Generic medicinal product portfolio from a regulatory and Business Development point of view

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EXECUTIVE SUMMARY

The portfolio of medicinal products forms the basis for the potential financial achievements of a pharmaceutical company. The addition of the most promising new products as well as an intelligent maintenance of existing products require the right decisions - in commercial as well as technical terms – to be made. In fact, technical and commercial issues actually can not be separated from each other.

Each step of the complete life cycle of a medicinal product, starting from the very first idea until the product is not profitable any longer, calls for the involvement of Regulatory Affairs. Therefore, all data relevant to the registration of a product are handled by the Regulatory Affairs team, causing it to represent the interface to almost all other departments of a pharmaceutical company, which in turn provides the privilege of a respective product overview.

Likewise, the initiation of a pharmaceutical development program or in-licensing of a product or sourcing existing products from alternative manufacturers or out- licensing or even withdrawing non-profitable products all represent business decisions, which will have to be put into practice by the Regulatory Affairs team.

Thus, it becomes evident that profound mutual implications exist between Business Development and Regulatory Affairs undertakings. Business strategies have to thoroughly consider the technical and administrative consequences, clearly necessitating the advice of the Regulatory Affairs team. Baring in mind the financial consequences of for instance a delayed approval or a rejected renewal application, regulatory performances obviously evenly affect the work of the Business Development team, which in both cases would have to in-license such medicinal product.

Hence, pharmaceutical business enjoys direct commercial benefit of a competent and effective Regulatory Affairs department.

ABBREVIATIONS

API:	Active Pharmaceutical Ingredient
BD:	Business Development
BE:	Bioequivalence
CHMP:	Committee for Medicinal Products for Human Use
CMS:	Concerned Member State
COMP:	Committee of Orphan Medicinal Products
CP:	Centralised Procedure
DP:	Decentralised Procedure
DI:	Drug Information
EEC:	European Economic Community
EFTA:	European Free Trade Area
EMEA:	Europen Medicines Agency
EU:	European Union
FDA:	Food and Drug Administration
FDF:	Finished Dosage Form
GMP:	Good Manufacturing Practice
MRP:	Mutual Recognition Procedure
MA:	Marketing Authorisation
MAH:	Marketing Authorisation Holder
NCE:	New Chemical Entity
NtA:	Notice to Applicants
OTC:	Over the Counter
PIL:	Patient Information Leaflet
PM:	Product Management
PSUR:	Periodic Safety Update Report
RA:	Regulatory Affairs
RMS:	Reference Member State
SmPC:	Summary of Product Characteristics
SPC:	Supplementary Protection Certificate
SOP:	Standard Operating Procedure
SPC:	Supplementary Protection Certificate
USP:	Unique Selling Proposition

1 INTRODUCTION

This Master thesis shall examine the factors relevant for managing a portfolio of generic medicinal products.

For any pharmaceutical company a good in-flow of new medicinal products is vital for its economic future. Likewise, to improve the cost-effectiveness of existing products and to lay off products that are no longer profitable will evenly affect each company's financial success.

Managing a portfolio of medicinal products essentially requires commercial understanding as well as a strong background in regulatory affairs since any decision regarding medicinal products will have business and regulatory implications at the same time.

Be it in-licensing, out-licensing or taking additional manufacturers on board, every such issue needs to be evenly considered from a regulatory and business perspective.

The thesis shall be structured as follows: at first, the general tasks when managing a portfolio of generic products and the different options for accessing the market will be presented.

An in-depth discussion of the criteria to be applied onto a portfolio of generic products, including the regulatory and commercial implications of the forthcoming new pharmaceutical legislation in EU, will follow.

Further in the spirit of a guide through the different aspects affecting licensing activities, the importance of high-quality cooperation partners, in particular with a view to manufacturers, is considered by reviewing the decisive criteria from a regulatory and business perspective.

For a proper decision analysis, actually all these criteria would have to be weighed against each other. In order not to extent the frame of this master thesis, the respective significance of the various aspects will not be subject to precise calculations. However, whenever a certain criterion is deemed as being essential, such will be clearly mentioned.

On the purpose of illustrating the practical meaning of the above, the practice of in-licensing will be exemplarily discussed in more detail. A special focus on a fast and efficient decision

process shall lead to a proposal for a coordinated flow of information and work between the involved departments.

It has to be mentioned that licensing activities in the originator industry additionally encompass the huge field of pre-clinical and clinical studies. In particular in early stage drug development, the risk of failure is quite high since the risk/benefit ratio of the future medicinal product could hardly be predicted. Thereby, licensing decisions concerning innovative drugs commonly have even bigger financial consequences (as compared to "generic licensing"), since the costs for e.g. phase III study programs could easily sum up to as much as 400 million Euro (and more).

