Balancing Regulatory and Economic Aspects in the Development of Generics – a Business Case

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Dr. Bernhard Wenkers

aus Münster/Westfalen

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Betreuer und 1. Referent: Herbert Jopp

2. Referent: Dr. Josef Hofer

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List of Abbreviations

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
CDER	Center of Drug Evaluation and Research
CEP	Certificate of suitability of the monograph of the European Pharmacopoeia
CFR	Code of Federal Regulations
CHMP	Committee of Human Medicinal Products
CMS	Concerned Member State
CP	Centralised Procedure
CRO	Clinical Research Organisation
CSE	Cholesterol synthesising enzyme
CTD	Common Technical Document
DCP	Decentralised Procedure
DMF	Drug Master File
EC	European Community
EEA	European Economic Area
EEC	European Economic Community
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HMP	Herbal Medicinal Product
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MHLW	Ministry of Health, Labour and Welfare
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure
NDA	New Drug Application
NCE	New Chemical Entity
OGD	Office of Generic Drugs
PAFSC	Pharmaceutical Affairs and Food Sanitation Council
PAL	Pharmaceutical Affairs Law
PDMA	Pharmaceutical and Medical Devices Agency
PL	Package leaflet
QA	Quality Assurance
QC	Quality Control
RMS	Reference Member State
RoW	Rest of the world
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
UK	United Kingdom
USA	United States of America

Macro-economic Situation in the Generic Business

Generic medicinal products enjoy an increasing importance vis-à-vis the innovative medicinal products. Due to cost-savings, they contribute significantly to the economic provision of medicinal products for the patients. Therefore, the generic competition is also a political issue.

Generic medicinal products have to be comparable with the respective innovator (originator) products concerning quality, safety and efficacy. This comparability has to be demonstrated to the regulatory authorities by means of appropriate chemical-pharmaceutical, and, if applicable, toxico-pharmacological and clinical bridging documentation submitted with the application for marketing authorisation. Special requirements on substantiating this comparability are applied to generic herbal medicinal products and biopharmaceuticals, because they are not only characterised by their complex therapeutically active principals and pharmaceutical forms, but also by their manufacturing processes.
At present, these requirements are being discussed between the regulatory authorities and the pharmaceutical industry regarding impact on cost when transferred into action. On dealing with these challenges also an economically acceptable time frame should be observed, in order to guarantee future financing of the health-care system.

A pre-condition for each pharmaceutical company to cope with these challenges is the compliance with regulatory demands on standard pharmaceutical products, e. g. tablets, capsules, liquids, creams and ointments. Therefore, the following business case is to reflect these basic demands.

1. Introduction

The generic market is characterised by strong competition and high pressures of costs and prices. Therefore, generic companies face the necessity to introduce continuously new products into the market as close as possible to the respective active substance patent expiry dates, in order to achieve maximum prices, sales and profits.
Within tight timelines a product has to be developed essentially similar to the originator's, registered and launched, while observing numerous patent and registration issues challenging to balance the regulatory stipulations and the economic aspects appropriately. Thereby, the management tools of the situation appraisal, decision analysis and potential problem analysis have to be applied to generate a differentiated overview of the situation, to derive substantiated decisions for the further activities and to assess the potential problems and risks.

This thesis is to present these management tools based on the example of the fictitious generic company *GenericsPharming GmbH* located in Pharmaburg in Germany developing and registering a new generic product in its main markets USA and in the EU within the rather short time frame of 18 to 24 months, respectively.
They are explained in combination with the economic situation and needs of the company and the current registration issues to be observed in the main markets USA and Europe and Japan as a future market. Conclusions and recommendations addressing generic companies in general should be developed.

2. Presentation of the Company

2.1 History and Profile of the Company

GenericsPharming GmbH is an established generic pharmaceutical company located in Pharmaburg in the south west of Germany.
The company has been founded in the year 1954 by the pharmacist Johannes Schmidt and the chemist Rudolf Müller. They specialised at first on the synthesis of active pharmaceutical ingredients. From the beginning of the 1980's they started the retail business with generic pharmaceutical products. Since 1990, Johannes Schmidt's son Tobias leads the company as the General Manager.
At present, the company markets 30 generic products mainly with the indications pain, rheumatism, cardiovascular metabolic diseases and gastro-intestinal disorders leading to a sales volume of about 1.5 Mrd. Euro generated mainly in the USA (975 Mio.) and Europe (510 Mio) and finally in the "rest of the world" (15 Mio). There are 5000 employees worldwide, about 1000 in the central location in Pharmaburg and the remaining ones in the subsidiary plants and offices in the USA, UK, Sweden, France and Germany (headquarter), respectively. An additional subsidiary office and a new production site are to be built up in Poland to address the new EU member states.

During its history, the company developed substantiated know-how in manufacturing active pharmaceutical ingredients (API, used synonymously for the term "active substance") as well as solid oral dosage forms like tablets, capsules, film-coated tables and modified release oral dosage forms. However, liquids creams and ointments are also produced.
A synthesis plant is located at the main location in Pharmaburg. Development, production and distribution sites are in Pharmaburg and the USA. Another distribution site is to be built up with the production site in Poland.

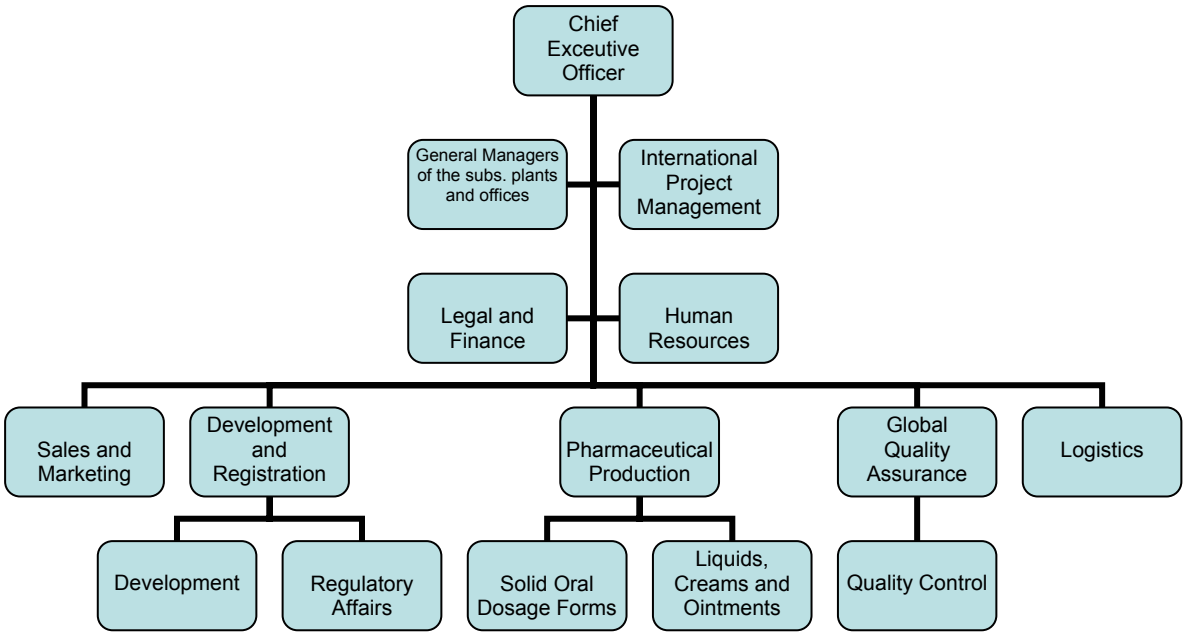
The company is aimed to use and develop

- substantiated know-how in the key indications pain/rheumatism, cardiovascular and metabolic diseases and gastro-intestinal disorders including regulatory affairs and marketing
- most efficient technological and analytical equipment

2.2 Organisation of the Company

Tobias Schmidt acts as the Chief Executive Officer of *GenericsPharming GmbH* in Pharmaburg and worldwide, respectively. The General Managers of the subsidiaries as well as the heads of the different staff groups like International Project Management, Legal and Finance and Human Resources and the business units Sales and Marketing, Development and Registration, Production, Quality Assurance (QA) and Logistics of the location Pharmaburg report to him. An organigramm of *GenericsPharming GmbH* is presented in Figure 1.

Figure 1: Organigramm of *GenericsPharming GmbH*



Sales and Marketing

The sales and marketing activities are coordinated within this department. There is a close cooperation with the International Project Management group.

Development and Registration

Within this unit the galenical and analytical development as well as the regulatory affairs departments are summarised. There are development departments in Pharmaburg and the USA and one global registration department in Pharmaburg. All development projects are coordinated by the staff unit International Project

Management in Pharmaburg preparing the launches in cooperation with the Sales and Marketing department.

Pharmaceutical Production

In both sites, Pharmaburg and the USA, solid oral dosage forms as well as liquids cream and ointments are manufactured. These plants have been approved by the FDA as well as several EU authorities. Another production site for solid oral dosage forms is presently being built in Poland.

Quality Assurance

Routine release and shelf life testing of the approved products is performed within the Quality Control units located at each production site. The Heads of QA monitor and document the observations of the GMP requirements according to the current standards. They report to the Head of Global QA in the headquarter in Pharmaburg.

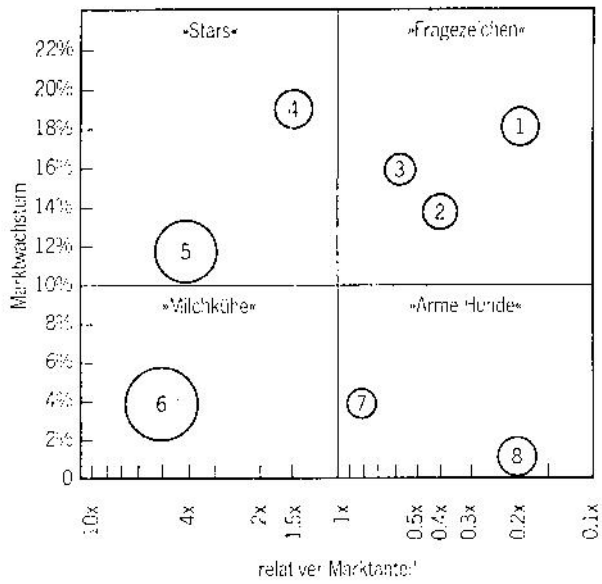
Logistics

There are logistics units at all production sites in Pharmaburg, the USA and to be established at the new production site in Poland.

2.3 Product Portfolio

The main business volume is covered by the products numbered 1 – 8 presented in Figure 2 in a market growth-market share-matrix as applied by the Boston Consulting Group [1, 2].

Figure 2: Portfolio presentation of the leading products 1 – 8 of *GenericsPharming GmbH*



Quelle: B. Heldey: Strategy and the Business Portfolio, in: *Long Range Planning*, February 1977, p. 12.

The sizes of the circle represent the magnitude of the business volumes achieved with these products. The vertical axis shows the market growth per year in per-cent ranging from 0 to 22 %. A market growth of 10 % (horizontal line) is considered high.

The horizontal axis shows the relative market share of the products in comparison to the brand leader products. The logarithmic scale enables to indicate the percentage change corresponding to position change in the diagram. A relative market share of at least 1 is considered high.
The products 1 and 2 and the new product 3 containing the active substance *antiarrhythmon* (tablets containing 50 mg, please refer to section 1.4) becoming patent-free in the middle of 2007 enter the diagram as so-called "question-mark" products needing high investment costs due to the market growth, which are not turned immediately into profit. Hence, the benefit for the company can be estimated only in the future and will be positive when turning to "cash-cows" located in the lower left quadrant.
The products 4 and 5 are to be addressed as "Stars" generating high cash, but also high re-investment needs, which compensate each other. With decreasing market growth they can generate more cash than make investments necessary and become to so-called "cash-cows", like product 6 is. Because of the rather low market growth the obtained cash are not to be re-invested into the same products, but into other ones. Hence, "cash-cows" provide the cash needed for other existing or new products, respectively.
The products 7 and 8 are the "dog" products. They do not require high investments, but do also not generate any cash to re-invest like the "cash-cow"-products. Therefore, they should be taken into account to be deleted.

The remaining 21 products generate comparably low profits and divide equally on the "cash-cow" products in very slowly growing markets and the "dog" products as discussed above.

