immune disorder. When the patented indication is included in the old SmPC, the competitors are not allowed to advertise this indication but they could simply refer to the Originator's SmPC in saying ‘we are similar to the originator’. Thus, such proceeding may also be a hindrance to generic competitors to 'use' their generic product in the treatment of an auto-immune disorder. However, when choosing this strategy the company should be aware of the rquirement to launch a complete new trade mark with all necessities i.e. increase in sales force, advertising literature etc.
- Change in the pharmaceutical form: Development of a new ready-to-use formulation with a patented buffer which is described in detail in section 4.2.1.
- Development of new drug delivery formulation as described in the next paragraph.

*Encapsulating the drug substance with liposomes*

It might be the point at issue if this judgement of the Court in Case C-106/01 and the Art. 6 (3) of the consolidated Directive 2001/83/EC can be also applied for those applications based on a full, independent dossier, and when extensive studies, non-clinical and clinical, are performed. Moreover, when the formulation as well as the pharmaceutical form differ considerably from the original product like the strategy described in the next paragraphs.

Liposomes are regarded as drug carriers in cancer treatment. Therefore, it is a common procedure for cytostatic drugs to encapsulate the drug substance with liposomes in order to modulate drug uptake or prolong circulation time in blood. A longer blood residence time will result in a greater efficiency per unit of the applied drug and therefore will lead to dose reduction. As result, this might cause in a reduction of dose-related side effects, too. To date, some cytostatic drugs are liposomal formulations like, for example doxorubicin, daunorubicin, cytoarabine[63].

The workload of such a development could be compared with the one of developing a new drug. Apart of the drug substance section (section 3.2.S of the CTD) and data of the toxicological studies concerning the drug substance all other parts of the dossier have to be compiled. Almost a complete clinical development programme will be required including new therapeutic studies to confirm the anti-neoplastic activity in the claimed indications. Moreover, even if the toxicology of the drug and the liposomes are known, at least non-clinical safety studies on the finished should be conducted[64].

When starting the development for liposomal drug, within a life-cycle management team the R&D department should evaluate in detail which part of the development could be protected by a patent in order to make a generic application more difficult. The simplest way might be to cover the development by several patents of some parts of the process development, i.e. on the encapsulating process or on the liposomal composition. One advantage of the investment on this drug delivery technolgy is the unique composition of liposomes in each case, on which also a patent could be obtained. The composition has an influence on pharmacokinetics, biodistribution, and tumour targeting which in the end are critical and influential factors for therapeutic efficacy[65, 66]. Hence, in case of a generic application, it would consist of another liposomal composition. Due to that reason, the generic company is constrained to provide additional tests, e.g. comparative clinical studies and non-clinical safety studies.
On the other hand such a development provides the opportunity for new treatment regimes due to selective accumulation of drug in solid tumours. Since extensive clinical studies are already necessary, it might be worthwhile to evaluate therapeutic efficacy other than the approved indications of the original product. If doing so, at the end of the R&D, an almost complete 'new' product with characteristics different from those of the original product would have been developed. Apart from the drug substance the new product would contain a different posology, indication, pharmacokinetic and composition.

In the light of the Sandimmun/Neoral judgement no reference should be made to the original product. Instead of, a 'stand alone' dossier should be submitted in order to make an attempt at starting a new period of protection. However, it is still a point at issue whether this application would be regarded as a 'new drug application' with regard to the concept of one 'global MA'. One might be used to the following arguments in support of the justification of the new drug application:

- That the new development differs considerably from the original product, especially in case when other indications than the original product are claimed.
- In addition, almost the entire R&D programme would have been performed in developing this new liposomal encapsulated drug.
- It could be regarded as excessive if no data and market exclusivity could be obtained, on order to protect the drug and ensure a return of investment.

In the past this was possible. For example, the drug substance memantine, a NCE, is now marketed under the trade name 'Axura'. Firstly, this product was authorised under another trade name and with other indications than the treatment of moderate severe to severe Alzheimer's disease. When developing the latter indication, the company was able to switch to the CP and the full period of data exclusivity was granted under the condition to withdraw the old product from the market. Hence, it could be imagined, that the competent authority requests the withdrawal of the original product, especially in case when the same indications are claimed as in the original product, when accepting this line extension as a new drug application.
Furthermore, a liposomal encapsulated doxorubicin was handled as NCE, despite the fact that the drug substance it self is not an NCE. This CAP is marketed in the EU under the trade name ‘Caelyx’.

In case of the recognition of a NCE, it should be noted, that the CP will become mandatory regardless if the previous product was approved by the MRP or DCP.

## 3.3. A brief overview of forthcoming legislation and it's impact

In the following two chapters an overview is given about the future regulatory environment. Although those guidelines and laws are not in force yet, they should be considered in the present new drug application as well as for further developments like variations or line extensions. In detail, two of the coming regulatory requirements are evaluated briefly:

- On the presentation and submission of the dossier in section 3.3.1
- On the proposed regulation on medicines for paediatric use in section 3.3.2.

### 3.3.1. *Electronic submission: The e-CTD*

The aim of introducing the eCTD is that to facilitate the review process at the authority through links within the files and the reduction of physical paper flow. Within the last two years progress was made in the implementation of the eCTD within the ICH region. The eCTD has finally reached step 4, the last step of the ICH process before moving into the final step of the process which is the regulatory implementation. From 01-Jun-2003, the EMEA's policy is that through the CP submitting the eCTD in parallel with the paper version is optional[67]. At present electronic submission alone is not valid since appropriate archiving laws, tools for management of the workflow as well as workflow organisation and SOPs are missing or have to be drawn up. Moreover, the EMEA wants to gain a little more experience with the process[68].

For the moment it is not certain when the eCTD becomes mandatory. It might be possible, that the transition period could last for years. According to the published draft guidance the e-submission will be foreseen for all submission during the product's life-cycle e.g. new applications, renewals or variations, which would fall under the evaluation of the EMEA. Although the IMPD is not mentioned in the draft guidance, one could be imagine, that this dossier might be also presented in eCTD-format in the near future.

For the moment the EMEA is accepting e-submissions without the eCTD 'xml-backbone'[69]. But it should be noted once an e-submission has taken place all subsequent submissions should be also done electronically. The rule "once electronic, always electronic" will be applied per individual product[70].

At present it is unclear, if all NCA would support the eCTD to the same extent as the EMEA[71]. Today, most NCA from the 'old' MS accept aside paper copies the documentation also electronically, preferably on a physical media i.e. CD-rom[72]. A complete survey of the state of readiness of the all NCAs is a moot point, in the survey published at the EMEA's e-submission website, the all NCA of the NMS are missing. Furthermore, only UK is given an estimated date for eCTD implementation.

The experience from the implementation of the electronic transmission of 'individual case safety reports'[73] shows, that despite a 'harmonised IT-specification' each of the participating NCA has a slight different translation into practice. In case of a MR-product, validation would have been done in every case with each of the RMS and the nine CMS, which will increase the workload and make the whole process more unpredictable. Moreover, one could be imagine when submission of, like renewals, should be done electronically and each of the NCA is using different encryption software. Like in other matters, dealing with the EMEA only, might guarantee a more harmonised procedure and proceeding than with the NCAs.