However, this thesis will primarily focus on perspective of the generic industry, though many aspects to be covered would have similar implications for the business of originator companies, too.

1.1 Management of a generic product portfolio

Portfolio analysis by means of a matrix (originally developed by the Boston Consulting Group), which displays the respective market share and growth rate of different therapeutic fields in general or existing products may serve as a decision tool to identify

- gaps in the product range (e.g. unserved market needs)
- where to invest (e.g. in further marketing activities) to increase market share ("stars")
- where cost savings would cause a profound increase in profitability (e.g. products with a high market share, but no or little further growth rates; "cash cows")
- products with little market share and little or even declining growth rates ("poor dogs"), which should probably better be out-licensed into more profitable markets.

Products with a high growth potential, but little market share („question marks") represent the forth segment within a portfolio analysis. Typically, products develop via "question mark" to "star", to "cash cow" until the stage of "poor dog" is reached. However, in the generic business, a thorough market analysis should help to avoid the "question mark" period.

1.1.1 Sourcing and contracting of new products

Partly related to the competition strategies described by Michael Porter (1980), three types of generic products are usually of interest for in-licensing:

- "Big" products. Due to their outstanding sales figures, they are the ones which almost literally every generic company is looking for. Thereby, lots of competition is to be expected, meaning a tough fight for the highest ever possible market share. The quantity and reputation of the respective sales force, strongly supported by high numbers of free samples, as well as the general expenditure on marketing are most decisive.

- Niche products. The above is contrasted by a different concept, which assumes little or no generic competition subsequent to the exclusivity expiry of originator products with comparatively small sales figures. In such case, the single generic company picking up that business, will enjoy a much higher market share (for the particular product), i.e., make profit by being the only one.

- Distinguished products. Such products are actually derived from "big" products, but in order to allow differentiation within the tough competition to be expected, these products boast "Unique selling propositions" (USPs). Such could be simply tablets with a score

line, allowing precise breakability or a more advantageous pharmaceutical form, e.g. an effervescent tablet instead of a regular tablet, etc..

1.1.2 Cost optimisation of existing products

In the generic pharmaceutical industry, the costs of goods are primarily driven by the cost of production, be it for the API or finished dosage form. Due to expanding Asian companies, which are offering medicinal products at very competitive prices, cost optimisation gains increasingly more importance. The desire to spend less money on e.g. production is to be carefully balanced against the need to maintain product quality at a high level. Moreover, such cheaper sources at first sight, i.e. low cost Indian or Chinese companies, need to be calculated including additionally necessary EU batch release and higher transportation costs. Besides, the different language and culture may also cause further problems, in particular when it comes to trouble shooting. In any case, all additional manufacturers will cause extra regulatory costs to include them in the registration dossier. The latter will bind money, time and significant regulatory capacity, which often does not form part of some CEO's considerations, when suggesting to switch production to low cost sources.

1.1.3 Out-licensing of non-profitable existing products

Even with sophisticated strategies in cost optimisation of existing products, at times certain older products within the portfolio will begin to loose market share, causing them to become less profitable. Reasons include out dated therapeutic principles or worsened risk benefit ratios (e.g. through formerly unknown adverse effects) or successful efforts by competitors to increase their market share at the costs of others. Similarly, regulatory authorities might extend their requirements, thereby bringing up new and cost intensive problems, or an altered portfolio strategy might be directed by the managing board. However, further out-licensing issues will not be discussed in depth.

1.2 How to access the market?

1.2.1 Development and registration

Depending on each generic company's individual capacities, the following represent the general strategic options for the development of medicinal products:

- In-house development. Requires availability of full equipment for production and analytical testing as well as the accordingly trained staff to operate these machines. Provided that such capacity is exists, it brings the enormous advantage of being independent and enjoying full control of product quality and its documentation. Further, by applying for more than the marketing authorisation(s) needed for own purposes, in-house development allows to sell the product and related documentation also to others.

  However, it is to be mentioned that the possibility to perform full in-house development might be disadvantageous when aiming at in-licensing products from other development companies. The potential to perform competing in-house development might cause the prospective partner to be hesitant to sign a contract, due to the risk that he might not actually be able to sell his product cost intensively developed, should the in-house development be preferred in the end.