<u>Assessment and conclusion</u>
The product portfolio of *GenericsPharming GmbH* is not sufficiently balanced. There are too less "question-mark"- and "start"-products developing potentially to "cash-

cows", but too much "dog"-products generating insufficient cash in relation to the investments. Therefore, these ones should be observed critically, if holding them on the market remains useful for the company.

As a generic company, *GenericsPharming GmbH* has to provide a higher number of new products in its pipeline to guarantee sufficient profits in the future.

2.4 Problem Statement and Situation Appraisal

GenericsPharming GmbH has to face, that the sales grow only at a marginal rate in the USA and no sales growth in Europe. This is not only due to the rapidly decreasing prices generally observed, but also the insufficient product portfolio as presented in section 2.3 before. The competitive pressure increases, which also is the consequence of not keeping abreast of the technology. Thus, one of the main goals of *GenericsPharming GmbH* as introduced in section 2.1 is concerned. Additionally, the production costs increase rapidly due to high costs of the raw materials as well as the production staff.

The situation appraisal including respective actions being proposed to be taken is shown in Table 1 [2].

Table 1: Problems and Situation Appraisal of *GenericsPharming GmbH*

Concerns	Separated concerns	Priority (High, Medium, Low)			Location of Process Steps	Proposals for resolution
		Seriousness	Urgency	Growth		
Decreasing sales and profits	Less attractive products	High (profit carriers)	High (resolution plan within 1 month)	High (monthly declining sales)	Decision analysis	Further advertising, service, **introduction of new products**
	Too much unattractive products	Medium (reliable, but insufficient cash)	Low (sales constant)	Low (long-term impact)	Decision analysis	Selling or deletion of "dog"-products
Keeping ahead of competi-tors in techno-logical advances	Attracting technical experts	High (advance skills)	Medium (one current vacancy)	Low (long-term impact)	Decision analysis	Recruitment of technical experts
	Expensive technology	High (competitive disadvantage)	Medium (necessary, but available equipment still suffices)	High (superior new technology)	Decision analysis, potential problem analysis	Investment in new technical equipment

Table 1 *(continued)*

Concerns	Separated concerns	Priority (High, Medium, Low)			Location of Process Steps	Proposals for resolution
		Seriousness	Urgency	Growth		
Increasing production costs	Costs of staring materials	High (exceeding budget)	High (immediately)	High (further increases expected)	Decision analysis	Finding most suitable supplier
	Personnel costs in the production	Medium (high costs, but experienced people)	Low (production still booked out)	High (decrease costs, in order to release resources)	Decision analysis, potential problem analysis	New production site in Poland

Immediate actions have to be taken to improve the marketing of the leading products, e. g. by further advertising and service to doctors and pharmacists. Furthermore, new products oriented closely to the current patent situation have to be introduced. This will be further outlined in detail for a product containing the active substance *antiarrhythmon* (see product 3 presented in section 2.3) effective against heart arrhythmias, of which the patent will expire at first on June 30th, 2007 in the USA. The originator product *Origorhyt* is marketed by *Origin Pharma S. A.* located in the UK and approved there in 1997. The new product has to enter the generic market immediately after the respective active substance expiry dates, in order to achieve maximum prices, sales and profits. Please refer to section 3.1.

The company is forced to invest in modern technical equipment, in order to keep ahead of competitors. The vacant position in the development department can be filled by a competent person as a long-term goal. The present personnel situation does not need to be changed, which also contributes to saving resources.

The production costs are to be reduced by choosing the most suitable sources of raw materials taking into account the in-house synthesis plant, which can produce substances or be released, if applicable. Additionally, the new production site in Poland can contribute to reduce production costs employing people requesting lower wages. Although, the production sites in Pharmaburg and in the USA are still booked out and experiences staff has been working there, the personnel costs have to be

reduced at least medium-term, in order to release resources for further necessary investments, especially in modern equipment.

The experts in marketing, development, production, finance and personnel are to be involved in finding appropriate solutions applying suitable decision and potential problem analyses, which provide a basis to evaluate alternatives and to substantiate the contingent problems. Additionally, suitable benchmarking to improve internal processes has to be performed.

Decision and potential problem analyses should be applied and discussed rigorously in the case of the most important issue: the introduction of a new generic product containing the active substance *antiarrhythmon* as presented above. The task has to be solved by the International Project Management group in cooperation with the development, regulatory affairs and marketing and sales departments, respectively. All involved departments must be aware of the tight timeline of 18 months for the USA and 24 months for the EU starting from January 1st, 2005, respectively. The priorities have to be defined and communicated clearly to all involved company departments.

2.5 Considerations prior to the introduction of the new product

The International Project Management Team performed further situation appraisals and market analyses prior to starting the development and introduction process of the generic *antiarrhythmon* 50 mg tablets. The estimated sales volume, the strategic fit, the patent situation, the availability of the product and the costs were considered [3].

- The originator company *Origin Pharma S. A.* achieves sales of its *antiarrhythmon* 50 mg tablets of about 300 Mio. Euro per year. The generic product is expected to develop to a niche product achieving a market share of maximally 20 % due to only few competitors (2 to 3) and due to the fact, that *antiarrhythmon* is a high price drug only used in therapeutically difficult situations. Estimating a price decrease up to 70 % of the originator's in the first year, the business case projects sales of about 252 Mio. Euro within the first 6 years, i. e. average sales of 42 Mio. Euro per year.
- The strategic fit of generic *antiarrhythmon* tablets into *GenericPharming*'s portfolio is advantageous, because this antiarrhythmic drug can be combined usefully with

the medicinal product effective against cardiovascular disorders like antihypertensive medicines and CSE inhibitors marketed by *GenericsPharming GmbH* as well.

- There are two patents held by the originator company *Origin Pharma S. A.*. *O*ne patent covers the active substance, and the other one is a galenical patent for a special microencapsulation method for the protection of the gastro-sensitive substance during the stomach passage. The substance patent will expire on June 30th, 2007 in the USA and on December 31st, 2007 in the EU, the galenical patent on July 31st, 2010 in the USA and January 31st, 2011 in the EU, respectively. Therefore, a suitable galenical formulation has to be developed, in order to circumvent this patent. The development work is carried out in the USA, because patented active substances are permitted to be investigated there (Bolar provision), which is still not possible in the EU. Please refer to chapter 3 for the description of the regulatory situations in the USA, EU as well as Japan.
- The product must be available on November 30th, 2005, in order to be submitted to the regulatory authorities then. The product should be submitted in the USA and in Finland to act as a Reference Member State in a Decentralised or Mutual Recognition Procedure involving Sweden, Norway, Denmark, Germany and the UK as Concerned Member States. A review time of 12 months is seeked, but 15 months are, at first, calculated for the USA and 18 months for the EU, respectively. Additionally, the file is intended for submission in Japan as well as in the international markets (so-called "rest of the world" – RoW) later.
- A budget of 2.5 million Euros has been provided for the development and registration of the product. If the sales of the product will develop as expected, these costs will be compensated within 1 year.

From these considerations 3 important questions are derived.

1. Is the proposed timeline realistic with respect to the proposed registration strategy?
2. Will the development work covering the galenical formulation, the analytical procedures and the bioequivalence study been done in time or should an appropriate dossier be searched for and licensed-in, in order to achieve the registration prior to patent expiry as a bridging solution?
3. What measures must be taken to launch the product as early as possible and which departments need to be involved?

In order to find an answer to the first question, the marketing authorisation procedures applied in the USA, Europe and Japan are presented in the next chapter. Chapter 4, deals with decision and potential problem analysis on licensing-in an existing dossier or the own development of a suitable tablet formulation. Issues regarding launching the product are addressed in chapter 5.

3. Regulatory Requirements for Marketing Generic Medicinal Products

3.1 General Considerations

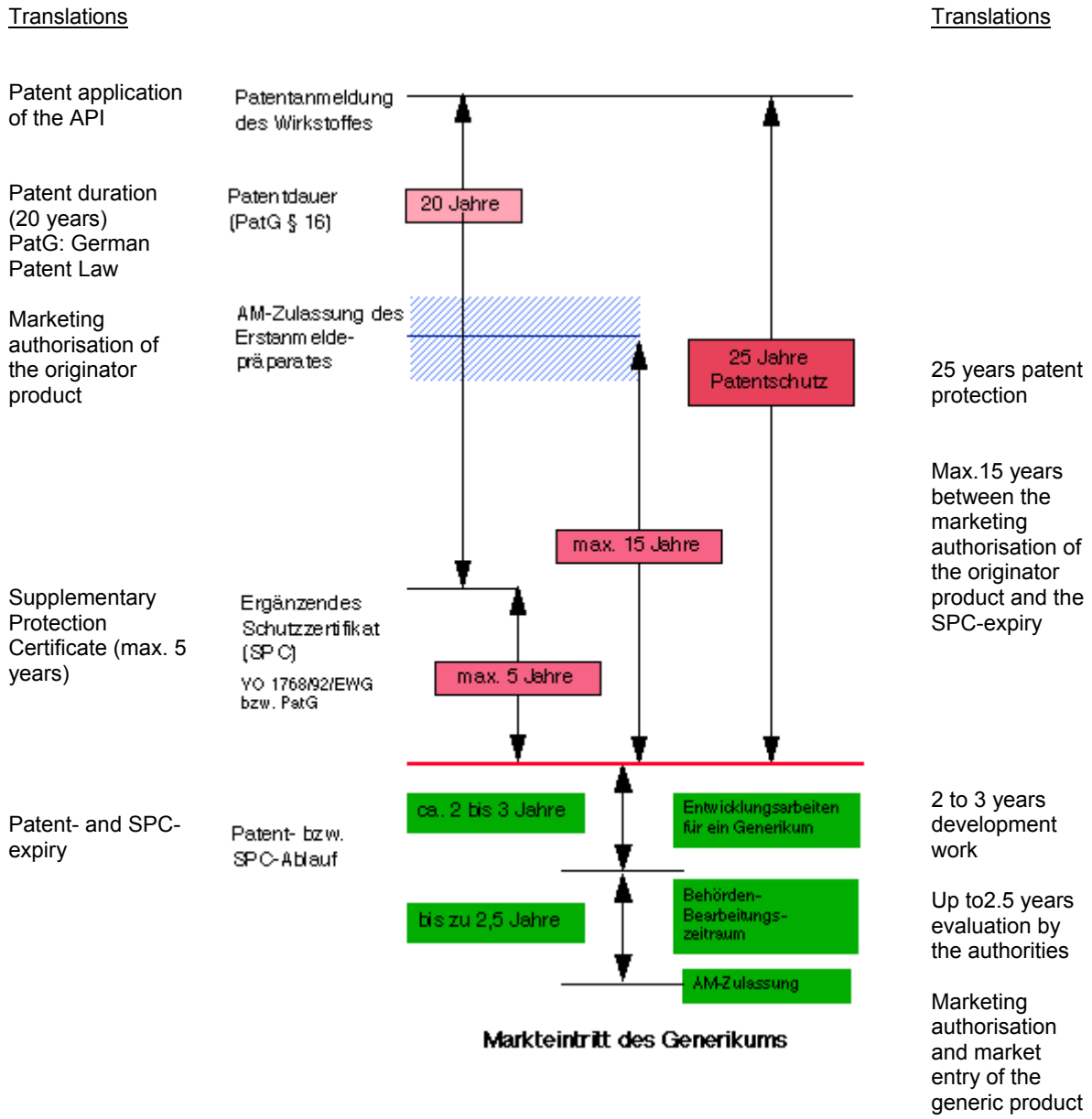
Any pharmaceutical company introducing a medicinal product containing a new chemical entity (NCE) for the very first time into the market is named the originator or, synonymously, the innovator of the respective medicinal product. Usually, the new active substance is patent protected, the galenical formulation and the manufacturing process may be as well.

A patent is a legal title, which protects a technical invention for a limited period. The patent enables its owner to exclude others from exploiting the invention in the territory, for which it has been granted [4]. It is normally valid for 20 years starting from the day of issue. According to the European Council Regulation No (EEC) 1768/92, of June 18th, 1992, the patent duration issued for medicinal products can be extended by a Supplementary Protection Certificate (SPC) for maximally 5 years, when the marketing authorisation has been granted less than 15 years ago, and the SPC has been applied for 6 months after granting the patent or the marketing authorisation, whichever is earlier. The context is illustrated in Figure 3 (modified according to [5], see overleaf).