The general accepted file format among others is the rtf- or pdf-format. Even if no e-submission is planned for the current application, there are some points, which should be paid attention for when compiling the necessary reports for the dossier:

- The overviews in module 2 shall be generated from an electronic source like 'word-document'. This is important when external experts write those overviews. An electronic version should be forwarded along with a hard copy to the company.
- Filing of pfd-files generated from scanned paper should be more or less avoided in order to enable the functions of search capabilities as well as 'copy and paste' for the eCTD. Instead of the reports, study protocols and manufacturing instructions etc should be generated from an electronic source.
- Only hand-written signatures are accepted for official purposes. In order to have the hand-written signatures on the reports, one possibility may be just to scan the page with the hand-written signatures only. With the rest of the document a pdf-file can be generated. A specific software can combine both pdf-files into one file. Another option may be to embed the hand-written signature as a graphic file within the word-file.

However, the company should take first actions for the implementation of the eCTD. The first achievement might be the implementation of a document management system. It should be acknowledged that those systems are subject to computer validation according to international guidelines[74]. Implementation of such a system is a huge entertainment, which involves almost all departments within the company i.e. quality, manufacturing, clinical development. Mostly all of them have to acknowledge the given filing procedure.

### 3.3.2. *Data on the paediatric use*

In order to obtain more detailed data on the paediatric patient population the European Commission adopted a proposal for a regulation on 'Medicinal Products for Paediatric Use', which is expected to come into force in 2006/2007[75]. This draft regulation was adopted in the intention to ensure that medicines are developed for children based on the therapeutic needs of children rather than just on the basis of economical aspects. Therefore, a paediatric investigation plan shall become an integral part for a new drug application as well as for applications for new indications, new pharmaceutical forms and new routes of administration when the original product is protected either by a SPC or by a patent, which qualifies for granting the SPC[76]. An exception is made for applications in accordance to Art. 10 and 10 (a) of the consolidated Directive 2001/83/EC (generic and bibliographic application, respectively) and application for traditional herbal as well as homeopathic products. The reward for the conduction of paediatric studies is a 6-months extension to either the SPC or to the basic patent[77]. It should be noted, that these additional extensions to the periods of exclusivity are not cumulative, i.e. if already an one year extension has been granted due to a new indication, the maximum periods of exclusivity are 11 years.

According to the time lines given in the draft regulation data for paediatric use will be required at the earliest in the second half of 2008 or rather beginning 2009[78] under the assumption that the draft is entered into force at the end of 2006. In the interpretation of this draft regulation it seems not to be mandatory for off-patent products to submit data on paediatric use. In order to stimulate R&D even for those off-patent products an incentive scheme is therefore foreseen

administrated by introducing a new kind of MA-type: 'paediatric use marketing authorisation (PUMA)' (for overview see review written by J. Beesley[79]).

Moreover, a paediatric committee will be established. One of the tasks of this committee is to develop an inventory of the therapeutic needs for that paediatric population, which shall be published and updated in a regular basis. It could be assumed once the need in a therapeutic area is recognized new submission for drugs used in this indication must contain paediatric data. However, in respect of the major therapeutic area 'cancer' there is definitely an urgent medical need to develop treatment schemata for the entire paediatric population regarding child-specific tumours. At present very few data are available so that the 'off-label-use' in this area is almost 100 %. In addition, the paediatric committee will be designated to set up lists of waivers for medicinal products or for classes of medicinal products. Considering the high percentage of off-label use and urgent medicinal need a waiver from this future requirement might be unlikely for cystostatic drugs in the major therapeutic area ‘cancer’. The company should take these requirements into account when developing the new indication or the new liposomal encapsulated drug as planned (for details see section 3.2.2. and 3.2.3).

At least one submission is scheduled within the period of patent protection in 2011 as outlined in section 3.2.2. At that very time the draft regulation will be in force. So when developing a new indication in the second half of 2006 it might be prudent to take possible investigations in the paediatric population into the overall project plan. The additional paediatric investigation might be not only jeopardised by the time line but also by the financing of the project. However, with regard to the claimed indication the company should apply for a waiver. It is still uncertain whether the paediatric committee can force the MAH to perform investigations in other than the claimed indications i.e. in other solid tumours frequent in the paediatric population like germ cell tumours. Although the most cytostatic drugs might not appear on a list of class waivers it should be pointed out that not all cytostatic drugs are used in the treatment of child specific tumours like acute leukaemia or germ cell tumour. In the present case the NCE is approved in the first line treatment for breast cancer or non-small lung cancer and is foreseen in the treatment for soft tissue sarcoma or non-Hodgkin’s lymphoma. One could argue in applying for a waiver that all these tumours almost predominately occur in adults.

In case the paediatric committee rejects the waiver a further option might be to ask for a deferral from the timing of initiation or completion of studies in children as foreseen in Art 21 of the draft regulation due to the following substantiation: Like all cytostatic drugs, this NCE has a high toxicity and therefore severe side effects. At the time when further developments are planed the product is marketed only for 1 to 2 years. It might be therefore more appropriate to gain extensive experience in adults prior to paediatric use. This seems especially applicable for the safety profile. Beyond this it might be functional for all cytostatic drugs.

# 4. Late state life-cycle management for an established product

In the second part of this master thesis potential regulatory strategies for an established product are analysed in the following fictive case scenario:

In 1993 the first marketing authorizations for a chemical defined cytostatic drug in the strengths 1 g, 2 g, and 4 g were granted in Germany based on results of clinical trails, pharmaceutical and pre-clinical tests. In the next year a new strength (5g) was approved in Germany. Via the old multi-state procedure marketing authorizations were granted in six other European Member States in 1994 for the strengths 2 g and 4 g. Through line extensions on a national level the ap-

proval of the 5 g strength was granted in 1997 in the other MS concerned. The pharmaceutical form is powder for solution for injection. The route of administration is injection or infusion.

## 4.1. Reducing workload through harmonisation

One of the objectives for late stage life-cycle management of an established product is to simplify the work for maintenance. Since the time when the MA had been granted the regulatory environment has been subject to ongoing changes. For instance, the MAs granted by the multi-state procedure were transformed into purely national MAs. Furthermore, many variations have been submitted since, resulting in some differences of the quality part of the dossier and, moreover in the SmPCs. Particularly, additional indications and/or other routes of administration could be obtained on the presentation of bibliographic data in some MS concerned.

Possible strategies might be the harmonisation of the quality part of the dossier or renewal dates. On the other hand the authorities predominantly drive harmonisation of the SmPC. In general the MAH try to avoid the SmPC harmonisation mainly due to the time consuming procedure and its risks (for discussion see section 4.2.1). In the next paragraphs of this chapter the course of actions for achievement of a partial harmonisations are outlined.

### 4.1.1. *Harmonisation of the renewal dates*

The approval dates for the various strengths in the MS concerned are different because of the registration procedure and national line extensions. Recently, the renewal documentation in the most MS include on the average the application form, current SPC and PIL, list of all variations submitted in the last five years and a short safety evaluation. However, with the implementation of the directive 2001/83/EC into national law, even for national approved products a PSUR including a scientific evaluation of the risk-benefit balance[80] became mandatory in the most of the MS. With the consideration of the high toxic potential of cytostatic drugs and the bad health status of this patient group, the number of of SAEs and SADRs even with fatal outcomes are considerably high. Hence, the PSUR might consist of several files encompassing several thousand SAEs depending on the drug substance and patient exposure. In accordance to the requirements laid down in Volume 9 each of the unexpected ADRs should be presented as an individual case history and discussed in detail. Therefore, the workload for compilation should not be underestimated.