- "Virtual" development. Shall be understood as guiding of and cooperating with an external company, which is physically performing the development steps. Such guidance does not actually require in house production and testing facilities, but clearly high level technical and regulatory expertise. A strong standing is necessary in particular when the contracted development company has different (most likely less costly) views on how to produce or test the product in question. Also one needs to be aware that there is a potential risk of training the cooperation partner until sufficient independent know how has been built up. Such has been experienced by a number of European companies dealing with the "black sheeps" of pharmaceutical companies in China, where the European partners found themselves left alone after having transferred their expertise.

- External development. The development company is more or less independent in terms of production and analytical testing and might simply provide raw data. Such documents would need to be compiled by the marketing company in order to create an adequate registration file thereof.

  The commercial purpose of the cooperation partner needs to be questioned. Why is he not applying for a MA by himself? Is it just a lack of expertise and/or capacity? Is there little or no sales force? When such cooperation is planned, the sharing of respective risk needs to be given good thoughts. In order to sell as much of his product as possible, the manufacturer probably would like to see as many marketing authorisations as achievable.

This brings up the question of how to limit competition. As every competitor is free to apply (with the registration file from the same source) at whatever authority, the most promising regulatory strategy needs to be well considered.

Concerning all above development options, the Regulatory Affairs department is playing a major role, since in any case the registration documentation needs to be generated. Taking it further, guidance of applying the adequate methods and tests as well as strategic input is required. The latter often includes recommendations from a technical and regulatory perspective based on the experience made with different potential development partners, which truly helps to avoid weakening business by contracting the wrong manufacturers.

1.2.2 Purchase of granted marketing authorisation/licence

This approach would normally only be followed in case of an urgent need of a certain product, often resulting in an expensive price to be paid. Further, it actually means being too late, otherwise the company would have shown interest in the product at a much earlier stage. With competitors being already on the market, it will be very difficult to build up a profitable market share. However, as the MA has already been granted, there is at least no risk of failing to achieve the desired licence.

For products authorised via MRP, a complex situation may occur, when a spare CMS licence is still available, but not the corresponding RMS MA. When it comes to variations, the different MAH's are likely to have divergent views about how the product/documentation should be modified. Who will coordinate the variations, e.g. the inclusion of specific additional batch releasing sites? What about costs for variations not asked for? In practice, also the process of creating PSUR's (comprising all data available) might be difficult to organise for by those MAH's which are not in the possession of the RMS licence.

1.2.3 Early entry in agreement with originator company

An originator company that agrees to an early generic entry into the market, resulting in a corresponding loss of the originator's market share, will charge a very high price for its consent. The generic company should carefully explore the originator's interests. For instance, there might be a technical problem with the product or a shortage in the related API or the products might already have lost market share over the previous years.

However, could a generic company afford the deal with the originator, it probably has the advantage of an established quality and might even build up a fruitful relationship (with co-marketing or co-promotion for other products to follow?).

Again, once the Business Development team has closed the deal, it is for the Regulatory Affairs team to put things into practice. In case of an early entry, most often the MA in form of a spare licence of the originator needs to be transferred to the generic company.

2 PORTFOLIO CRITERIA

2.1 Essential criteria

Each medicinal product of interest to the generic industry needs to fulfil all of the following mandatory criteria, otherwise it will not be worth investing the money. At the same time, all of these criteria have strong regulatory implications.

2.1.1 Quality

The term quality is to be understood not only for the product itself, but also refers to the documentation going along with it. A high quality product with a well presented documentation will substantially reduce time to approval, but will of course have to be paid for. Also at an earlier step, the probability of a successful BE-study raises significantly in case of a high product quality (e.g. by reducing inter-individual diversity). For instance would flawless stability data help to reduce storing and transportation costs, in particular if there is even no sensitivity towards light or moisture. Lastly, high quality products will cause less problems in multinational procedures such as MRP or DP, simply since the involved authorities will have one potentially critical issue less to discuss.

However, the question might be worth asking what had to be done to reach such high level of quality. Is the product difficult to produce or to test (causing it to be more expensive)?

2.1.2 Time to market

Ensuring to enter into the market straight after the original product has lost its exclusivity is vital for a generic company, as usually the first weeks or even days determine the major part of the achievable market share. Time to market is not only much affected by the product quality, but also depends substantially on the chosen regulatory strategy. Where has the registration file been submitted and when? In case a national registration in a certain Member State is the goal, will it be better to submit direct or to submit in another EU Member State and to perform a MRP subsequently, once the RMS MA has been achieved? Similarly, the internal capacity available and, in case of external development, the capacity of the manufacturer is crucial. How long will it take to reply to deficiency letters (generate new required data, answer the questions properly)? An external development allows less control and discussions might come up, if all requested extra investigations have to be performed

indeed (with whom to pay for ?) or whether an alternative, more theoretical, literature based approach could be made in order to sufficiently answer the questions risen.