When a patent or SPC on an active substance has expired, the active substance can be used by other pharmaceutical companies to develop and manufacture a comparable medicinal product concerning dosage strength, pharmaceutical form (galenical formulation) and bioavailability. These products are named generic products or generic drugs, because they have been generated from the corresponding originator products.

In countries with strict patent legislation, e. g. in Europe, generic companies are not allowed to perform development and clinical studies with patented active substances during the protection period. Calculating a time period of 2 to 3 years for developing a generic product and of about 2.5 years, until a marketing authorisation is granted, a generic product could be marketed only 5 to 6 years after patent or SPC expiry. Therefore, many generic companies established research and development centres in countries permitting studies with patented active substances like the USA and Canada or without any product protecting patent legislation like India or Bangladesh, respectively.

Figure 3: Protection of an originator product due to patent, supplementary protection certificate and market entry of a referring generic product



When applying for a marketing authorisation of a medicinal product containing an NCE, the originator company has to provide data on the quality, safety and efficacy by means of a so-called "stand-alone" application (full dossier). With the approval of the originator's product, the regulatory authority issues a data exclusivity period on the respective dossier preventing generic applicants to refer to it. The data exclusivity period may last from several months, e. g. for paediatric exclusivity in the USA, to 10 years for centrally authorised products in the EU, calculated from the approval date of the originator product.

After the expiry of the data exclusivity period, a generic applicant is allowed to refer to the originator's dossier, which is usually unknown to him, submitting data only on the quality of the generic product and its bioequivalence to the originator's. Hence, pre-clinical and clinical data gained by the generic applicant are not required. The marketing authorisation granted by the regulatory authority may, however, be used only after the expiries of the originator's patents. The patent issues are not ruled by the regulatory authorities, but often subjects of litigations between the originator and the generic companies. Therefore, any generic company has to take into account patent litigations when developing the product, filing the dossier and preparing the launches after approval, especially in the case of the very first generic product on the market.

Generic medicinal products are reimbursed and marketed to significantly lower prices than the originator products. These prices are ruled by the national health insurance systems and, therefore, contribute to an economic healthcare provision. Because the prices of generic medicinal products decrease rapidly after patent expiry – up to 70 % of the originators' in the first year and then up to 25 % in the following years – the corresponding manufacturers are forced to introduce as many new products as possible within tight timelines trying to reach the market entry at the date of the respective patent expiries, wherever possible.

Special medicinal products like herbal medicinal products and biopharmaceuticals are also referred to as originator products by generic applicants. At present, the stipulations for recognising essential similarity concerning these medicinal products are discussed between the regulatory authorities and the pharmaceutical industry. Please refer to the section "Macro-economic Situation in the Generic Business" at the beginning of this thesis. The current situation is summarised in the next section 3.2.

3.2 Special Generic Products

Herbal medicinal products and biopharmaceuticals are special medicinal products, for which essential similarity to an originator product has to be substantiated and justified in detail.

a) Herbal Medicinal Products

The composition of herbal medicinal products (HMP) is determined by the manufacturing process (product by process) and the quality of the herbal drug. The whole herbal drug preparation is regarded as the active substance [6, 7]. It is derived from an herbal drug, which is processed applying special extraction and formulation techniques influencing significantly the quality of the resulting finished product. Hence, these formulation factors have to be taken into consideration, when assessing essential similarity of two herbal medicinal products of comparable pharmaceutical forms and derived from the identical herbal drug.

According to the European "Points to Consider on the biopharmaceutical characterisation of herbal medicinal products" (EMEA/HMPWP/344/03) [6] two herbal medicinal products are pharmaceutically equivalent, if

- the extraction solvent is the same
- the drug:extract ratio is the same
- no differences in solubility exist (not less than 90 %)

If the herbal drug preparation contains defined constituents known to be responsible for their therapeutic activity, e. g. the anthraqinone glycosides in Senna leafs, only the identical quantity of these constituents and a drug to extract ratio comparable to the reference medicinal product are required.

In the USA, a stricter definition applies. Information on the bioavailability and pharmacokinetics of the generic herbal medicinal product are required generally. An abbreviated new drug Application (ANDA) may be submitted for an herbal medicinal product (called "botanical drug product" there), which is the same drug for the same indication as a previously approved drug product. The generic version of the previously approved drug would have to be pharmaceutically equivalent and bioequivalent to such drug [8, 9].

According to the FDA "Guidance for Industry –Botanical Drug Products" from June 2004 [9] the type of bioavailability or bioequivalence study, that is appropriate for a specific botanical drug product, is based on (1) the information on the active constituent, if known; (2) the complexity of the drug substance; and (3) the availability of analytical methods. In cases, where it is difficult or impossible to perform standard in vivo bioavailability and pharmacokinetic studies, an acute pharmacological effect as a function of time using an appropriate biological assay method can be measured. If this is not possible, the bioavailability of a botanical drug should be based on clinical effects observed in well-controlled clinical trials.

b) Biopharmaceuticals

Biopharmaceuticals are biotechnology derived proteins and peptides used as active substances [10 – 12]. Recombinant DNA- and hybridoma techniques followed by special fermentation procedures are applied during their manufacture. Hence, the manufacturing process significantly defines the quality of the resulting finished medicinal product. Considering a generic drug showing the identical sequence of amino acids, but manufactured by means of a different process as the originator's, e. g. using different expression or vector systems, production and purification processes, facility, equipment and analytical techniques, respectively, may be difficult and subjected to an individual case assessment of the regulatory authorities.

In the USA, there is no regulatory mechanism at present for the approval of generic biopharmaceuticals. However, there are economic needs to make lower cost alternatives for originator products, of which the patents will expire in the near future [13].

In the European Union the "Guideline on comparability of medicinal products containing biotechnology-derived proteins as active substance: Quality issues" (EMEA/CPMP/BWP/3207/00) [11] and the draft "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005) [12] are applicable to products, of which either the production process is changed by the manufacturer due to significant improvement measures or being claimed to be essential similar to an

originator product. A comparability exercise is required to demonstrate, that two products have similar profile in terms of quality, safety and efficacy. This conclusion has to be deduced from appropriate quality studies and supported by bridging pre-clinical and clinical studies, which depend on the nature of the active substance and formulation, the complexity of its molecular structure as well as possible differences between the originator and the generic (biosimilar) finished product and the active substances, e. g. regarding physicochemical properties, biological activity, impurities, stability and galenical aspects, respectively. The biosimilar medicinal product is not required to have the same pharmaceutical form, formulation and strength as the reference product, although this would facilitate the comparability exercise. Additionally, the biosimilar manufacturer has to demonstrate, using state-of-the-art analytical methods, that the active substance used in the comparability exercise is representative of the active substance present in the reference medicinal product. Hence, considerable effort has to be taken to substantiate the similarity of a biotechnology-derived medicinal product to a reference (originator) product.

Returning to the situation of *GenericsPharming GmbH* intending to launch the generic product *antiarrhythmon* 50 mg tablets in the USA and the EU at the respective patent expiries in the middle and at the end of 2007 is emphasised.
In the following sections 3.3 – 3.5 the different pre-conditions for approving and marketing generic products in *GenericPharming*'s main markets USA, Europe and, in the future, Japan are presented considering the definition of generic products, bioequivalence, data exclusivity periods and patent protection, applications, pricing, reimbursement and advertising. A comparison of the situations in the 3 markets is given in section 3.6.

3.3 Marketing Generics in the USA

General Requirements

A generic medicinal product must comply with the definition of pharmaceutical equivalence given in 21 CFR 320.1, in order to be approved for sale in the United States. To gain FDA approval, a generic drug must [13, 14]:

- contain the same active ingredients as the innovator drug, i. e. the same salt and ester of the same therapeutic moiety. Inactive ingredients may vary.
- be identical in strength, dosage form, and route of administration
- have the same use indications
- be bioequivalent to the originator product
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products (21 CFR 211)

Bioequivalence means according to 21 CFR 320.1 "the absence of a significant difference in the rate and extent, to which the active ingredient or the active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action, when administered at the same molar dose under similar conditions in an appropriately designed study" [15]. This means, that the same amount of active ingredient is delivered to the body at the same time and used by the body in the same way.

21 CFR 314.3 requires the originator preparation referred to in the generic application for marketing authorisation to have an effective approval under section 505(c) of the act of safety and effectiveness holding a listed drug status or may not be withdrawn from sale, for what FDA has determined reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations", the so-called "list", or any current supplement thereto, as a drug with an effective approval.

Reference listed drug means the listed drug identified by the FDA as the drug product, upon which the applicant relies in seeking approval of its generic application for marketing authorisation.

The FDA publishes and maintains the "Approved Drug Products with Therapeutic Equivalence Evaluations" as the so-called "Orange Book". Therein, therapeutically equivalent products (Category A products further subdivided into 5 categories) are listed allowed to be substituted for one another as well as products, that are not therapeutically equivalent (Category B products). Products may also be defined as "AB" indicating, that actual or potential bioequivalence problems have been resolved.

The Orange Book also serves as a basis for patent certification and litigation, as all patents held by the originator related with the FDA are listed.

Data Exclusivity and Patent Protection

Generic companies have to submit an abbreviated new drug application (ANDA) for obtaining a marketing authorisation. The Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman-Act, made generic applications possible by creating a compromise in the pharmaceutical industry. Generic companies gained greater access to the market for prescription drugs, and innovator companies gained restoration of patent life of their products lost during FDA's approval process [13, 14].

Benefits for generic companies:

- 180 days generic exclusivity for applicants submitting substantially complete ANDA's, amendments or supplements containing a paragraph IV certification for a listed patent on the same first day
- "Bolar Provision" allowing generic companies to perform studies using the originator product to perform studies required for the approval process

Benefits for the originator companies:

- ANDA's referring to a listed drug must include certifications on the status of all patents applicable to the listed drug. There are four types of certifications
    - Paragraph I – patent information has not been submitted to the FDA (via the Orange Book)
    - Paragraph II – the patent has expired
    - Paragraph III – the applicant states the date, on which the patent will expire

- Paragraph IV – the product or use patent is invalid, unenforceable or will not be infringed.

  The generic applicant has to notify this filing to the originator. The originator company is allowed to sue the generic applicant for patent infringement within 45 days from the receipt of notice. In such cases the approval of the ANDA will be delayed by the FDA up to 30 months pending resolution of the litigation. Hence, the FDA approval can only be effective, when all patents expire, the 30 months-period has elapsed or the generic applicant wins during the patent litigation.
- Supplement viii statement (for a method of use patent) – the use, for which the applicant is seeking approval, is not claimed by the method of use patent.

- Market exclusivity of up to 5 years for NDA-applications of a new chemical entity (NCE) containing study data gained for approval, 3 years for non-NDA's or supplements requiring clinical trials
- Patent Term Restoration allowing innovator companies to recover the patent time lost during the FDA approval process of up to 5 years. This patent extension must be claimed within 60 days of the NDA approval, and the total marketing exclusivity for a given drug cannot exceed 14 years.