In the NTA, Volume 9 'Pharmacovigilance' more details on the content and format as well as the period of time covered by a PSUR are laid down:

> *'Each PSUR should cover the period of time since the last update report and should be submitted within 60 days after the last data lock point. The marketing authorisation holder should submit the PSUR together with the renewal application at least three months before the expiry date of the marketing authorisation in the EU. This may be submitted earlier in order to facilitate co-ordination with the regular cycle of the PSUR. Marketing authorisation holders should lock their data no more than 60 days before submitting the application for renewal. The PSUR should cover the intervening time period since the last PSUR[81].'*

As a consequence, those requirements result in a repeated compilation of PSURs for the different strengths within a short time frame due to the distinct renewal dates. Once the renewal

dates will have been harmonised, ideally just one PSUR covering a five-year time period encompassing all strengths will have been drawn up for all MS concerned[82].

In order to achieve this objective the company might proceed as follows (see also flow chart 4 for overview): Although the MAs were granted on a national level, it might be wise to harmonise the quality part of the dossier for all strengths concerned on a national level prior to the renewal dates as outlined in one MRFG Best practice guide[83] (for further details see section 4.1.2). This kind of harmonisation is strongly recommended by the MFRG for MR products e.g. after the MRP finalised through a referral or in case of quality issues raised by the CMS, but might be also used on a national level in order to achieve harmonisation on a national level. As the next renewal according to the EBD is due in 2008, it might be feasible to ask the NCA for a common renewal date for all strengths before the renewals are due on various dates in 2007 for the 5 g strength in six MS, ideally after the submission of the compliance update of the quality part of the dossier. In order to allow enough time for internal co-ordination and discussion with the NCA the common renewal date should be proposed somewhere in the third quarter of 2006. When agreement could be reached, the company should submit the PSUR covering a five-year period together with the renewal application three to six months (depending on the national requirements in the MS) before the determined common renewal date. However, some NCAs might not accept a renewal date other than the IBD or EBD. The company should take into consideration that a late approval of the dossier update concerning the quality part would jeopardise the subsequent submissions. Because most authorities appreciate no other submission during the evaluation of the first one. In this context it should be stressed, that using the EBD for harmonisation of the renewal dates is not mandatory. In case of rejection by some NCAs, the company should proceed as agreed with the other NCA. For practical purposes, harmonisation would be done in 2008 only for those NCA who insist on the usage of IBD or EBD. This seems feasible, because even a partial harmonisation would reduce the amount of PSURs which otherwise would have to be compiled in 2007 as wells as for the upcoming PSUR intervals (see also next paragraph). In this context the preparation of annual PSURs seems to be more practicable, especially considering the number of unexpected ADRs. The annual reports would be summarised in a PSUR bridging summary report utilised for submission[84].

Moreover, when the text of the consolidated Directive 2001/83/EC comes into force, the intervals of submission of a PSUR will have been shortened from five to three years[85]. As a counter move, the renewals for products older than five years will be ceased and the MA will become valid for an unlimited period[86]. Once the product is renewed another renewal will only have to be performed on justified grounds relating to pharmacovigilance. For the re-evaluation after five years, Art. 24 (2) of the consolidated Directive 2001/83/EC outlined that:

> *'(...) the marketing authorisation holder shall provide the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted (...)'.*

One could interpret that the meaning of the 'consolidated version of the file' is a complete update of all parts of the dossier encompassing all variations. At present it seems not clear whether this renewal documentation is also applicable for products approved and renewed prior to the new legislation. If this will become mandatory the complete dossier must be updated and re-formatted to the CTD-format. Moreover, new overviews and summaries have to be compiled. One could argue that for products older than five years the product profile including safety profile is well established. Therefore it could be manageable that the renewal documentation

consists of a 5-year PSUR together with the SPC and list of variations might be enough. If for those products also more or less a complete dossier update will be compulsory it would be a huge task for both, industry and authorities, especially on a national level. It might be interesting whether and when the text of this consolidated Directive will be implemented into national law. However, at least at that very time, the PSUR periods should be harmonised within the MS concerned.

| **Activities** / **Year** | **2005** | | | | **2006** | | | | **2007** | | | | **2008** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quarter** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **1** | **2** | **3** |
| **1. Project: Harmonisation of the renewal dates** | | | | | | | | | | | | | | | |
| Request at NCA | | | | | | | | | | | | | | | |
| Compilation of a 5-year PSUR | | | | | | | | | | | | | | | |
| Submission | | | | | | | | | | | | | | | |
| Approval | | | | | | | | | | | | | | | |
| **2. Project: Harmonisation of the quality part of the dossier** | | | | | | | | | | | | | | | |
| Preparation of revised quality part in CTD format (module 3) | | | | | | | | | | | | | | | |
| Preparation of new quality overall summary (module 2.3 of the CTD) | | | | | | | | | | | | | | | |
| Preparation of the 'consolidated list of changes' together with the local subsidiaries | | | | | | | | | | | | | | | |
| Compilation of the necessary supportive documentation | | | | | | | | | | | | | | | |
| Submission | | | | | | | | | | | | | | | |
| Preparation of answers arisen from the local authority regarding the new dossier (ongoing period) | | | | | | | | | | | | | | | |
| Estimated approval in the MS concerned (ongoing period) | | | | | | | | | | | | | | | |
| **3. Project: Development of a solution for injection** | | | | | | | | | | | | | | | |
| Preparation of a new drug product part (3.2.P of the CTD) | | | | | | | | | | | | | | | |
| Preparation of quality overall summary (module 2.3 of the CTD) | | | | | | | | | | | | | | | |
| Medical expert report for substantiation of the 4% concentrated solution for injection | | | | | | | | | | | | | | | |
| Preparation of module 1 of the CTD | | | | | | | | | | | | | | | |
| Information local authority about the application | | | | | | | | | | | | | | | |
| Submission of variation Type II or line extension | | | | | | | | | | | | | | | |
| Preparation of answers arisen from the local authority | | | | | | | | | | | | | | | |
| Expected approval & launch period | | | | | | | | | | | * | *; # | # | # | |

*Flow chart 4: Proposed project plan for late stage life-cycle management for an established product*

The project plan for late stage life-cycle management of an established product gives an overview of the chronological sequence of activities necessary for implementation of the proposed projects. Thus, simplification of the work for maintenance and improvement of the existing product by adding a new pharmaceutical form will be achieved more easily. It should be noted that all the three projects are directly linked. As soon as one approval is received the next variation should be submitted. Since the marketing authorisations for the different strengths are solely national ones time to approval and the assignment for the type of change are falling within the responsibilities of the local authorities. Most authorities seem to be following the European requirements for the documentation but this seems not to be applicable for the time lines of evalutation. Therefore, the time to approval could only be expected within a defined period. Regarding the approval of the project 'development of a solution for injection' depends also on the assignment of the change as type II variation or line extension. Despite the EU requirements, the company should be equipped for the submission of supplemental and/or other country-specific documentation not listed in the NTA or corresponding guidelines. For further details see text.