2.1.3 Patent situation

Nowadays, the patent situation gets more and more critical and, if patents are handled properly, allows to make extra profit or at least to avoid loosing money. Originator companies claim increasingly more patents to keep generic competitors off the market. Also in this respect the technical expertise of the RA team will prove especially useful, since surely the employees with a pure economic background will have their difficulties in assessing complex patents.

When searching for feasible ways to circumvent certain formulation or process patents, some generic companies even start to claim their own patents. Thereby, the perhaps only way to get around the originator's patent will also be blocked and the claiming generic company ensures competitors cannot enter the market. Therefore, the patent legislation in the market of interest as well as specific claims around the product in focus need to be evaluated very carefully, be it through an in-house expert or with the help of a cooperation partner. Baring in mind that the outcome of related costly court cases is often uncertain, some generic companies might decide not to take that risk and prefer to be fast followers.

2.1.4 Bioequivalence studies

In-acceptance of BE studies recurrently contributes to the failure of applications for marketing authorisations. As outlined above, the product quality is of significant influence, but also the country and its population chosen might affect the outcome of the BE study. Depending on the race, the pharmacokinetics might vary to a significant extent, and in case of a drug sensitive in this respect, it might be more difficult to compare the original product against the generic test product.

Further typical issues of financial as well as regulatory relevance include the selection and number of volunteers or whether a waiver is claimable. How many strengths need to be investigated? Are there metabolites possible and/or to be measured? Moreover, the chosen study design (e.g. fast and/or fed conditions, duration of study, number of samples taken) and the subsequent analytical testing strongly affect costs and outcome of a BE study.

2.1.5 Costs

For the sake of completeness, costs as such shall be discussed briefly. How much is to be spent on a product depends mostly on how badly the product is wanted and also on the internal capacity as well as expertise available. What are the alternatives (if any)? Is there a certain form of exclusivity granted? Is the product difficult to produce and/or to test? Did the negotiations yield a fair sharing of risk and profit?
Of course short term as well as long term costs will have to be considered evenly. At the end of the day, the limiting factor often might be as simple as "how much can the company currently afford"? As pointed out above, a good regulatory team will help to spend money on the right projects and to avoid unnecessary costs.

Major concerns related to any of the items listed under 2.1.1 – 2.1.5 will definitely result in a negative decision towards the medicinal product offered.

2.2 Other important criteria

The following criteria are comparatively less crucial, but still to be carefully considered:

2.2.1 Gaps in existing portfolio – market need

Market need and gaps in the existing portfolio need to be thoroughly balanced against each other. It might well be that the class of a certain product once looked for is now assigned a worse risk-benefit ratio, in particular in the light of better alternatives available by now. In short: the product in question might be new to the portfolio, but it has to be evaluated if the market (still) would need (more of) it. Also, it is to be considered whether the product on offer constitutes a new therapeutic area or a new therapeutic class or whether it is for instance the fifth ACE-inhibitor? Likewise, it has to be estimated if a market extension is possible or even likely and if yes, to what extent, since such would strongly affect the market share of a generic company.
At times there is more to it than just closing a gap within the portfolio, as a drug might simply be expected to be in the range of products of every generic company. ASS might serve as an example for such drug, where it would be odd for a generic company not to offer it. In those cases, little profitability might be acceptable, considering almost all competitors are probably selling such medicinal product.

Nowadays in Germany, with statutory health insurance funds (so called "Krankenkassen") partly starting to sign contracts with pharmaceutical companies, there might be a further reason build up a full range portfolio.

2.2.2 Competitors and their strategy

When estimating its future market share for a certain medicinal product, a generic company needs to find out how many competitors are to be expected. Do they already have a similar product? Will the product in question match their strategy? Similarly, the generic company should know if the sales force of the competitor visits the "right physicians" for this specific product. Do they have the contacts and will they be able to afford an early entry into the generic market? Such will usually cause the (remaining) market to be significantly smaller compared to the situation if all competitors enter into the market more or less at the same time, usually straight after the originator's exclusivity expiration.

2.2.3 Strategic partnerships

Does the potential deal around the product of interest constitute the opportunity to initiate a long term partnership? At times, alliances start off with a small project of comparatively little profitability for a generic company, but the partner might feel he is "owing a favour", e.g. when the question of exclusivity comes up for a subsequent, bigger product. However, it remains open whether the potential partner will indeed consider this.
Further, other products of interests are to be evaluated in order to find out if there is potential for a synergy. Obviously, a strategic cooperation between an API manufacturer and a generic company producing finished dosage forms might prove very lucrative for both parties. When thinking about strategic partnerships, soft factors such as the respective reputation or a common/different culture and language should be taken into account, too.