Applications

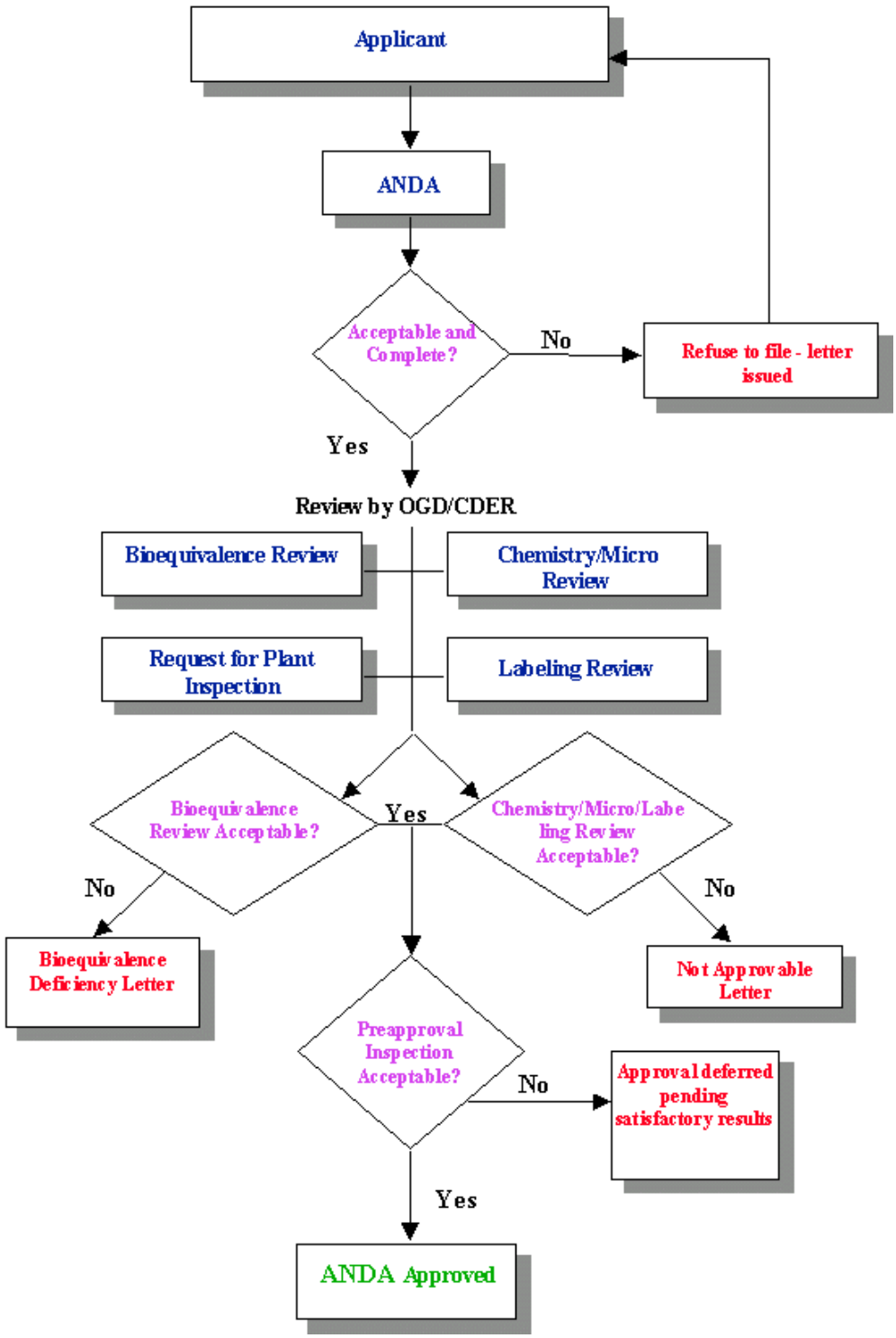
Detailed requirements for the format and content of ANDA's are given in 21 CFR 314.94 and the current version of "Guidance for Industry – Organisation of an ANDA" issued first in February 1999. The abbreviated applications are reviewed by the Office of Generic Drugs (OGD) joined to the Center of Drug Evaluation and Research (CDER). The review process is illustrated by Figure 4 [14].

At first, the ANDA has to be acceptable due to formal requirements and concerning its reference to a suitable originator product as defined in 21 CFR 314.92 and 93. Unless there is compliance, a refuse-to file letter will be issued.

The reviewers examine four areas: Bioequivalence, labelling, chemistry/microbiology and request for plant inspection. Demonstrating bioequivalence is the most important issue. The labelling must be the same as the labelling approved for the reference listed drug except for changes required by the FDA as regards quality, bioavailability, pharmacokinetics and labelling revisions. If objections are raised resolvable for the applicant an approvable letter will be issued, otherwise a not-approvable letter stating

the requirements by means of deficiency letters. If the issues have been resolved and also a satisfactory pre-approval inspection has been finalised, the approval letter is granted.

Figure 4: ANDA-Review Process performed by the Office of Generic Drugs



The review process lasts about 12 – 24 months. The marketing authorisations are valid unlimitedly. Annual reports must be provided including pharmacovigilance data. No registration fees are required for generic drugs.

Pricing, Reimbursement and Advertising

The prices of medicinal products in the US are controlled by a free-market enterprise system. The prices are set by drug manufacturers, wholesalers, and dispensers. Private market competition controls the price for drugs.
The FDA is not involved in reimbursement issues. The reimbursement policies for drug expenses in the U.S. are set by commercial health insurance companies [13, 16].

The rules and regulations for advertising are the same as for innovator products. The FDA is responsible for regulating and enforcing prescription drug and biological product advertising to the healthcare professionals as well as to the consumer (21 CFR 202). This includes advertisements found in published journals, magazines, other periodicals, and newspapers, as well as advertisements broadcast through media such as radio, television, and telephone communication systems [13].

Assessment and conclusion for *GenericsPharming*'s registration strategy in the USA

GenericsPharming GmbH intends to file an ANDA containing a paragraph IV statement, that the existing patents on the active substance antiarrhythmon and the galenical formulation of the originator product are not infringed.
180 days generic exclusivity should be achieved, if possible.

3.4 Marketing Generics in the EU and EEA

General Requirements

The regulatory position concerning generic products within the EU including the EEA[1] and also recognised by Switzerland is rather complex:

The most important legal basis for marketing medicinal products is the Directive 2001/83/EC supplemented by, among other things, the "Notice to Applicants", which is part of "The Rules Governing Medicinal Products in the European Union" published by the European Commission [20 – 25].

On May 1st, 2004 the Review of the Pharmaceutical Legislation has come into operation. The respective directives are to be transferred to the national laws of the member states until October 31st and November 20th, 2005 [25].

Generic products gaining for approval within the EU have to demonstrate essential similarity to an original/reference product authorised within the EU for not less than 6 or 10 years, respectively.

According to Chapter 1 of the Notice to Applicants, Volume 2A [20], an original medicinal product a medicinal product, that has been authorised within the EU for not less than 6 or 10 years. The marketing authorisation of this medicinal product is based on a complete dossier.

A reference medicinal product is a version of the original medicinal product, which is marketed in the EU-member-state, for which the application is made and which is used to claim essential similarity. In this member state the reference medicinal product can be authorised for less than 6/10 years. This reference medicinal product might be of another strength or pharmaceutical form or be approved for other indications or have other excipients than the original medicinal product.

A medicinal product used as a comparison for bioequivalence study, where a bioequivalence study is applicable, is a version of the original medicinal product, that is authorised within the EU. This medicinal product is normally the same as the reference medicinal product.

[1] European Economic Area: Iceland, Liechtenstein, Norway

According to article 10 of the Directive 2004/27/EC amending Directive 2001/83/EC a medicinal product is considered essential similar to an original/reference product medicinal product when satisfying the criteria of having

- the same qualitative and quantitative composition in terms of active principles/substances
- the same pharmaceutical form
- of being bioequivalent

The terms "same qualitative and quantitative composition in terms of active principles/substances" and "same pharmaceutical form" are to be understood in a broad sense [20]:

The term "same qualitative and quantitative composition in terms of active principles/substances" covers all products containing the same active substance and having the same properties with regard to safety and efficacy. Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives showing the same active therapeutic moiety are not considered as new active substances, unless they differ significantly from each other in properties regarding safety and efficacy. The applicant has to provide evidence on the same properties regarding safety and efficacy of a different salt, ester or other derivative of the same active substance. Usually, additional data showing, that there is no change of the pharmacokinetics of the moiety, the pharmacodynamics and/or the toxicity affecting the safety and efficacy are required (appendix IV of [20]).

The composition of the product with respect to excipients may vary, but may not lead to a medicinal product differing significantly from the original medicinal product as regard efficacy and safety.

The term "same pharmaceutical form" refers to the current version of the European Pharmacopoeia document "Standard Terms – Pharmaceutical dosage forms – Routes of Administration – Containers". All oral solid pharmaceutical forms for the immediate release, e. g. tablets and capsules are regarded as the "same pharmaceutical form" for the purpose of the concept of essential similarity.

The "Note for Guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98) [21] defines the terms "bioequivalence" and "bioavailability":

Bioequivalence means the bioavailabilities of two medicinal products being similar to such degree, that their effects, with respect to both safety and efficacy, is essentially the same. The medicinal products must contain the same active substance as defined above, but may vary as regard the pharmaceutical form and strength.

Bioavailability is defined as the rate and extent, to which the active substance or active moiety is absorbed from the pharmaceutical form and becomes available to the site of action. When intending to exhibit a systemic therapeutic affect, the active substance or moiety present in the general circulation is in exchange with the substance at the site of action. Hence, in a more practical sense, bioavailability can be understood as the rate and extent, to which a substance or its active moiety is delivered from the pharmaceutical form and becomes available in the general circulation.

A generic product may even be different to the one against which essential similarity is claimed as regard the pharmaceutical form, strength, route of administration or indications. In such cases, according to article 10 (a) (iii), last paragraph, of the current Directive 2001/83/EC, the applicant is allowed to submit pre-clinical and clinical data obtained from bridging studies to support his application.

Data Exclusivity and Patent Protection

At present, the data protection period may be 6 or 10 years as follows [20]. The period starts from the date of the first marketing authorisation of the product in the EU except for Switzerland (see above).

- 10 years for all medicinal products submitted through the Centralised Procedure of Regulation (EEC) No. 2309/93
- 10 years for all medicinal products approved under the former ex-concertation procedure according to Directive 87/22/EEC
- 10 years (by single decision) for other medicinal products in Belgium, Germany, France, Italy, the Netherlands, Sweden, United Kingdom and Luxembourg

- 6 years in Austria, Denmark, Finland, Ireland, Portugal, Spain, Greece, the new EU-member-states Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovakia and Slovenia and also for the EEA-states Norway and Iceland

An application for marketing authorisation of a generic product may be filed, when the data protection has expired. Evidence of the date of authorisation for more than 6/10 years should be provided in the application.

According to article 10 of Directive 2004/27/EC amending Directive 2001/83/EC the data protection will be extended to 10 years in the EU including the EEA from November 1st, 2005 [26, 27]. It can be extended for 1 year, if the innovator introduced one or more new indications within the first 8 years of these 10 years showing a significant benefit when compared with the established therapies. On the other hand, generic applications are simplified, since the generic applicant may submit his application for marketing authorisation after 8 years of these 10 years and may refer to a version of the original medicinal product as the reference medicinal product approved within the EU and not necessarily in the member state, where the application is made (so-called "EU-reference-product").

Generic manufacturers are only allowed to market their product from the expiry date of the patent and, if applicable, the supplementary protection certificate relating to the originator's original product.

Applications for marketing authorisation are generally possible, if not prevented by any data protection period as described above. However, the provision of samples may represent a patent infringement in some member states [18].

At present, there is no "Bolar Provision" like in the USA enabling to conduct studies with the patented active substance. This will be changed, when the new pharmaceutical legislation will have come into force on November 2005 [26, 27].

Applications

The format of an abridged application for a generic product under article 10 (1) (a) (iii) of the current Directive 2001/83/EC should be organised as required for the Common Technical Document (CTD) in the Notice to Applicants ,Volume 2B.

- Module 1 containing administrative data with information about the original and reference medicinal products and the medicinal product used within the bioequivalence study, the proposed Summary of Product Characteristics (SmPC),

package leaflet (PL) and labelling, information on the quality, clinical and non-clinical experts and a summary stating the reasons for claiming essential similarity

- Module 2 providing the quality overall summary and the non-clinical and clinical overviews
- Module 3 documenting the quality of the generic medicinal product as regard the active substance (European Pharmacopoeia certificate of suitability (CEP), Drug Master File (DMF)), comparison studies of the generic product with the originator preparation, e. g. dissolution and impurity profiles, information on the excipients, the primary packagings, the finished product specification at release and during shelf life and stability data according to ICH-requirements.
- Bioequivalence data provided in section 5.3.1.2 of Module 5. Separate non-clinical and clinical documentations (Modules 4 and 5, respectively) are normally not required.

When submitted nationally to the authority of the chosen European member state, the review time including answering the deficiency letters is in practice about 1 – 3 years.

When submitting another application for marketing authorisation of the same medicinal product in the name of the same applicant, this will trigger a European marketing authorisation procedure, the Mutual Recognition Procedure (MRP) according to article 5 of the Commission Communication 98/C229/03. This procedure is applicable to marketing authorisations to be granted within in a number of selected European member states (article 28 of Directive 2001/83/EC). However, this procedure can, of course, be initiated by the applicant. This is even mainly the case and suitable to apply for marketing authorisations within a number of selected European member states [22].

The European member state granting the first marketing authorisation of the medicinal product in the EU will act as Reference Member State (RMS) and provide an assessment report to the involved member-state authorities (Concerned Member States, CMS). The Concerned Member States are to evaluate the applications and to decide within 90 days to recognise the marketing authorisation granted by the RMS.