*) Expected approval when the change will be allocated as Type II variation; #) Expected approval when the change will be designated as line extension

### 4.1.2. *Harmonisation of the quality part of the dossier*

For more then 10 years the product and its various strengths have been marketed in different MS. Since the last line extension for the 5 g strength many variations have been introduced. In consideration of the mode of operation within a multinational operating company, it seems quite probable that some of them have not been submitted by the local Regulatory Affairs Department. Furthermore, the dossiers that were submitted on different application procedures like new drug application procedure or line extensions on the national level are not identical. With regard of those differences and the old NTA-format as well as the new regulatory environment in the MS, the assessment of the required documentation for upcoming changes done by the head office are complicated. Moreover, a harmonised quality part of the dossier would not only alleviate the regulatory workload or the workload at the manufacturing site, i.e. not to take note of different shelf life specifications or batch sizes, but would also reduce the overall costs in the economic sense. With regard to the launch of the pharmaceutical form ‘solution for injection' and the harmonisation of the renewal dates a prior harmonisation of the quality part of the dossier for all strengths might be one option (see also section 4.2.1). The harmonised drug substance can be used for the upcoming submission for the addition of a new pharmaceutical form (see also proposed project plan in flow chart 4 and section 4.2.1).

In order to achieve a harmonised quality part for all strengths in the MS concerned the company should submit a single (composite) Type II variation[78] as planned in the third quarter of 2005. This compliance update of the quality part of the dossier in CTD-format should encompass all changes introduced in last 5 years including a proposed 10-fold increase of the batch size of the drug substance. This change is critical, because with the current approved batch size a shortage of drug substance will be foreseen on the launch of the new pharmaceutical form. In this context it is substantial to evaluated the differences between the new version and the version of the quality part submitted at the MS concerned together with the local subsidiaries. Those differences would be summarized in a consolidated list of changes, which would lead to a different set of co-coordinated variations in the respective MS. One example of those lists is shown in flow chart 5. As pointed out in the proposed project plan in flow chart 4, the head office should prepare the supportive documentation as required by the current guideline (for details see flow chart 5).

The submission of a compliance update is planned in the first quarter of 2006 and should contain in general:

- application form
- a consolidated list of all changes encompassing the dossier update including necessary documentation according to the guideline, which is not part of the dossier
- updated local SmPC and PIL
- local artwork of the inner and outer packaging
- new module 2.3 (Quality Overall Summary)
- revised module 3
- GMP certificate
- Payment of fees

| Assignment of change[1] | Description | Reason | Supportive documentation[2] |
|---|---|---|---|
| Change No 1:<br><br>Type I A<br>Variation no 37a | Tightening of limits for two impurities in the end of shelf-life specification | These limitations ware done solely to respond to accumulated scientific experience. | • New shelf-life specification in section 3.2.P.5.1 |
| Change No 2:<br><br>Type I B<br>Variation N10 | In the synthesis of drug substance one extraction step for purification is eliminated. | In order to simplify the manufacturing process and increase the yield of the drug substance the extraction step was abolished<br>A comparison of the impurities profiles shows only insignificant differences. | • New description of manufacturing process in section 3.2.S.2.2<br>• Batch analysis data in section 3.2.S.4.4<br>• New process validation in section 3.2.S.2.5<br>• Approved release specification in section 3.2.S.4.1<br>• Direct comparison of both process (separate report in the attachment) |
| Change No 3:<br><br>Type 1 B<br>Variation<br>No 42 A (1) | Change in the shelf life of the finished product from 3 to 5 years | In order to respond the scientific process new stabilities have been performed according ICH | • New stability data provided in Section 3.2.P.8.3<br>• New Shelf life specification in Section 3.2.P.5.1<br>• Revised SmPC and PIL |
| Change No 4:<br><br>Type I B<br>Variation No 42 B | Change in the shelf life of the reconstituted solution from 4 days to 8 days. | In order to respond the scientific process new stabilities have been performed according ICH | • New studies regarding stability of the reconstituted solution in section 3.2.P.8.3<br>• Revised SmPC and PIL (in the attachment) |
| Change No 6:<br><br>Type I B<br>Variation No 11 C | Change of batch size of the drug substance more than 10-fold compared to the approved batch size | An increase of the batch size of drug substance would lead to continuous manufacturing process of the finished product which is now limited due to shortage of drug substance | • New process validation in section 3.2.S.2.5<br>• Two Batch analysis of the validation batches (in proposed batch size) in section 3.2.S.4.4<br>• New manufacturing procedure in section 3.2.S.2.2<br>• Comparative batch analysis of the approved and the proposed batch size (separate report in the attachment) |

*Flow chart 5: Example of the 'consolidated list of changes'*

In order to achieve a harmonised quality part of the dossier for all strengths approved in the different Member States, a consolidated list of changes will have to be prepared. This list reflects all differences in the dossier submitted by the local authority and the proposed dossier. In dependence on the submitted dossiers the list will differ from country to country. The table above gives one example how such a list can look like.
Harmonisation would be achieved by a set of co-ordinated variations as indicated in the consolidated list of changes. Aside the assignment of each change to a kind of variation a short description and justification of changes should be included as well as the required supportive documentation. For further details see text.
[1)] According to the Regulation (EC) No 1084/2003; [2)] According to the 'Guideline on dossier requirements for type 1A and type 1B notifications'

It should be noted, that not all MS has implemented the variation regulation into national law, like Germany or Belgium. In general, most of the NCAs follow the EU-variation procedure for national approved products like dossier requirements. But this seems not to be applicable for the time lines. Therefore, as outlined in flow chart 4 time to approval for the implementation of this variations only could be roughly estimated from three to nine months including answers to questions raised by the NCA regarding the new quality part. As soon as the company would receive approval from the NCA, the documentation for the project 'development of a solution for injection' should be submitted in the MS concerned.

## 4.2. Strategies for improvement of the product

Although at this stage there is no more protection it might be still financially worthwhile to improve the product i.e. by offering the same product in various pharmaceutical forms or new forms of drug supply. In order to meet medical needs and to respond to the scientific process

the development might contain e.g. new strengths in case of new treatment regimen, another additional package size and/or container, adding another pharmaceutical form (see also chapter 3.2; section 3.2.3). In consideration of the present case study a possible strategy for the development of a ‘solution for injection'.

### 4.2.1. *Development of a ‘solution for injection' – Change of the pharmaceutical form*

The pharmaceutical form is ‘powder for solution for injection’ and contains beside the drug substance no excipients. In general, the preparation of a ‘ready-to-use’ solution is subject to certain conditions due to the toxicity of the drugs and has therefore to be performed by specialized pharmacies only. According to the SmPC the powder is dissolved in an isotonic NaCl-solution in order to reach a 4%-concentrated solution. When the re-constituted solution is planned to be administered as infusion, further dilution can be performed in common solutions for infusion like isotonic NaCl solution or Ringer's solution as already described in the SmPC.