2.2.4 Product baskets

Within the commercial field, it is common to receive a kind of "bulk discount" if more than one product will be acquired at once; the same goes for the generic industry. A way to raise manufacturer's expectations for future series of products could be to offer a combination of existing and new products, i.e. the manufacturer might produce some of the old products and on top new products out of his pipeline.

2.2.5 Unique selling propositions

As outlined under 1.1.1, generic companies are regularly looking for products with distinct extras to allow differentiation within the tough generic market. Especially for such USPs, the question of exclusivity is of great financial importance, as a USP will only make sense if not every competitor will be able to offer it. Such has of course to be balanced against the higher price to be paid for an exclusive USP. Beforehand, it should be always calculated whether the USP will actually be acknowledged by the market, as otherwise the whole investment would have been wasted.

2.2.6 Long term therapy

From the perspective of the pharmaceutical industry, treatment of chronic illnesses secures long term sales with every single patient being prescribed that particular medicinal product. In terms of volume and sales, it is beneficial for a company if a certain drug needs to be administered repeatedly during the day. However, the latter is contrasted by a reduced compliance of the patient, who would always prefer to administer his medicine just once daily (if not to be avoided completely). The latter causes him to be prone for a more "comfortable" treatment.

Lastly, also the duration of the therapeutic effect needs to be considered. In case it is likely to diminish over time, the patient will be prescribed a different drug (possibly marketed by a competitor).

2.2.7 Fit with existing portfolio

For each portfolio candidate, it needs to be evaluated whether it would match the company's reputation or whether it might contrast its philosophy. For instance life style products would hardly match a generic company of high ethical standards.

Another aspect reflecting the existing portfolio are the physician groups already visited by the sales force. Especially with a relatively broad portfolio, no generic company could afford to include all different kinds of medical doctors in its "to visit" list. Hence, it is worthwhile to consider whether a new medicinal product justifies visiting a completely new group of physicians. Further, it is questionable if a) the sales representatives will be able to reliably asses the specific market and b) if the physicians in question will acknowledge these sales

representatives as reputable and sufficiently qualified or if they simply feel they are about to be sold just "anything". These considerations are even more important in case a pharmaceutical company decides strategically to commence marketing medicinal products for exclusive use in hospitals.

2.2.8 "Unique" opportunities

At times, unexpected opportunities arise for a pharmaceutical company, offering the prospect of an extraordinary attractive deal. In such cases two major aspects are decisive whether or not the company could secure this chance: a) is there enough money available to be spent? b) Will the company be able to grasp the opportunity by acting flexible and rapidly enough? Otherwise, a competitor with a superior timing will take full advantage of the situation and make the deal.

In section 3 the role of the different departments involved in such decision processes is exemplarily analysed and consequently, a proposal for a fast and efficient process is made.

2.2.9 Manufacturers involved

Different offers for medicinal products usually represent different manufacturers. Referring to the essential criteria outlined earlier on, this will have vast impacts on e.g. the product quality, the time lines, costs, etc. Moreover, it has to be distinguished between EU and non-EU manufacturers, not only in terms of distances or differences in language and culture, but also regarding additional certifications needed or additional EU batch releasing sites required. These topics will be discussed in more detail in chapter 2.5.

For the majority of the aforementioned issues, the RA department may contribute greatly to making the right decisions as it will not only be able to appraise different alternatives technically (e.g. product quality, BE studies or eligibility of manufacturers), but also strategically (regulatory tactics with a view to time to market) as well as financially (e.g. multinational authority fees plus internal costs associated with variations).

2.3 Implications of the new pharmaceutical legislation in EU

As a result of the former Council Regulation 2309/93, which foresaw a general report on the experience made with the procedures laid down therein, the entire European regulation of pharmaceutical products had been reviewed. Reflecting the results of this "Review 2001", two legal documents have been agreed upon: Council Regulation (EC) 726/2004 which will replace Council Regulation 2309/93 and Directive 2004/27/EC which shall amend Directive 2001/83/EC.

This revised pharmaceutical legislation in the EU, most which will come into force in autumn 2005, will bring substantial changes to the whole pharmaceutical industry in Europe. The most significant issues from the point of view of generic companies are presented and discussed in the following.

2.3.1 Data exclusivity

Data exclusivity on the pharmacological/toxicological and clinical data of the originator company means that within Europe, no authority will accept generic applications making reference to these safety and efficacy data. Hence, in addition to the patent protection, the originator effectively enjoys market exclusivity until the data exclusivity period expires plus the time needed to register and place the generic medicinal product on the market.