This is especially the mutual recognition of the Summary of Product Characteristics (SmPC), which is discussed intensively during the 90 days-procedure.

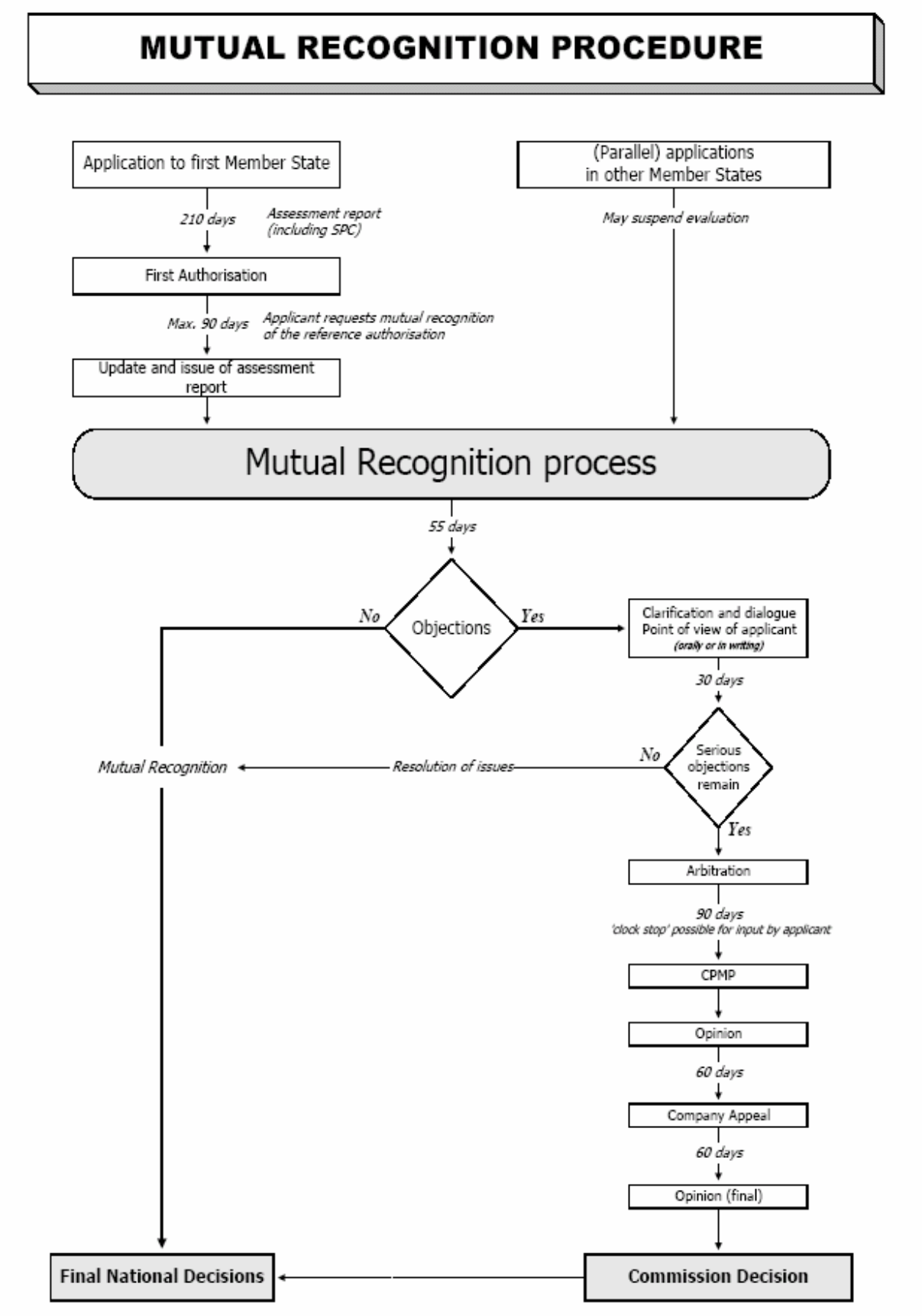
If an agreement cannot be achieved with all CMS, an arbitration procedure according to article 29 of the Directive 2001/83/EC is started followed by an oral explanation with the applicant, if necessary and a binding decision of the Committee for Human Medicinal Products (CHMP) established at the European Medicines Agency (EMEA). However, the applicant is allowed to withdraw his application for marketing authorisation from that/those CMS not prepared to recognise the marketing authorisation.
Afterwards, the applicant submits the national versions of the adapted SmPC, PL and labellings to the CMS-authorities applying for granting the national licenses. This may last another 30 – 60 days.
In total, the Mutual Recognition Procedure will lead to the licenses within 120 – 150 days adding the time for the national procedure in the RMS.
The fees to be paid depend strongly on the national legislation in the member states. For the MRP planned by *GenericsPharming GmbH* in Finland (RMS), Denmark, Germany, Norway, Sweden and the UK total fees of 57 422.71 Euro at present have to be scheduled distributed among Finland invoicing 12 800 Euro, Denmark 8581.41 Euro, Germany 15 843 Euro, Norway 4266.50 Euro, Sweden 7721 Euro and UK 8210.80 Euro.

The nationally granted licenses are valid for 5 years and are to be renewed at least 3 months before their expiries. With the renewal applications pharmacovigilance data must be provided [23].

In future legislation, there will be only 1 renewal after 5 years, after that the licenses will be valid without limitation. However, licenses granted for medicinal products not marketed within the following 3 years will be deleted (so-called "sunset-clause") [26, 27].

The Mutual Recognition Procedure is illustrated in Figure 5 [22].

Figure 5: Mutual Recognition Procedure



In article 28 of Directive 2004/27/EC amending Directive 2001/83/EC in November 2005 the Decentralised Procedure" (DCP) is introduced. This procedure is applicable, if no marketing authorisation for a medicinal product has been granted [26 – 28].

The Reference Member State chosen by the applicant is to prepare an assessment report as well as the draft-SmPC, -PL and –labellings within 120 days after the receipt of a valid application including a clock-stop of up to 3 months [28].

The CMS are to evaluate and to decide within 90 days as described above, if they recognise the assessment report and the SmPC, PL and labellings. Those CMS prepared to recognise the marketing authorisation can approve the product within 30 days after the receipt of the national versions of the SmPC, PL and the labellings from the applicant. The concerns of the CMS not prepared to grant a marketing authorisation can be discussed under the supervision of the Mutual Recognition Facilitation Group (MRFG) within another 60 days to achieve an agreement, nevertheless. The MRFG already exists in the present regulatory framework to discuss potential problems and discrepancies between the RMS, CMS and the applicants during the MRP, but does not have the legal status foreseen by the amended Directive 2001/83/EC valid from November 1st, 2005.

If an agreement can still be achieved by the CMS, the national licenses will be granted within another 30 days after the receipt of the national texts adapted by the applicant. Unless it is, the application will be forwarded for arbitration according to article 29 of the Directive 2001/83/EC.

The described finalisation of the procedure will apply to the Mutual Recognition Procedure accordingly, when the new pharmaceutical legislation will have come into force.

The Decentralised Procedure and the revised Mutual Recognition Procedure are illustrated in Figures 6 and 7 [27]. Including a clock-stop period of 3 months and a 60 days period for granting the national marketing authorisations it will last 360 days (about 12 months).

Figure 6: Decentralised Procedure according to the new pharmaceutical legislation

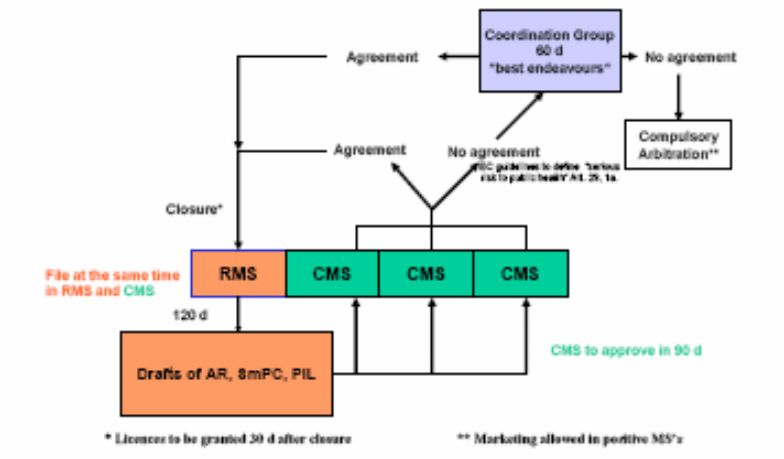
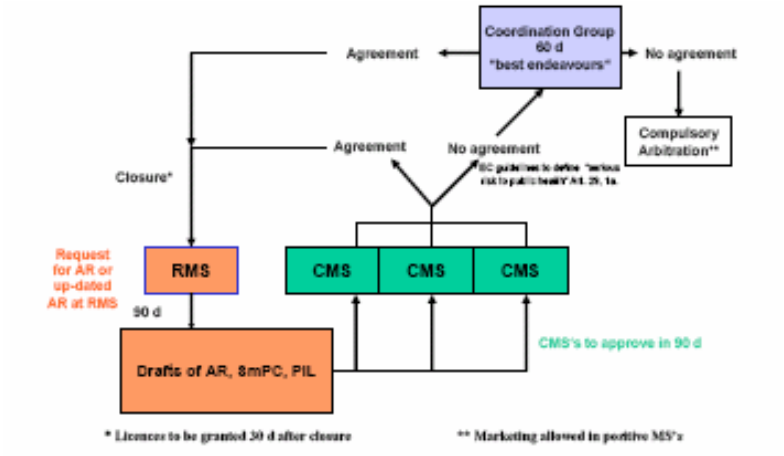


Figure 7: Mutual Recognition Procedure according to the new pharmaceutical legislation



Centralised Procedure

According to the Regulation (EEC) No. 2309/99 the centralised procedure (CP) is mandatory for new biotechnology products (Part A) and innovative products concerning the active substance(s), the pharmaceutical form, manufacturing process, indications as well as orphan drugs (Part B). An abridged application for marketing authorisation referring to a centrally approved original medicinal product has to be evaluated by means of the centralised procedure as well according to the Commission Communication 98/C229/03 [20, 24, 25].

In future legislation, according to the Regulation (EC) 726/2004 effective from November 20th, 2005, it will be mandatory for new biotechnology products, orphan drugs, and medicinal products containing an innovative active substance against AIDS, cancer, neurodegenerative disorders, diabetes and, from May 20th, 2008, autoimmune diseases and other immune deficiencies and virus diseases. An innovative medicinal product as regard the pharmaceutical form, the production process or the indication as well as generic version of an originator's product approved by means of the centralised procedure may then be also be approved by the centralised procedure, but alternatively on the national level by means of a national application, Mutual Recognition or Decentralised Procedure.