Therefore, another strategy might be to develop a 'ready-to-use' solution in order to omit the time consuming reconstitution step. Thus, making the handling of the product more convienent for the pharmacist. In case of parenteral solutions no bioequivalence studies are required when containing the same actice substance in the same concentration as the currently authorized product[87]. The ready-to-use solution is planned for the strengths 2g, 4g, and 5g.

The change in the pharmacetuical form from a ‘powder for solution for injection’ to a ‘solution for injection’ does not lead to a change in the route of administration. According to the table in Annex II of the variations regulations[88] an addition of a new pharmaceutical form is considered as an extension of the current MA. The mode of administration is emphasised in the pharmaceutical standard term ‘powder for solution for injection’. More details regarding the definition of the pharmaceutical form can be found in the ‘Guideline on the categorisation of extension applications versus variations applications[89]’:

> *‘If the physical form in which the product is supplied by the manufacturer is different from that in which it is to be administered to /used by the patient, that is, if transformation of the product is required before it can be administered, both these elements of information need to be conveyed within the term.’*

However, in this guideline an example for the current change is not given. It only expresses that in case of a deletion of the solvent this is classified as Type II variation, but the case vice versa is not mentioned. Additionally; the following definition of ‘pharmaceutical form’ can be found in the judgement of Case C-106/01:

> *‘A pharmaceutical form is defined as the combination in which a pharmaceutical product is represented by the manufacturer and the form in which it is administered, including the physical form.’*

Both definitions express, that the pharmaceutical form is a combination of the physical form represented by the manufacturer and the one at administration. Taking this definition into account, the administered pharmaceutical form is identical in both cases as well as the administered concentration.

In comparison to the original form the ‘solution for injection’ contains the same quantity of drug substance and the impurities are within the approved limits. The only differences are:

1. Adding one excipient, a phosphate buffer, in order to stabilise the drug substance in the aqueous solution. The low concentration of phosphate has no medical relevance. This aspect together with a medical justification of the use of the 4% 'solution for injection' would be discussed in detail in the medical expert report accompanying the application. This phosphate buffer used in combination with this drug substance buffer is protected by a patent, which hinders the generic competitors from using this 'solution for injection'.
2. The shelf life of the 'solution for injection' form' will be reduced to 2 years instead of 5 years of the 'powder for solution for injection'. The reduction is necessary in order to remain within the original shelf life specifications, because after six months storage under accelerated conditions some impurities exceed the limits within the specification in some batches[90].
3. The immediate packaging of the finished product, stopper and vial, will be different.

It is still uncertain if this change will be classified by the NCAs as a Type II variation or as a line extension, because this change will fall under the scope of national legislation. However, the company should firstly try to submit a (Type II) national variation to the NCA concerned, due to shorter time to approval and lower fees. In case of rejection from one NCA, a new application for line extension should be made in this MS in accordance with the provisions of Art. 8 (3)(i) of the consolidated Directive 2001/83[91] in order to avoid re-formatting of the non-clinical and clinical parts of the dossier in CTD-format. One condition for the line extension is that the name of the product remains unchanged apart from the inclusion of a subsidiary term to enable differentiation form the existing product[92]. The trademark of the original product is well introduced the new product will be named into 'trademark – solution for injection'.

As soon as the (common) renewal is approved the documentation for the adding another pharmaceutical form can be submitted (as shown in flow chart 4). Concerning the quality part of the dossier only the module 2.3 (QOS) and the drug product part needs to be newly compiled. The drug substance part from the update of the quality part of the dossier can be incorporated in the dossier (see also section 4.1.2). Further documentation includes the local SmPC and PIL with the same indications and routes of administrations as granted by the NCA for the original product. The advantage for a national proceeding is, that the product can be marketed as soon as it is approved by one NCA independently from the decisions of the other NCAs. Thus, saving time and workload in comparison to a MRP as described in the next paragraph.

The company has still the choice to opt for the MRP[93]. Prior to the MRP the company will have to harmonise the SmPCs, which are not identical in the MS concerned yet (see also introduction to this chapter). Harmonisation could be either reached through a set of co-ordinated national variations or a referral according Art. 30 (1) of the consolidated Directive 2001/83/EC. There is a very likelihood to lose one or more indications and/or routes of administration because the principle of the lowest common nominator apply. In particular, if those indications and/or routes of administrations are not very well documented in the literature or through clinical studies performed by the company. Furthermore, for both proceedings several months should be estimated with an uncertain outcome regarding the content of the SmPC. Regarding the referral even a potential withdraw of the MA in one or more MS should be taken into consideration. About the SmPC harmonisation via national variation, it should be expressed that the MRP, i.e. a new drug application, can only be filed after all seven MS concerned have agreed on the submitted variation(s). From experience it seems likely that not all MS will approve the application for a harmonised SmPC, meaning that one or more MS reject the variation (s) or have other comments. If no consensus can be reached the MRP cannot be started.

Even when a complete new application[94] will be submitted in accordance to Art 28 (3) of the consolidated directive 2001/83/EC a subsequent harmonisation of the line is highly recommended or might be directly driven by one of the NCAs via a referral according Art 30 of the consolidated directive 2001/83/EC. Such a referral will have also an impact on the existing MAs for the 'powder for solution for injections'. Besides, the workload of re-formatting of the non-clinical and clinical part of the dossier in CTD-format should be considered as well as the age of the data, which might require additional studies. In view of those uncertainties the company shall give serious thought about starting this or the previously described procedure.

With regard to explanation above, the company should be aware, that in the future the CG will promote such SmPC harmonisation, including those for national authorised products[95]. A forced harmonisation of SmPC for medicinal products authorised in the MS will be reached through a referral according to Art 30 (1).

# 5. Conclusion and outlook for future strategies

Against the background of the reform of the pharmaceutical legislation and of upcoming legislations the regulatory environment is becoming more and more complex. Moreover, with the EU-enlargement Regulatory Affairs have to deal with 25 opinions and positions from the MS.

## 5.1. The new types of marketing authorisations and its impact on data protection

A good point for industry is the implementation of new procedures that promise shorter times to approval. However, up to now exact details about their enforcement are missing. With regard to the DCP, the increasing number of MS involved and thus increasing number of questions, it might be helpful to have more time in order to address all questions properly, i.e. through a clock stop of several months. This might avoid a referral or other measures like incorporation of special warnings or deletion of an indication. Moreover, the new CG may solve the conflicts elevated by the different positions during the MRP or the DCP, in order to prevent referrals. For CAPs a temporary MA will be foreseen to allow patients quicker access to innovative medicines. This kind of MA seems to be very attractive for cystostatic drugs because it enables early market access, e.g. after phase II studies with promising results. This gives a MAH the opportunity to market drugs 2 to 3 years earlier in comparison to the old application procedures. The terms and conditions of how the temporary MA will be converted into a permanent MA still remain to be clarified. One possible scenario might be that the MAH submits a complete quality and non-clinical part of the dossier as well as module 1 for the application for temporary MA. As soon as one study is finished, the study results should be submitted in CTD format so that the dossier will be completed step by step in an ongoing process. After the end of the successful phase III studies, under the submission of the finalised SmPC as well as clinical and non-clinical overview and summaries, the temporary MA will be converted into a permanent one. This early market access has an impact on the period covered by the SPC as laid down in the Regulation (EEC) No 1768/92 (*'date of first authorisation to place the product on the market'*). It might be highly probable that for the calculation of the period which is granted by SPC and which shall not exceed 15 years, the date of the temporary MA will apply.