Replacing the former set of laws, where in some European member states a data exclusivity period of 6 years (e.g., Austria, Denmark, Finland or Spain) and in others one of 10 years (e.g., France, Germany, Italy or Great Britain) exists, a new harmonised concept has been set up. For the sake of completeness, it should be mentioned that until November 2005, a common 10 year period is also granted for originator products having gained their MA through the centralised procedure (CP, for details see under 2.3.8.2).

For MA's granted after the new legislation will have come into force, a data exclusivity period of 8 years will be apply in all EU Member States. Thereafter, the originator company will be protected by a further period of 2 years of market exclusivity. Nonetheless, generic applications can already be submitted, assessed and even approved therein. Moreover, also pricing and reimbursement negotiations can be hold and finalised.

A further extension of one additional year of market exclusivity is foreseen, if the originator obtained approval for one ore more new indications during the first eight years. The latter provision may only be used once per group of related marketing authorisations (i.e., the same API coming in different pharmaceutical forms). Furthermore, explicit clinical studies investigating the potential new indications must have been conducted, demonstrating a significant clinical benefit compared to existing therapeutic options. However, it is deemed quite likely that generic companies, which could not (yet) claim the new indication could profit indirectly from the new indication granted to the originator company by means of off label use. Once a physician has understood that a certain drug could also be used for the new indication, he is very prone to use the medicinal product to treat the new indication even if such is not listed in the generic SmPC.

With respect to the prospective nature of the above provisions, the first generic applications under this "8 + 2 + 1 year" formula, which will be independent of the route of authorisation, will not take place before late 2013.

However, in comparison to the previous 6 or 10 years data exclusivity periods (with ca. 9 and 13 years of effective market exclusivity), generic companies will then only be allowed to submit their applications 2 years later in the former 6 year countries, but 2 years earlier in the previous 10 year countries. Hence, generic companies will be able to initiate the registration process after eight years and even commence manufacturing. The positive or negative effects of these changes obviously depend on the markets served by the respective generic company. It is tempting to speculate that some generic companies might reconsider their market strategy accordingly and turn to former 10 year countries, additionally supported by the greater size of these markets. Such approach would mean that the submission strategy would directly reflect the market strategy.

The revised legislation also provides one year of data exclusivity for a switch of "prescription only" classification to "over the counter" status, if supported by sufficient new (pre-)clinical data. This of course may affect a generic approach, e.g. for company which does not market OTC products and consequently does not employ a sales force addressing pharmacies. Here, significant investments would need to be made to finance such a strategic change.

Contrastingly, no data exclusivity will be granted for line extensions to approved medicinal products. Thereby, the originator company cannot extend its market protection period by

trying to gain MA's for amended or derived versions of an already marketed product. Any additional strength, pharmaceutical form, administration route or variation to the original product will belong to the same "global marketing authorisation".

Lastly, one non-cumulative year of data exclusivity will also be awarded for a new indication for medicinal products with proven well established use[1], provided the new indication is evidenced by significant pre-clinical or clinical studies.

Generic companies having had a bibliographical application on their minds by claiming "well established use" themselves will therefore have to exclude the new indication from their application file. This in turn might cause the necessity of a time and cost binding Type II variation, should the new indication be claimed, too.

2.3.2 European reference product

In article 10 of the Directive, the following has been laid down: *"…if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted… the applicant shall indicate in the application the name of the Member State in which the medicinal product is or has been authorised."* Thereby, generic applications will be permitted to refer to medicinal products (having been) authorised some time in any EU Member State.

Taken together with the concept of a "global marketing authorisation" this revised legislation will have significant impacts on generic registration options. It will overcome the almost "classic" originator strategy to lengthen their market monopoly by at first trying to gain exclusivity for line extensions and later to withdraw the product from the least profitable markets to prevent generic competition.

[1]According to Article 10(1)(a)(ii) of Dir. 2001/83/EC as amended, results of (pre-)clinical tests may be replaced by detailed references to published scientific literature if it can be demonstrated that the constituent(s) of a medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety for a specific therapeutic use. This concept refers to medicinal products, where there is no reference product to which essential similarity can be claimed. A systematic and documented use for more 10 years within the European Community (administration to a sufficient number of patients) and on-going scientific interest, with a coherent scientific assessment (as reflected in the published literature) is to be demonstrated.