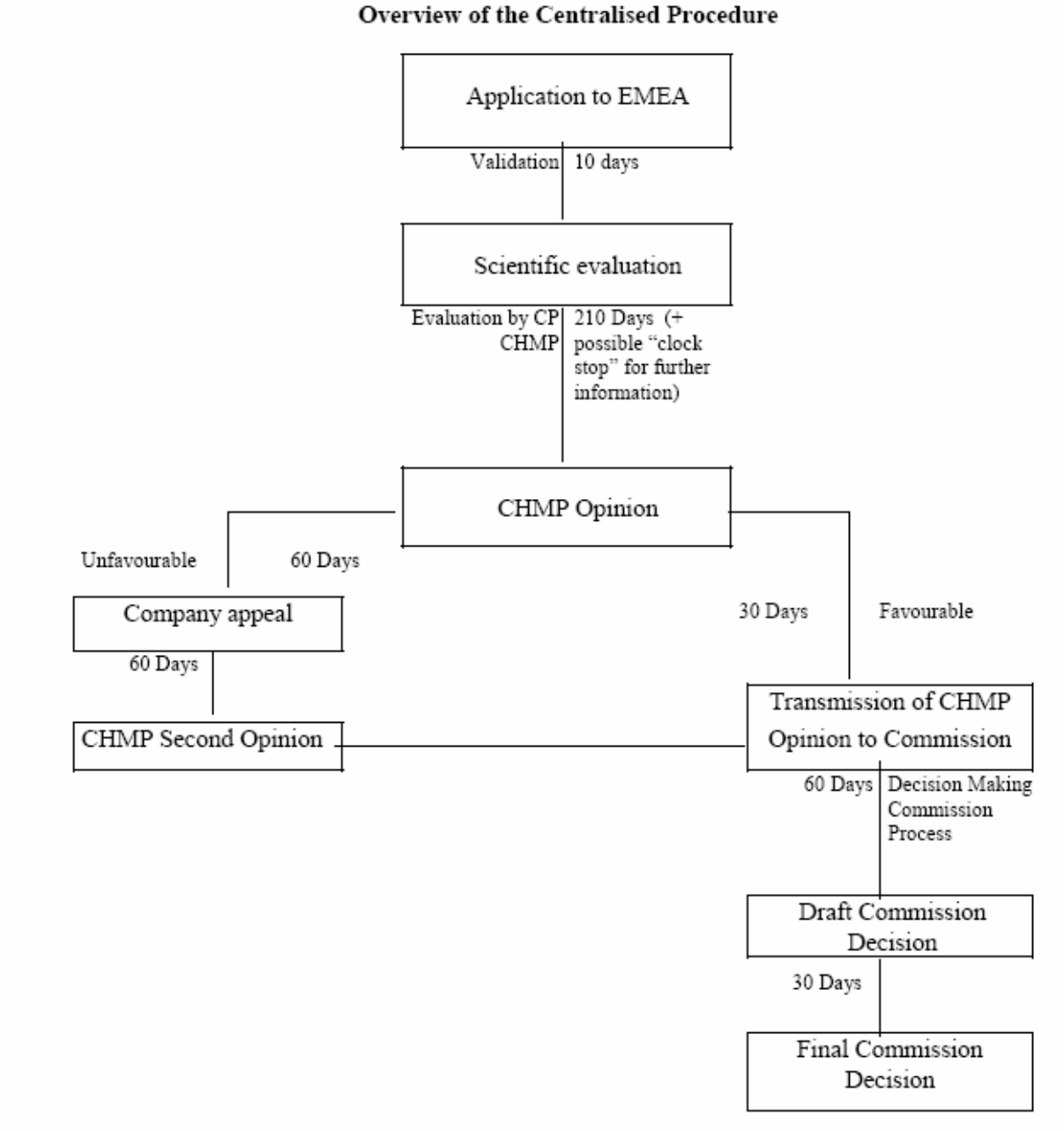
The application is made at the European Medicines Agency (EMEA) for 1 trademark and for a definite number of pack sizes. These will be valid in all 25 EU member states as well as the EEA-states Norway, Iceland and Liechtenstein.

The procedure is accompanied by a rapporteur and a co-rapporteur elected by the Committee of Human Medicinal Products (CHMP) established at the EMEA due to their scientific knowledge and experience with the product to evaluate and the applicant's favours.

The procedure is described in detail in chapter 4 of the Notice to Applicants [23]. A graphical illustration is given in Figure 8 [25] (see overleaf).

Including the clock-stops for answering the deficiency letters and clarifying further issues it lasts about 410 days. The fees are 116 000 Euro for 1 strength and pharmaceutical form as the basic application, per additional strength and form 23 200 Euro, for each additional presentation per strength and form 5 800 Euro and additionally 75 600 Euro per year after approval covering all authorised presentations. Hence, for *GenericsPharming*'s *antiarrhythmon* 50 mg tablets 116 000 Euro would have to be paid to the EMEA at the time of submission.

Figure 8: Centralised Procedure



Pricing, Reimbursement and Advertising

Pricing and reimbursement are different in each European member state.

The classification (e. g. prescription only), labellings and advertising are the same as those applied to non-generic products depending strongly on the national legislations. There is no European list or catalogue of approved generic products [19].

Assessment and conclusion for *GenericsPharming*'s registration strategy in the EU

GenericsPharming GmbH prefers to apply for a Decentralised Procedure with Finland acting as the Reference Member State and Denmark, Germany, Norway, Sweden and the UK as Concerned Member States instead of a Mutual Recognition Procedure. For the latter one, a national authorisation in Finland would be the necessary, which is followed by the Mutual Recognition Procedure taking about 150 days including the national approval phases. The 24 months time period from the expected availability of the EU-dossier in January 2006 and the substance patent expiry in the EU in December 2007 may be too short for covering the national registration, the MRP-phases and the company launches. This time frame, however, may be applicable to the Decentralised Procedure, which is available from November 2005, when the Reference Member State and the Concerned Member States evaluate the applications together taking probably about 12 months. Hence, the Decentralised Procedure is preferable to the Mutual Recognition Procedure due to shorter time frames, although there is still lack of experience with this new marketing authorisation procedure.

3.5 Marketing Generics in Japan

General Requirements

In Japan, generic medicinal products are understood according to article 14-4 of the Pharmaceutical Affairs Law (PAL) as "medicines other than new medicines" including, hence, "me-too"-products as well [29].

A new medicine is defined as a medicine, of which active ingredients, composition, administration, dosage, indication and effect are clearly different from those of already approved medicines.

In the Guidelines for Bioequivalence Study of Generic Drugs (PMSB/ELD Notification No. 786 dated May 31st, 2001), generic drugs are defined as the same type of drug as an advance drug in terms of the quantity of effective constituents, and dosage and administration.

According to the "Guideline for Bioequivalence Studies of Generic Products for Topical Use" (July 2004) bioavailability has been defined as the rate and extent of absorption of parent drugs or active metabolites from a dosage form into the active site.

Bioequivalent products are those drug products having the same bioavailabilities. The acceptable range of bioequivalence is generally 0.8 – 1.25 for the test/reference ratio of average values, when the parameters are logarithmically transformed. These requirements are comparable to those set in the USA and the EU [15, 21].

Data Exclusivity and Patent Protection

The term of data exclusivity is not defined clearly in the Pharmaceutical Affairs Law and other regulations in Japan. Although it is considered as an independent intellectual property right, detailed stipulations are not given. The market exclusivity of products containing new active substances is 6 years at present [29].

Moreover, the granting of a patent provides the patentee with the rights to exploit commercially the invention. However, the patents do not provide any protection of the underlying data and no protection for the data generated in preclinical and clinical research as well. However, the generic applicant has to submit information, whether substantial patents exist with respect to the active substance. If so, additional information is required showing, that the manufacture/import of the medicinal product is possible without delay after its approval (PAB/PCD Notification No. 762 from

October 1994). There is no "Bolar Provision" permitting studies using the patented active substance [29].

Hence, generic manufacturers are recommended to orientate themselves to the respective patent expiry dates when filing their applications.

Applications

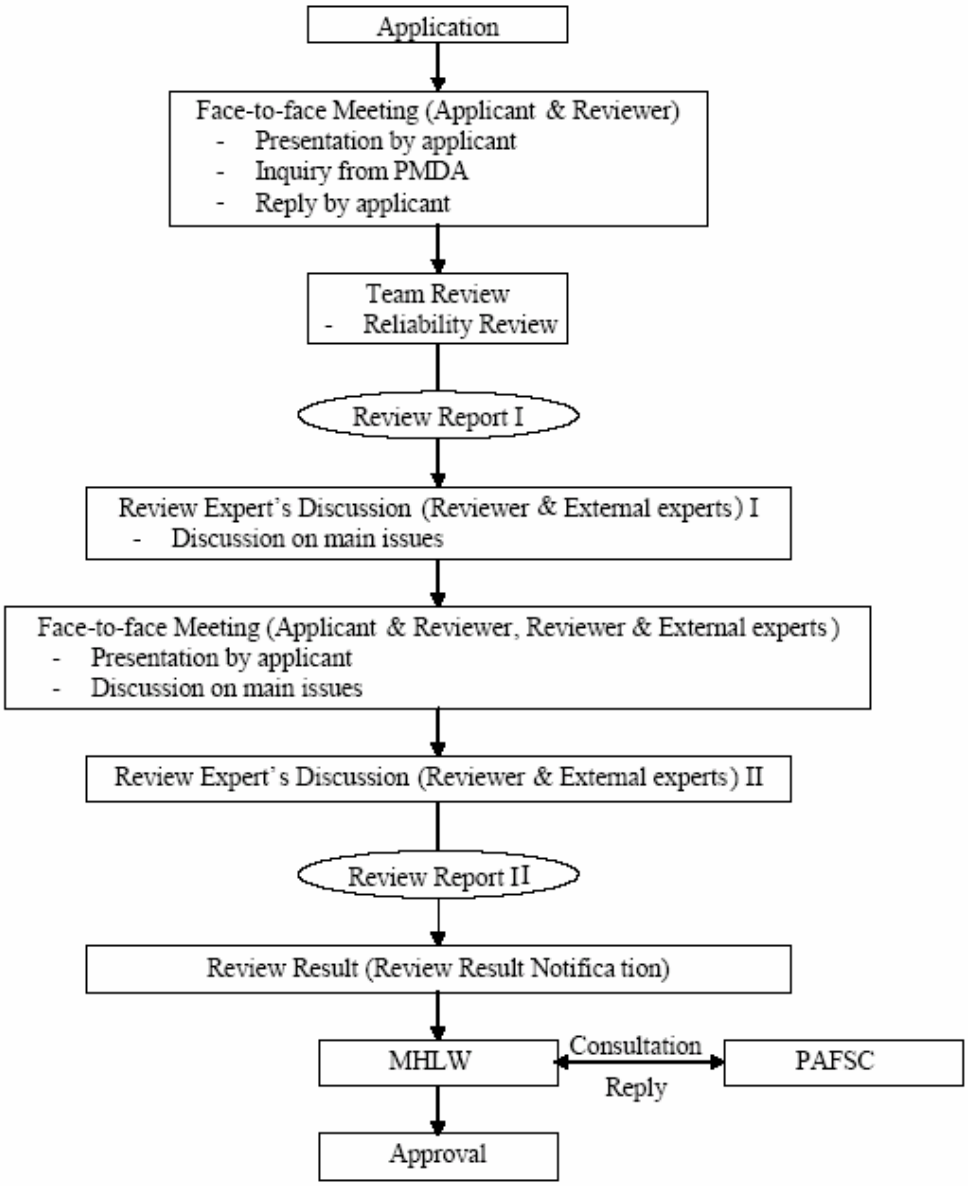
With generic applications data and information on the pharmaceutical quality, especially the specifications and test methods, stability studies and the bioequivalence must be provided [29 – 31]. Information about the quality of the active substance is accepted as a Drug Master File. The documentation can be submitted in the CTD-format in English language. However, the overviews and summaries arranged in Module 2 are to be provided in Japanese language corresponding to the former outline of data to be provided called "Gayio" [31].

The generic applications are reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA) including oral explanations, in Japanese language, about the objections raised by the experts of the authority as well as external ones. The results of the experts' review of the submitted documents and data are reported to the Ministry of Health, Labour and Welfare (MHLW) granting approval and licenses for manufacturing and import following positive reporting and consultation of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC). The process is illustrated graphically by Figure 9 [30].

The approval is valid 4 – 10 years as per the period of re-examination requiring also pharmacovigilance data, the duration of validity of the manufacturing and import licenses is 3 years granted for each application [32]. The registration fees required for the approval of generic products to be reviewed by the PMDA are at present up to 415 200 Yen (3030.96 Euro) and, additionally for the manufacturing/import licenses 206 800 Yen (1509.64 Euro) payable to the PMDA and 22 300 Yen (162.79 Euro) payable to the MHLW, respectively [33].

The standard review period for submission is 12 months which is notified by Notification PMSB No. 327 dated on March 28, 2000. The hearing is held within 6 months after application resulting in more than 100 questions and instructions. This set of time expects an applicant to reply to inquiries within 1 and 2 years as maximum. In case of a longer time to respond to the inquiries an applicant shall withdraw a submission [30].

Figure 9: Review process performed by PMDA



MHLW: Ministry of Health, Labour and Welfare
PAFSC: Pharmaceutical Affairs and Food Sanitation Council

Pricing, Reimbursement and Advertising

Generic products are taken up in the National Health Insurance price list once a year. Corresponding pricing applications have to be addressed to the Economic Affairs Division of the MHLW granting the prices and publishing them in the Official Gazette [34].

The basic rules for the advertisement of medicinal products in Japan are postulated in the Chapter VIII of the Pharmaceutical Affairs Law (PAL): The claims in advertisement should not be exaggerated, the advertisements for prescription medicines can be placed only on media accessible for the health professionals [35].