Another plus for the industry is the abolition of the periodically five years renewals within the product's life-cycle and the introduction of one five-year renewal on the basis of a re-evaluation of the risk-benefit ratio. On the encounter the PSURs have to be submitted more frequently. It

might be plausible that after the first renewal the MAH might be obliged to propose a long-term pharmocovigilance investigation program. Such a program might consist of pharmaco-epidemic studies or similar surveys in order to evaluate the safety profile in special patient groups.

With regard to the new legislation and current case law the position of the generic companies are strengthened. With the introduction of the '8 + 2 + 1' formula a harmonised period of data and market exclusivity for all medicinal products in the Community will be introduced. Generic applications can be filed at the end of the data protection period. In the context it should be noted that for the next 10 years two periods of exclusivity have to be observed: the period of exclusivity granted under the old legislation and the one which will be granted under the new legislation. At present it remains unclear who will keep the protection period under surveillance in case of a generic application. Especially when the reference product is not authorised in the country of the generic application. In Art 10 (1) of the consolidated Directive 2001/83/EC it is laid down that a generic application can be filed if *'(…) the applicant can demonstrate that medicinal product is a generic of a reference medicinal product (…)'*. In general the MAH of the reference product will not know whether a generic application is planned. If he is informed about a generic application in advance, he might be able to take actions against e.g. to allow another MAH a generic 'informed' consent application so that this product will be on the market first. Without accusing the generic companies of doing so, but it seems not appropriate to hold generic companies solely responsible for the demonstration that the period of data exclusivity is expired. One solution might be that the competent authorithy shall have to ask the RMS or EMEA whether the generic application is allowed. This procedure might be much easier, if at the EMEA all these data are electronically recorded in an extended version of the 'product index', which already exists for MR-products and CAPs. Moreover, to those data only the HoA should have access. Standard operation procedures have to be drawn up to ensure that each of NCA is obliged to enter the required data.

### 5.1.1. *Impact of the concept of the global marketing authorisation*

One drawback for the pharmaceutical industry doing R&D is the introduction of the 'global MA' and the current case law, which limits the possibilities for protection of line extensions. Historically, expanding the use of the product into new indications or adding new strengths have been common methods of prorogating a product's life-cycle. These procedures are regarded to be less costly, quicker and less risky than a complete re-formulation of the product, like encapsulation the drug substance with liposomes. In light of the new legislation and the current case law, the possibilities for protection of line extensions are deteriorating. In the future a MAH must weigh more against market demand and expected return of investment than in the past. In order to cope with the new regulatory environment the MAH has to design a tight life-cycle management plan long before approval. All this ensures early submissions of line extensions and variations within the product's life-cycle when the periods of exclusivity are still valid. It would be also plausible if no protection of further developments of the product could be obtained like patent or prolongation of the period of data market exclusivity, the MAH might avoid the investment in this R&D. There is a risk that such environment might prevent research for innovation.

With regard to the draft regulation on 'medicinal products for paediatric use' the new type of 'paediatric use marketing authorization' grants a full period of data and market exclusivity according to the '8 + 2+ 1' formula. However, in the light of the judgement in case C-106/01 it might be questionable if the data protection is applicable for the whole dossier or just for the

submitted paediatric data. This is an important point and needs to be clarified prior to entry into force of this regulation. In addition, it has to be seen to what extent a waiver or deferral would be approved. Those additional requirements on data for paediatric use may also affect smaller and medium size companies who have neither the capacity nor finical resources to perform additional studies.

### 5.2. Implications on off-patent products

For the regulatory work in a multinational operating MAH on the national level one has to keep an overview of about 25 slightly different national versions of the consolidated Directive 2001/83/EC and other directives issued within the last three years. However, all MS should comply with the text of the new legislation by 30th October 2005, but there is reasonable doubt if all MS states will do so. Therefore the text of the new legislation will come into force at different times. These circumstances will complicate the regulatory work for national MA. Due to the different positions between the MS a harmonised approach is almost impossible, especially with regard to the dossier requirements and the times for review and approval, which vary extremely between the MS. Therefore calculation for launch or implementing a change could only be roughly estimated. These extreme differences can lead to a non-compliance status in the 'fast' countries. This is the case, for instance, when the product is manufactured at only one site and a change in the manufacturing process is intended. The MAH has to wait until approval from all MS involved. The 'fast' countries would expect an implementation soon after their approval and not a year later. This could be extreme critical if an inspection of an authority is scheduled. Therefore, a pragmatic approach might be that the competent authorities should accept application with a reference, and that the implementation of the change will be done after notification only.

## 6. Summary

A number of new regulations, directives and corresponding guidelines have been revised within the last years and a few more will be coming soon. So that regulatory environment is becoming more and more complex. Moreover, with an expanded EU with its different national positions does not make the regulatory work in a multinational operating company much easier. Against this background developing regulatory strategies for product life-cycle management is becoming more and more essential to improve the return of investment. Therefore, the pharmaceutical company might establish an effective life-cycle management team. In addition to regulatory affairs, key personnel from the following departments should be considered for inclusion in the team: e.g. R&D, patent counsel, manufacturing, marketing, licensing, and perhaps someone in the upper management.

The framework of this master thesis is intended to evaluate the assets and drawbacks of the regulatory strategies for life-cycle management of chemical defined cytostatic drugs in a multinational operating company. With the focus on the recent reform of the pharmaceutical legislation, regulatory life-cycle strategies for a NCE in an early life-cycle stage and for an established product in the late life-cycle stage are exemplified with case studies. Beside, the impact of forthcoming legislations is also evaluated briefly.

With regard to a fictive case scenario for a NCE the appropriate application procedure (taking into account the new procedures as well) and future strategies for further developments of the product are evaluated. For the selection of the application procedure the company has to take

various details into consideration like time to market, number of countries involved, future handling of variations, fees as wells as the period of data and market exclusivity. With regard to all these details the CP with the accelerated assessment procedure as proposed under the new Regulation (EC) 726/2004 seems to be the right choice. In comparison to the previous 10-year data and market exclusivity granted for CAP, in the future for all new products only an eight-year data exclusivity and a 10-year market exclusivity will be granted according to the '8 + 2 + 1' formula. An extension of the period of exclusivity by one additional year will be only granted when a new indication is obtained during the first eight years of the MA.

For further developments the new draft regulation on 'Medicinal Products for Paediatric Use', should be taken into consideration when the original product is protected either by a SPC or by a patent, which qualifies for granting the SPC. According to this draft regulation a paediatric investigation plan shall become an integral part for a new drug application as well as for further developments. Moreover, the MAH should undertake first steps in the direction of the implementation of the eCTD, like the implementation of a document management system.