2.3.3 Bolar provision

The so called "Bolar-(Roche)[2]" provision permits performance (in the EU) of all activities needed to compile a registration dossier and to have the application assessed and approved during the patent protection period: *"conducting the necessary tests and trials with a view to the application…and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates…".*

In practice, all of the following will in future not be considered as patent infringing anymore:

- development, manufacture and import of starting materials and API
- production of FDF validation batches
- BE studies
- pre-clinical tests and clinical trials (as bridging data)
- compilation of the registration file
- application for and granting of MA
- submission of samples (of intermediates, API, impurities, FDF)

The above actually reduces patent infringing activities to the production of commercial batches ("stock piling"). This may affect the selection of cooperation partners, since as of the time the new pharmaceutical legislation will have been implemented EU wide, generic companies will no longer have to turn to cooperation partners in "(EU) patent free" countries.

[2]In 1984, Roche Products, Inc. vs Bolar Pharmaceutical Co., Inc. case came to court. A few months before Roche's patent for Flurazepam HCl went off-patent, Bolar undertook studies in support of an MAA to the FDA. Roche sued Bolar for patent infringement. The District Court for the Eastern District of New York held that no infringement had occurred, because of the de minimis and experimental nature of Bolar's use of flurazepam HCl (Roche Products, Inc v Bolar Pharmaceuticals Co., No. CV 83-4312, US District Court for the Eastern District of New York, 572 F. Supp. 255; 1983 US Dist. LEXIS 12799, 13 October 1983). However, the Court of Appeals for the Federal Circuit reversed this decision, holding that the use of a patented pharmaceutical to test a generic version for FDA approval could not be considered as an experimental use and, therefore, constituted a patent infringement (Roche Products, Inc. vs Bolar Pharmaceutical Co., Appeal No. 84-560, US Court of Appeals for the Federal Circuit, 733 F.2d 858; 1984 US App. LEXIS 15006; 221 USP.Q. (BNA) 937, 23 April 1984, Decided (certiorari denied by the Supreme Court of the US, 469 US 856)). This meant that testing for the purpose of FDA approval could not take place before the expiration date of the patent. Still in 1984, in response to Roche vs Bolar, US Congress passed the so called "Hatch-Waxman Act" which created a FDA testing exemption, an amendment to the Federal Food, Drug and Cosmetic Act (FDCA, 35 USC. 271 (e)).

From then onwards, development, manufacture and testing may be performed within the EU area, bringing back business into Europe which was almost thought to have been lost to countries like India, Canada or Israel to name a few. However, due to the exclusion of manufacturing batches of commercial batch size, it remains to be established to what extent pharmaceutical development activities will indeed be moved to Europe.

Whether or not European companies will be able to offer their services at prices which will stand the competition with the aforementioned countries remains to be established. At least in some of the old EU 15 Member States, with Germany at the forefront, costs of labour will make it very tough, if not impossible, to compete in this respect. Eastern EU countries are likely to benefit from the situation and will try to get as much of the business as possible.

2.3.4 Definition of "generic"

In article 10, paragraph 2 of the Directive, a "generic medicinal product" is defined as follows: *"…a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard safety and/or efficacy."*

The above outlined legislation will obviously lower the hurdle for generic applications and, further, will allow a wider approach in terms of product sourcing. What is more, it opens up new strategic opportunities for generic companies, which will have more ammunition to compete against each other by claiming own patents, perhaps for the only way to circumvent the originator's patent, thereby keeping ahead of potential competitors.

However, it should be mentioned that the above definition does not include different polymorphic forms, which, unsurprisingly, is taken full advantage of by the originator companies trying to block generic development by claiming numerous patents around this physical attribute of an active substance. Similarly, even certain particle sizes are at times covered by patent protection, causing it to be very hard to develop a medicinal product with the same pharmaceutical properties such as the dissolution rate.

2.3.5 SmPC harmonisation

Though protected by data exclusivity and patents/SPCs, originator companies at times try to keep SmPC's for the very same product in diverse EU Member States different to each other, thereby creating additional hindrances. In practice, this means for generic applicants trying to enter into these markets via MRP or DP (for details see 2.3.8) that they have to refer to and harmonise documents which are in fact not intended to be harmonised. In such cases, generic companies often have to miss out indications, but have to incorporate the adverse effects, precautions and warnings, contra-indications, etc. of all CMS' SmPCs. Being hampered by such restrictions, generic companies thereby loose potential profit, with originators keeping greater market share at the same time. What is more, every disharmony between the SmPCs of reference products constitutes a serious risk to public health.