Assessment and conclusion for *GenericsPharming*'s registration strategy in Japan

An application for marketing authorisation of antiarrhythmon 50 mg tablets in Japan will be filed according to the regulations in force apply. It will be submitted in due course, since the Japanese market is no key market for *GenericsPharming GmbH* at the moment.

3.6 Comparison of the marketing requirements in the USA, EU and Japan

The requirements for marketing medicinal products in the USA, EU (including Iceland, Liechtenstein, Norway as well as Switzerland) and Japan are summarised in Table 2.

Table 2: Comparison of the requirements for marketing medicinal products in the USA, EU and Japan

Item	USA	EU	Japan
Criteria for generic drugs	Approval as an generic drugs when	Claiming essential similarity to an original/reference product, when satisfying to have	Generic drugs are defined as the same type of drug as an advance drug in terms of the
	• contain the same active ingredients as the innovator drug, i. e. the same salt and ester of the same therapeutic moiety. Inactive ingredients may vary.	• the same qualitative and quantitative composition in terms of active principles/ substances	• quantity of effective constituents
	• be identical in strength, dosage form, and route of administration • have the same use indications	• the same pharma-ceutical form	• dosage and administration
	• be bioequivalent to the originator product • meet the same batch requirements for identity, strength, purity, and quality	• of being bio-equivalent *(same composition and pharmaceutical form to be understood in a broad sense)*	• bioequivalence
Bioequivalence	The absence of a significant difference in the rate and extent, to which the active ingredient or the active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action, when administered at the same molar dose under similar conditions in an appropriately designed study.	Bioavailabilities of two medicinal products being similar to such degree, that their effects, with respect to both safety and efficacy, is essentially the same. The medicinal products must contain the same active substance as defined above, but may vary as regard the pharmaceutical form and strength.	Bioequivalent products are those drug products having the same bioavailabilities varying within a defined range.

Table 2 *(continued)*

Item	USA	EU	Japan
Data protection	5 years	6 – 10 years From Nov. 2005: 10 years + 1 year for an additional indication, submission of applications after the first 8 years	Not defined. Marketing exclusivity of 6 years for new active substances
Bolar provision	Yes	No , from Nov. 2005: Yes	No
Authority	FDA (CDER, Office of Generic Drugs)	EMEA and national authorities	PMDA enclosed to the MHLW
Application	ANDA, CTD format accepted	CTD format mandatory from 01.04.2005	NDA, CTD format accepted
Review time	12 -24 months	1 – 3 years depending on the procedure	2 – 3 years
Validity of the marketing authorisation	Unlimited, annual reports to be provided including pharmacovigilance data	To be renewed all 5 years including pharmacovigilance data, annual reports for products authorised by the centralised procedure, from Nov. 2005 still one renewal after 5 years, then unlimited validity	Approvals: 4 – 10 years as per the re-examination period requiring pharma-covigilance data Licenses: 3 years
Registration fees	No fees required for generic drugs	Centralised Procedure: 1 strength and pharm. Form (basic): 116 000 €, per additional strength and form: 23 200 €, each additional presentation per strength and form: 5 800 €, Annual fee: 75 600 € for all authorised presentations MRP, DCP, national applications: Depending on national regulations	Approval of generic product: 415 200 Yen Manufacturing/Import licenses: To PMDA: 206 800 Yen To MHLW: 22 300 Yen

Assessment and conclusions:

Drawing a comparison registering generic drugs in the USA seems to be simplest since there is only 1 single authority to cooperate with, there is Bolar provision established, the data protection period is comparably low (5 years), and the review times are reliably within 12 – 24 months.

Referring to the submission of the application for marketing authorisation of *antiarrhythmon* 50 mg tablets in the USA as the first of the planned applications (see section 1.5) is useful as regard the market size and realistic as regards the timeline.

In Europe, the definition of generic products is wider than in the USA as well as Japan, and there are several possibilities to address the member states, either all by the Centralised Procedure or selectively by means of a Mutual Recognition, Decentralised or national procedure, if applicable. Additionally, the future legislation (Review 2004 coming fully into operation in November 2005) will bring further advantages for generic product manufacturers like Bolar provision, EU reference product and only one renewal 5 years after granting the marketing authorisation. The Decentralised Procedure is expected to shorten the review times within a selected number of European member states significantly to about 12 months.

In Japan, the national stipulations for filing generic applications for marketing authorisation have to be followed orientation to the originator's patent expiry dates as a pre-condition to market the generic product after approval. When compared with the systems established in the USA and the EU, the conditions are less transparent and flexible. Further clarification may be expected in the future.

4. Decision and Potential Problem Analyses on the Development Strategy

4.1 Decision Analysis

Decision analyses support the responsible managers in assessing the alternatives to achieve defined objectives and finding substantiated solutions [1]. In optimisation models optimum solutions are searched for using mathematical methods. Heuristic models are used to find "acceptable solution" out of a high number of alternatives, e. g. the places for building a new production plant. Resources and time are saved by reducing the number of considered items, e. g. building the plant only in bigger towns offering better traffic connections. Therefore, heuristic models are suitable to deal with more complex problem situations.
However, in the discussed context of development and registration of a new generic product, only a distinct number of items is to be considered. From these items, the optimum alternative is to be found out, and, therefore, the optimisation models are used.

There are 4 optimisation models relevant in marketing [1]:

1. the differential calculation. The maxima and minima of an exactly formulated problem function, e. g. the profit resulting from the price, are calculated.
2. the mathematical programming. A target variable is optimised by applying explicitly defined restrictions, e. g. the profit as a function of advertisement and distribution measures, limited and modified by explicit restrictions, e. g. the limited budget of advertisement.
3. the statistical decision theory. An appropriate number of clearly defined action alternatives, their consequences and their statistical probabilities are considered and their statistical expected values calculated. The alternative showing the maximum expected value is chosen.
4. the playing theory. Similar to the statistical decision theory an appropriate number of action alternatives is considered. However, not the maximum expected value, but the maximum avoidable loss is tried to find out assuming, that the involved competitors act carefully, because they cannot anticipate in total, how the other competitor will behave.

As the most advantageous strategy for developing and marketing *antiarrhythmon* 50 mg tablets, the statistical decision theory is chosen, because it enables to find out the most favourable alternative from differentiated considerations of the clearly defined alternatives, which will be presented in the following. Due to this reason, the playing theory is not applicable, because it focuses on the possible, but generally unknown, but estimated behaviour of the competitors. In order to apply the differential calculations and mathematical programming models, the alternatives would have to be described as mathematical function, which is not applicable in this context.

The 3 alternatives to be considered are

- in-house keeping
- out-sourcing, co-development and
- licensing-in

of the capacities for the development, registration and marketing of the new product.
As presented in section 2.1, the company aims to use and develop substantiated know-how on the products, technologies and regulatory affairs. Therefore already, as much information as possible should be kept in-house. However, useful out-sourcing, co-development or licensing-in of the product dossier and its manufacture contribute to reduce the costs appropriately.

The decision criteria to be defined can be differed in "must"-criteria (M), which need to be fulfilled and "want"-criteria (W), which can be fulfilled according to the company goals.

a) Criteria

The following product related criteria are to be applied.

- active substance, pharmaceutical form
- bioequivalence study
- production

All these items are must-criteria (M), since they must comply with the patent situation and current regulatory requirements like pharmacopoeial monographs, bioequivalence guidelines and GMP directives, respectively.

The regulatory part is represented by

- Regulatory resources (W)
- Applications, maintenance (M)
- Pharmacovigilance (M)

The applications are to be filed as required by the guidance given by the FDA and the EU authorities, and the regulatory fees are necessary to be paid. Their height depends on the marketing authorisation procedure chosen according to the marketing strategy. The maintenance of the following marketing authorisations and the pharmacovigilance and monitoring measures are to be performed. Hence, these items are to be addressed as "must"-criteria (M). The regulatory capacities to solve them, in-house, out-sourced or those of the license partner, are "want"-criteria (W), respectively.

As marketing issues

- markets (USA, EU, later Japan as well as RoW – "rest of the world")
- distribution
- timing
- budget

are to be considered. These items are all "want"-criteria (W) according to the marketing goals of the company.

b) Importance of the criteria

The importance I of the criteria is assessed by means of a score of 1 to10. High importance is addressed to values of 7 to 10, medium one to 4 to 6 and low importance to 1 to 3.

The access to the markets of the USA, the EU (Finland, Denmark, Germany, Norway, Sweden, UK) and Japan and RoW later on is considered as most important criterion at all (value 10). To achieve this access at the expiry date of the active substance enable entering the generic market at first and, therefore, promises maximum profit (value 9). The costs should be kept as low as possible, but the necessary investments must be taken (8).

The quality and availability of the active substance must be guaranteed and a galenical solution to circumvent the respective originator patent must be found (7). The formulation must be demonstrated to be bioequivalent to the originator preparation organised by a suitable Clinical Research Organisation (CRO) (6) and produced and controlled observing the current state of science and technology including the GMP requirements (5). Although, the production and quality control can be realised by the company sites, contract manufacturing may be advantageous.
The distribution in the USA and the EU is performed by the subsidiary companies. For Japan and the RoW markets, appropriate co-distributors can be ordered (4).
The own regulatory capacities (3) are able to file the dossier and the necessary applications and perform the maintenance of the intended marketing authorisations (2) enabling also to keep the important product information in-house. These considerations also apply for the pharmacovigilance and monitoring issues (1). Nevertheless, filing the dossier and making the applications externally may reduce the costs significantly.

c) Decision analysis table

The above mentioned considerations result in the following decision analysis table (Table 3).

Table 3: Decision analysis table

Criteria Must (M), Wants (W)	Importance I (low: 1 – 3, medium: 4 – 6, high: 7– 10)	Alternatives and ranking (R)					
		in-house		out-sourcing, co-develop-ment		licensing in	
Product		**R**	**I·R**	**R**	**I·R**	**R**	**I·R**
Active substance, pharmaceutical form (M)	7	3	21	2	14	1	7
Bioequivalence study (M)	6	1	6	3	18	2	12
Production, quality control (M)	5	2	10	3	15	1	5
Subtotal Product			**37**		**47**		**24**
Regulatory							
Regulatory resources (W)	3	3	9	2	6	1	3
Applications, maintenance (M)	2	2	4	3	6	1	2
Pharmacovigilance (M)	1	2	2	3	3	1	1
Subtotal Regulatory			**15**		**15**		**6**
Marketing							
Markets (W)	10	3	30	2	20	1	10
Distribution (W)	4	3	12	2	8	1	4
Timing (W)	9	3	27	2	18	1	9
Budget (W)	8	3	24	2	16	1	8
Subtotal Marketing			**93**		**62**		**31**
Total			**145**		**124**		**61**

Based on the total weighted scores (i. e. overall sums), the activities should be kept preferably in-house meeting the initially mentioned company goals. Out-sourcing and co-development is a considerable alternative, especially as regards the bioequivalence study, but no convincing one. Licensing-in is clearly no alternative.

However, when observing the subtotals of the 3 categories product, regulatory and marketing, the advantage of keeping the activities in-house is only clear for the marketing of the new product. The regulatory activities can be out-sourced with a comparable risk/benefit ratio and the product can even be developed and produced more effectively, when co-developed or produced by a contract manufacturer, respectively. When taking away the bioequivalence study, which is to be performed necessarily by a CRO, there is a slight advantage of the development and production in-house (31) when compared to co-development and out-sourcing (29). Therefore,

developing and producing the product in-house remains the first recommendation. As already presented in section 2.5, the development and bioequivalence investigations can, at present, only be performed in the USA and Canada (only bioequivalence studies), permitting investigations on patented active substances (Bolar provision).

Maintaining the regulatory activities in-house is not less effective than out-sourcing, but has the advantage of holding the knowledge about the product within the company. Therefore, the regulatory activities should be kept in-house as well.

Assessment and conclusions

The decision analysis clearly suggests keeping the product-related, regulatory and marketing activities preferably in-house. If applicable, another decision analysis should be taken for the out-sourcing of the bioequivalence study to a suitable and reliable CRO.