In the second case scenario life-cycle strategies for an established product are analysed. Even for those national approved products it could be one objective to simply the work of maintenance through harmonisation of the quality part of the dossier or renewal dates. A harmonised quality part of the dossier might be achieved through a set of co-ordinated variations covered in an update of this dossier part. Thus, would not only alleviate the regulatory workload or the workload at the manufacturing site, i.e. not take note of different shelf life specifications or batch sizes, but would also reduce the overall costs in the economic sense. Moreover, the required documentation of future developments could be assessed and assembled more easily. Subsequently, the harmonisation of the renewal dates could be carried out in order to reduce the amount of PSURs, which now have to be issued for each national renewal. Moreover, when the text of the new legislation comes into force, the intervals of submission of a PSUR will have been shortened from five to three years. As a counter move, the renewals for products older than five years will be ceased and the MA will become valid for an unlimited period.

All in all the new legislation promises shorter times to approval and the new CG may help to prevent a referral at the of the MRP or DCP. However, up to now exact details of the new application procedures and their enforcement are missing. One drawback is the introduction of the concept of one 'global' MA deteriorating the protection of further developments of the product. In order to cope with the new regulatory environment the MAH has to design a tight life-cycle management plan long before approval to ensure an early submission before the periods of data and market exclusivity are expired. Another option might be to protect further developments of the products like new pharmaceuticals forms by a patent. It would be also conceivable if no protection of further developments of the product could be obtained like patent or extension of the period of data market exclusivity, the MAH might avoid the investment, and thus could be preventing research for innovation.

# 7. References

[1] Note:
When reference is made in this Master Thesis to the new legislation this includes the consolidated directive 2001/83/EC and Regulation (EC) No 726/2004

[2] *Note:*
For the purpose of this document the Directive 2001/83/EC EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC shall be referred as 'consolidated Directive 2001/83/EC'. All references to 'consolidated Directive 2001/83/EC' integrate the newly adopted amendments.

[3] Art. 71 (1) of the consolidated Directive 2001/83/EC.

[4] As laid down in Art. 3 of Regulation (EC) No 847/2000.

[5] HCPMP/EWP/205/95H *Revision 2* Note for Guidance on Evaluation of Anticancer Medicinal Products in Man (CPMP adopted July 2003).

[6] HCPMP/EWP/462/95H Note for Guidance on Clinical Investigation of Medicinal Products in Children (CPMP adopted March 97).

[7] 'Benefits and drawbacks of the new EU procedures'; Script 2004; No 2929; p. 8.

[8] Rick Clayton: The future Decision-Making Process in the EU; Regulatory Affairs Journal 2004: 339 – 343.

[9] Arises from Art. 27 (1) of the consolidated Directive 2001/83/EC.

[10] "The Mutual Recognition Co-Ordination Groups Established By Directives 2004/27/EC and 2004/28/EC" Report from the Ad Hoc Working Group, July 2004 (Confirmed by HoA on 08-Sep-2004).

[11] Arises from Art. 27 (3) of the consolidated Directive 2001/83/EC.

[12] 'Reflection Paper on Organisational Aspects of Phasing In of Commission Decisions Concerning Centrally Authorised Products (CAPs) in new Member States'; Doc.Ref.: EMEA-PERF-Acq-3-04-Final.

[13] Arises from NTA, volume 2a; chapter 7 'General information', revision 7 from January 2004

[14] Regulation (EC) No 807/2003 of 14 April 2003 adapting to Decision 1999/468/EC the provisions relating to committees which assist the Commission in the exercise of its implementing powers laid down in the Council instruments adopted in accordance with the consultation procedure (unanimity).

[15] In Art. 10 (2) of Regulation (EC) No 726/2004 reference is made to Art. 87 (3) which refers to management procedure in Decision 1999/468/EC.

[16] R. Clayton: The future Decision-Making Process in the EU; Regulatory Affairs Journal 2004: 339 – 343.

[17] 21 CFR 312.80 – 312.88 (expedited development) and 314.500 – 314.560 (accelerated approval)

[18] M. Ericson, Ch. Webster, and F. de Crémiers: Accelerated Assessment and Temporary Marketing Authorisation in the European Union; Regulatory Affairs Journal 2004: 645 – 649.

[19] Accelerated evaluation of products indicated for serious diseases (Life threatening or heavily disabling diseases), DOc-Ref.: CPMP/495/96 rev1 dated 18 September 2001.

[20] See web site: http://www.emea.eu.int/htms/human/presub/q08.htm

[21] See web site: http://www.fda.gov/cder/rdmt.internetftap.htm

[22] See web site: http://www.emea.eu.int/htms/human/presub/q08.htm

[23] Arises from EMEA Pre-submission guidance available at the website of the EMEA http://www.emea.eu.int/htms/human/presub.

[24] Content of the pre-submission request available at the website of the EMEA under Hhttp://www.emea.eu.int/htms/human/presub/q01.htmH and
'Guidance for companies requesting scientific advise and protocol assistance', Doc.Ref.: EMEA-H-4260-01-Rev.2 from June 2003.

[25] As laid down in Art 14 (11) of Regulation (EC) No 726/2004 and Art. 10 (1) fourth subparagraph of the consolidated Directive 2001/83/EC.

[26] D. Harnden: EU-Enlargement – What happens Next?; Regulatory Affairs Journal 2004: 335 – 336.

[27] According to Art 13 (4) of Regulation 2309/93.

[28] Annex IV (2) to Art 22 of the Act of Accession signed on 16-April-2003.

[29] See web site of the EPO; http://www.european-patent-office.org/legal/epc/e/contents.html.

[30] Judgment of the Court of First Instance (Fifth Chamber, extended composition) of 26 October 2000. # Bayer AG v Commission of the European Communities. # Competition - Parallel imports - Article 85(1) of the EC Treaty (now Article 81(1) EC) - Meaning of "agreement between undertakings" - Proof of the existence of an agreement - Market in pharmaceutical products. # Case T-41/96.

[31] For Overview see: U M Gassner: How recent changes in EU competition and pharmaceutical law will affect parallel trade; Regulatory Affairs Journal 2004: 655 – 662.

[32] OPINION OF ADVOCATE GENERAL JACOBS dated 28 October 2004 #Synetairismos Farmakopoion Aitolias & Akarnanias (Syfait) and Others versus Glaxosmithkline AEVE # Case C-53/03.

[33] As laid down in the deadlines for the transposition of amending directive 2004/27/EC; Art. 3.

[34] Arises from Art. 24 paragraph 4 of the consolidated Directive 2001/83.

[35] See NTA, volume 2A, chapter 2, section 5.

[36] Guide for applicants: 'National law relating to the EPC'; page3; published by the European Patent Office in March 2003 (12th edition).

[37] Source: http://www.european-patent-office.org/epo/members_d.htm.

[38] Guide for applicants: 'How to get a European patent'; published by the European Patent Office in April 2004 (10th edition).

[39] Arises from deadlines for the transposition of amending directive 2004/27/EC; Art. 3 and Art. 89 of (EC) No 726/2004.

[40] Judgement of the Court (Fifth Chamber) of 16 September 1999. # Farmitalia Carlo Erba Srl. # Reference for a preliminary ruling: Bundesgerichtshof - Germany. # Proprietary medicinal products - Supplementary protection certificate # Case C-392/97.

[41] Annex II: List referred to in Art. 20 of the Act of Accession published in the Official Journal of the European Union on 23 September 2003. Arises from Art 20 (2) in which is laid down that *'This Regulation shall apply to supplementary protection certificate SPC granted in accordance with national legislation of (..*Note: listing of all NMS except Hungary..*) prior to the date of accession*'.

[42] As laid down in Art 13 (2) of Regulation (EEC) No 1768/92.

[43] As laid down in Art. 3 of Regulation (EEC) No 1768/92.

[44] Source: http://www.european-patent-office.org/epo/members_d.htm

[45] Arises from and Art. 3 paragraphs 2 and 3 of Regulation (EC) No 1084/2003 and its Annex II.

[46] According to Art. 10 (1) fourth subparagraph of the consolidated Directive 2001/83/EC. A similar wording is found in Art 14 (11) of Regulation (EC) No 726/2004.

[47] According to Art. 6 (1) second subparagraph of the consolidated Directive 2001/83/EC.

[48] Arises from JUDGMENT OF THE COURT (Fifth Chamber) of 3 December 1998 # Case C-368/96 (Medicinal products - Marketing authorisation - Abridged procedure - Essentially similar products).

[49] Arises from 'BAH-Rundschreiben' RS30/2004 dated 13-Sep-2004.

[50] Arises from NTA, volume 2A, chapter 5, section 3.3.5, dated February 2004.

[51] According 'Note for guidance on evaluation of anticancer medicinal products in man', Doc.Ref.: CPMP/EWP/205/95 rev 2. – corr.

[52] According NTA, volume 2A, chapter 5, section 3.3, dated February 2004.

[53] According NTA, volume 2A, chapter 5, section 4.3, dated February 2004.

[54] According to Art. 13 (3a) and 4 of Directive 2001/20/EC.

[55] According to Art. 9 (2) of Directive 2001/20/EC and in connection with 'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial', dated April 2004.

[56] According to Art. 6 paragraphs 5 and 6 of Directive 2001/20/EC.

[57] According to Art. 7 of Directive 2001/20/EC.

[58] Arises from Art 9 (5) of Directive 2001/20/EC.

[59] According to Art. 9 paragraphs 3 and 4 of Directive 2001/20/EC.

[60] Arises from NTA, Questions and Answers – Clinical trial documents, question No 5, dated January 2005.

[61] Arises from a judgment of the Court (Sixth Chamber) of 29 April 2004. #The Queen, on the application of Novartis Pharmaceuticals UK Ltd v The Licensing Authority established by the Medicines Act 1968 (représentée par The Medicines Control Agency) # Medicinal products - Marketing authorisation - Procedure relating to essentially similar products. # Case C-106/01.

[62] According to NTA volume 2a, chapter 1, section 6.3.

[63] For overview: JM Francis and T Huany: Liposomal technology; Drug delivery Technology, online article available at http://www.drugdeliverytech.com.

[64] According to ICH Topic M3, CPMP/ICH/286/95: 'Non-clinical safety studies for the conduct of Human clinical trails for pharmaceutical'.

[65] J. Senior, C. Delgado, D. Fischer, C. Tilcock, G, Gregoriadis: Influence of surface hydrophilicity of liposomes on their interaction with plasma protein and clearance from the circulation: studies with Poly(ethylene glycol)-coated vesicles; Biochim. Biophys. Acta 1991 (vol. 1062): 77 – 82.

[66] A. A. Gabizon: Stealth liposomes and tumor targeting: one step further in the quest for the magic bullet, Clinical Cancer Research 2001 (vol. 7): 223 – 225.

[67] From the web site of the EMEA regarding esubmission; http://www.esubmission.eudra.org/EMEA.html

[68] Practical guidance for the paper submission of regulatory information in support of a marketing authorisation application when using the Electronic Common Technical Document (“eCTD”) as the source submission; Doc. Ref: EMEA/C/6148/04/v 0.3 dated 09-June-2004.

[69] See Pre-submission guidance on the EMEA's web site 'List of questions and answers No 24’ under http://www.emea.eu.int List of questions and answers No 24.

[70] Practical guidance for the electronic submission of regulatory information in support of a marketing authorisation application using the Electronic Common Technical Document (“eCTD”) following the Centralised Procedure; Doc. Ref: EMEA/C/14868/03/v 0.4/Draft dated 09-June-2004.

[71] Arises from 'Question and answer document in support of the eCTD implementation in Europe'; Version 0.3 dated 09-Sep-2003, Question No 16.

[72] See web site: http://esubmission.eudra.org/ectd-readiness-report.doc

[73] See web site: http:// www.eudravigilance.org

[74] Annex 11 'Computerized Systems' and Annex 15 'Qualification' to volume 4 (GMP Guide) 21 Code of Federal Regulation part 11 (US)

[75] Press Release ' Regulation on medicines for children : frequently asked questions' dated 29-September-2004 available on the web site http://pharmacos.eudra.org/F2/home.html.

[76] According Art. 8 and 9 of the Proposal for a regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Council Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004, adopted on 29 September 2004.

[77] Arises from Art. 36 paragraphs 1 and 2 of the Proposal for a regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Council Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004, adopted on 29 September 2004.

[78] Arises from Art. 56 (2) of the Proposal for a regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Council Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004, adopted on 29 September 2004.

[79] J. Beesley: RAJ Briefing – The Proposed EU Regulation on Medicines for Children; Regulatory Affairs Journal 2004: 809 – 811.

[80] As laid down in Art. 104 (6) of the Directive 2001/83/EC.

[81] According to NTA Volume 9, Part I section 1.4.2.5; dated June 2004.

[82] Arises from NTA Volume 9, Part I section 1.4.2.1; dated June 2004.

[83] As outlined in MRFG Best Practice Guide for handling renewals in the Mutual Recognition Procedure; Revision 2, October 2003.

[84] Arises from NTA Volume 9, Part I section 1.4.4; dated June 2004.

[85] Arises from Art 104 (6) of the consolidated Directive 2001/83/EC.

[86] Arises from Art 24 (3) of the consolidated Directive 2001/83/EC.

[87] Arises from 'Note for guidance on the investigation of bioavailabilty and bioequivalence'; chapter 5.1.6; Doc.-reference CHMP/EWP/QWP/1401/98 dated 26-Jul-2001.

[88] see Annex II of the regulations (EC) No 1084/2003 and 1085/2003.

[89] Guideline on the categorisation of extension application versus variations applications / Revison 3; NTA, volume 2 c - Regulatory Guidelines.

[90] Arises form 'Note for Guidance on Stability testing for a Type II variation to a marketing authorisation'; Doc.-Ref:CPMP/QWP/576/96 dated 22 April 1998; in combination with 'Note for Guidance on Evaluation of Stability Data'; section 2.4.1.2; Doc.-Ref:CPMP/ICH/420/02 dated 20 February 2003.

[91] MRFG: Applications under Annex II of Regulation 1084/2003 in the Mutual Recognition Procedures – Member states recommendation, last update January 2004.

[92] Arises form NTA, volume 2 a, chapter 2, section 2.4.

[93] According to 'Commission communication on the Community marketing authorisation procedures for medicinal products'; Doc-Ref: 98/C229/03.

[94] As pointed out in MRFG: Applications under Annex II of Regulation 1084/2003 in the Mutual Recognition Procedures – Member states recommendation, last update January 2004.

[95] Arises from Art. 30 (2) of the consolidated Directive 2001/83/EC.