4.2 Potential Problem Analysis

When transferring the decision of developing, filing the registration dossier and applications and marketing the new medicinal product *antiarrhythmon* 50 mg tablets in-house, exact implementation steps and timelines have to be defined considering the patent situation and the necessary internal preparation and approval processes. The International Project Management group developed a state action plan addressing the following items:

- Provide the necessary amounts of the active substance with required quality
- Galenical and analytical development, stability testing
- Investigational Medicinal Products, bioequivalence study
- Filing technical data package, bioequivalence study report
- Filing technical dossier and applications
- Submission to the FDA
- Submission to the EU authorities
- Review and approval in the USA
- Review and approval in the EU
- Preparations of the product launches

In combination with these potential problems have to be anticipated and assessed. These are raised mainly from external sources, namely the active substance supplier, the CRO and finally the regulatory authorities. The internally caused problems like failure of the development work and extension of the scheduled timelines are not considered. In these cases, which are of high seriousness, the whole project organisation must be reviewed. On the other hand, they are implied to be less probable due to the knowledge and experience of the involved departments. Additionally, the proposed steps and timelines are to be approved by the involved departments, supply chain, development, regulatory affairs and project/launch management, respectively, in order to guarantee its feasibility from the company point of view. The priority of this project has to be defined and confirmed by the General Management and communicated to all involved departments of the company.

The approved state action plan is presented in Table 4 together with the anticipated potential problems. The actions are to be started from January 1st, 2005.

Table 4: State action plan and anticipated potential problems

State Action Plan: Development and Registration of *antiarrhythmon* 50 mg tablets			Anticipated potential problems
Action	*Responsibility*	*Deadline*	
Provide the necessary amounts of the active substance with required quality	Supply Chain, Project Management	21.01.2005	Required amounts not available
Galenical and analytical development, stability testing	Development Department	15.11.2005	
Investigational Medicinal Products, Bioequivalence study	Production, Development department, CRO	31.10.2005	No bioequivalence demonstrated with the new formulation for patent circum-vention
Filing technical data package, bioequivalence study report	Development department, CRO	15.11.2005	Extension of the timeline by the CRO
Filing technical dossier and applications	Regulatory Affairs department	15.12.2005	
Submission to the FDA	Regulatory Affairs department	19.12.2005	
Submission to the EU authorities	Regulatory Affairs department	02.01.2005 (appointment up to 6 months before, when performing a DCP)	
Start of launch preparations	Project Management	02.01.2007 (USA) 31.03.2007 (EU)	
Approval in the USA	FDA	31.03.2007	Extension of the review time
Approval in the EU	National authorities	30.09.2007	Extension of the review time
Product launches at patent expiry dates	Project Management	30.06.2007 (USA) 31.12.2007 (EU)	

The assessment of the anticipated problems and possible measures to minimise the risk are shown in Table 5.

Table 5: Assessment of the anticipated potential problems and counteractive measures

Anticipated potential problem	Probability	Seriousness	Counteractive Measures
Required amounts of active substance not available	low	high	Close contact with the supplier, switching to synthesis in-house
Bioequivalence not demonstrated with the formulation for patent circumvention	low	high	Conscious product development and planning of the study, involvement of the CRO in time
Extension of the timeline to file the bioequivalence study report by the CRO	low	medium	Conscious time and capacity planning
Extension of the review time by the FDA	medium	high	Accept risk, postpone the launch, appropriate advertising
Extension of the review time by the EU authorities	medium	high	Accept risk, postpone the launch, appropriate advertising

The anticipated potential problems regarding the availability of the active substance and the performance and finalisation of the bioequivalence study are, of course, of high and medium seriousness, respectively, but of low probability, because they can be avoided by conscious planning and involvement of the corresponding partners in time. Switching the synthesis of the active substance to the synthesis plant in Pharmaburg, when the Bolar provision will be in force apply also in Europe from November 2005, should be taken into account.

The probability, that the review times will be extended by the FDA and the EU authorities is of at least medium probability due to the tight time planning and of high seriousness, since a delayed market entry after the patent expiry will reduce the achievable sales and profits significantly. Nevertheless, this risk has to be accepted and the launch postponed accordingly, but all efforts should be taken to avoid this case by defining clear internal priorities and appropriate negotiations with the authorities in due course. Since the product is implied to develop to a niche product, however, a high number of competitors is not expected and an appropriate advertising may help to reduce the risk of less sales.

Assessment and Conclusions

The potential problems analysis substantiates the risk of extending the review times by the regulatory authorities caused by the tight time planning. Although it should be avoided, it can be considered as justified because the product is implied to develop to a niche product with a less number of competitors. Nevertheless, the internal priorities should be set clearly directed to keep the delay as short as possible.

5. Launch Preparations

When the marketing authorisations will have been granted, the product should be launched in the corresponding markets immediately, this means at the patent expiry dates, if achievable. These tasks will be fulfilled by special launch mangers in the International Project Management group. The country launch phases and the involved departments of the company are summarised in Table 6 [3].

Table 6: Country launch phases and involved company departments

Launch phase	Involved company departments
Logistic preparations, Setting up the launch team	Logistics, Planning, Supply Chain Project Management
↓	
Checking the launch pre-requisites, commitment of the headquarter in Pharmaburg and the subsidiary organisations to launch the product	Project Management, headquarter in Pharmaburg, subsidiary organisations
↓	
Preparation of country specific packaging, Preparation of supply-chain- and QA-setup, Preparation of operational IT-system	Packaging, regulatory affairs Supply Chain, QA/QC IT
↓	
Entering the first orders of the subsidiary organisations, Arrangement of the production, packaging, QA-release and the shipment of the first orders	Project Management, Planning Production, QA/QC, Logistics, Supply Chain

The time planning for the launch phases is 3 to 6 months starting at least 3 months before the expected grants of the marketing authorisations. This is in line with the time schedule for the introduction of *antiarrhythmon* 50 mg tablets presented in section 4.2 considering a preparation time of 6 months prior to the approvals.

6. Summary and Conclusions

The collected information on the economic and regulatory issues influencing the introduction of a new generic product containing a still patented active substance and the derived conclusions and recommendations are summarised as follows.

The generic company *GenericsPharming GmbH* located in Pharmaburg/Germany was introduced facing the problems of reducing sales due to an insufficient product portfolio, the increasing competitive pressure and the increasing production costs. The situation appraisal illustrated the problems in detail and created a basis to formulate suitable counteractive measures.

Due to the situation appraisal, introducing new products to increase the product portfolio was recognised most necessary. This was described in detail exemplifying the development and registration of a generic tablet formulation containing 50 mg of the patented antiarrhythmic drug *antiarrhythmon* in the USA until the patent expiry date, which will be June 30th, 2007 and in the EU December 31st, 2007, respectively. Although, the product will probably develop as a niche product, it fits advantageously to *GenericPharming*'s portfolio, while only being by few competitors. The development, regulatory affairs and marketing and sales department must cooperate and be coordinated efficiently by the International Project Management group for achieving this goal, which is to be reached within in the tight time schedule of 18 to 24 months, respectively.

The marketing authorisation procedures applicable to the USA, the EU and Japan were presented setting an important time frame for planning the marketing activities of a new generic product. These are most transparent in the USA facing one competent authority.
Within the EU, marketing generic products will be simplified further, when the new pharmaceutical legislation will come fully into force in November 2005. One example is the Decentralised Procedure enabling to grant marketing authorisations by selected European member states shortening the review times significantly. Therefore, this procedure is recommended for *GenericsPharming* to use for registering its new product in Europe.

In Japan, more detailed requirements for generic products will have to be defined, in order to create more transparent and flexible conditions.
The regulatory affairs department is to observe any further changes of the regulatory requirements and to evaluate opportunities for the company on an ongoing basis. Therefore, it should be involved already in the early steps of the product development and monitor each product over the entire life cycle, especially in the market introduction process.

Performing the development and registration activities as well as the marketing in-house was analysed convincingly by means of a decision analysis. The potential problem analysis identified the tight timelines for gaining the approvals of the regulatory authorities as the most critical, but still acceptable risks. These can be minimised by comprehensive and detailed development and registration work and complete and anticipating launch preparations coordinated effectively by the International Project Management group.

In summary, differentiated situation appraisals, decision analyses and potential problem analyses enable to balance the regulatory and economic aspects appropriately by substantiated decisions and actions. These are the more important, the more competitive the markets are.
Substantiated decisions and effective cooperation between all involved company departments and, last but not least, high product quality, are necessary to pass future challenges.

7. References

[1] P. Kotler, F. Bliemel, Marketing-Management, 10th edition 2001, Schäffer-Poeschel, Stuttgart

[2] Jopp & Wilkens, Königstein/Taunus, Operational Management Techniques, hand-outs during Module 12 "Decision Analytics" of the German Society's for Regulatory Affairs (DGRA) education "Master of Drug Regulatory Affairs", University of Bonn, September10th/11th, 2004

[3] Sandoz GmbH, Professional Management Training, hand-outs during the course held in Vienna, February 2nd – 4th, 2005

[4] German Generics Association (http://www.generika.de), March 30th, 2005

[5] European Patent Office (http://www.european-patent-office.org), April 10th, 2005

[6] Points to Consider on the Biopharmaceutical Characterisation of Herbal Medicinal Products (EMEA/HMPWP/344/03), July 2003

[7] Guideline "Good Substitution Practice" of the German Pharmaceutical Society (DPhG), March 2002

[8] IDRAC-database (http://www.idrac.com), Explanatory text "How to Market Herbal Products – Botanical Drug Products" (United States), June 2004

[9] Guidance for Industry –Botanical Drug Products, June 2004

[10] W. Kreis, G. Baron, G. Stoll, Biotechnologie der Arzneistoffe, Deutscher Apotheker Verlag, Stuttgart 2001

[11] Guideline on Comparability of Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Quality Issues (EMEA/CPMP/BWP/3207/00), December 2003

[12] Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005), March 2005

[13] IDRAC-database (http://www.idrac.com), Explanatory text "How to Market Generics" (United States), June 2004

[14] Homepage of the Office of Generic Drugs of the FDA, http://fda.gov/cder/ogd, April 10th, 2005

[15] Guidance for Industry, Bioavailability and Bioequivalence, Studies for Orally Administered Drug Products — General Considerations

[16] IDRAC-database (http://www.idrac.com), Explanatory text "Fees (United States)", August 2004

[17] IDRAC-database (http://www.idrac.com), Explanatory text "Pricing and Reimbursement (United States)", June 2004

[18] IDRAC-database (http://www.idrac.com), Explanatory text "Advertising/ Promotion (United States)", June 2004

[19] IDRAC-database (http://www.idrac.com), Explanatory text "How to Market Generics" (European Union), March 2005

[20] Notice to Applicants, Volume 2A, chapter 1, Marketing Authorisation, February 2004

[21] Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)

[22] Notice to Applicants, Volume 2A, chapter 2, Mutual Recognition, June 2004

[23] Notice to Applicants, Volume 2C, A Guideline on the Processing of Renewals in the Mutual Recognition Procedure, March 2000

[24] Notice to Applicants, Volume 2A, chapter 4, Centralised Procedure, December 2002

[25] IDRAC-database (http://www.idrac.com), Explanatory text "Marketing Authorisation Procedures (European Union) / European Centralised Procedure" (European Union), April 2005

[26] IDRAC-database (http://www.idrac.com), Explanatory text "New Pharmaceutical Legislation (European Union)", April 2005

[27] B. Kintzel, Review of the Pharmaceutical Legislation ("Review 2001"), Presentation held at the DGRA-education, Module 9 "International Registration", University of Bonn, 23./24.01.2004

[28] Mutual Recognition Facilitation Group (MRFG), Decentralised Procedure Member States Standard Operating Procedure (draft), March 2005

[29] IDRAC-database (http://www.idrac.com), Explanatory text "How to Market Generics" (Japan), January 2005

[30] IDRAC-database (http://www.idrac.com), Explanatory text "Marketing Authorisation Procedures (Japan) / Procedure for Initial Application" (Japan), July 2004

[31] B. Fiedler, International Registration Procedures: Japan, Presentation held at the German Society's for Regulatory Affairs (DGRA) education, Module 9 "International Registration", University of Bonn, February 2004

[32] IDRAC-database (http://www.idrac.com), Explanatory text "Marketing Authorisation Procedures (Japan) / Procedure for Renewal", September 2004

[33] IDRAC-database (http://www.idrac.com), Explanatory text "Fees (Japan)", April 2004

[34] IDRAC-database (http://www.idrac.com), Explanatory text "Pricing and Reimbursement (Japan)", January 2005

[35] IDRAC-database (http://www.idrac.com), Explanatory text "Advertising/ Promotion (Japan)", February 2005