The revised pharmaceutical legislation provides a legal basis for SmPC harmonisation, aiming to ensure the same standards for all European citizens. This will surely be most welcomed by the generic industry, in particular since a provision to overcome patent usage problems is foreseen, i.e., generic SmPCs will not have to include patented indications (as well as patented dosage forms). From the perspective of the generic industry, patent infringing data in the SmPC would, in their ideal world, only temporarily removed in those Member States where the indication patent is in force. It could be argued that thereby patients would benefit from all indications at an early stage (no Type II variation necessary) and multiple MR-/DC- procedures could be avoided.

More harmonised SmPC's within Europe will encroach on the selection of countries to include in MRPs/DPs, since today, it is very common to leave out those member states from multi-national registration procedures, who are well known for insisting on their specific national wording (with France as classic example). By being able to include more countries within one MRP/DP, competent authorities as well as generic applicants could save time, costs and capacity.

2.3.6 Renewals

Under the revised EU legislation, MA's will be valid for an unlimited period once they have undergone one 5 year renewal and provided pharmacovigilance data does not indicate the need for a further renewal. The aforesaid shall be compensated by an increased frequency

of PSUR submissions and illustrates the strengthened role of safety evaluation within the life cycle of a medicinal product.

Such is in fact to the advantage of the generic industry, since per definition a generic drug represents a medicinal product with an already established efficacy and safety profile. As a result, generic medicines are less likely to reveal unexpected safety data, worsening the risk/benefit ratio. Consequently, when compared to the originator companies, generic competitors will probably have to spend less money on maintaining their MA's. This, in turn, allows them to invest their money e.g. in their sales force, thereby trying to diminish the originator's market share to their favour.

2.3.7 "Sunset clause"

In article 24 of the Directive, it is pointed out that *"…any authorisation which within three years of its granting is not followed by the actual placing on the market…shall cease to be valid…"* and further, if *"…an authorised product previously placed on the market …is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid."*

For products approved via MRP, the question what "placing/present on the market" exactly means has not yet been fully answered by the competent European institutions. Contrastingly, an unambiguous statement has been provided for products which underwent a CP, where a launch in just one Member State already fulfils the above criterion.

On a national level, medicinal products are authorised in divergent ways in some EU Member States, an example of which would be Italy, where individual licences are issued even for different pack sizes. In case "placing/present on the market" would necessitate all MA's to be marketed within all CMS, what to do with these "extra" licences? A similar problem comes up when generic products are in anticipation of a court ruling, which will, due to the different national timing of court decisions, make it impossible to start marketing in all CMS simultaneously. The latter also applies to divergent patent/SPC expiry dates. Hence, in line with the interpretation addressing CP products, it appears justified having to market the medicinal product in question in only country.

Another aspect to be taken into account is the fact that for strategic purposes, pharmaceutical companies often keep spare registrations alongside the licences actually marketed. This concept could evidently not be followed any longer, once the revised EU legislation comes into force. Thereupon, it appears adequate to speculate that for the same medicinal product, the number of MA's applied for in parallel will be reduced in the near future. Consecutively, such will diminish potential Business Development opportunities, as the aforementioned spare registrations were frequently subject to in- or out-licensing activities.

2.3.8 Regulatory procedures in the EU

Besides the two already existing multinational registration procedures, i.e., CP and MRP, a third route of authorisation will be introduced. As of late 2005, a pharmaceutical company will thereby have three options if marketing in more than one EU country is intended. The eligibility of which of the three will depend on the individual situation. In order to illustrate the different concepts, the key features of these registration procedures are outlined in the following.

2.3.8.1 Mutual recognition procedure (MRP)

The MRP is set out in Directive 2001/83/EC, as amended by directive 2004/27/EC, and further guidance is provided in form of the NtA. A MRP requires an existing national MA in any EU Member State, which automatically becomes the RMS. The applicant is free to choose the CMS into which to extend the RMS licence. The period of data exclusivity starts already with approval in RMS. Each MRP is limited to 90 days, i.e. there is no „clock stop" foreseen. In case of divergent opinions of certain CMS, the applicant may withdraw his application in these countries without loosing the other CMS. However, if the pharmaceutical company decides not to withdraw, it risks arbitration with unknown outcome and substantial loss of time.

Those CMS which were positive about the reference dossier will grant a separate MA each, thus allowing to transfer the individual licences and to perform co-promotion.

Labelling/packaging is not harmonised and different trade names (permitting co-marketing) as well as a different prescription status in the CMS are possible. The applicant may opt to

include further CMS via repeat use MR procedures. Besides the latter, allowing sequential extension of the marketing territories, a MRP appears advantageous if flexibility is required and if a company is interested in a limited number of markets.

2.3.8.2 Centralised procedure (CP)

Filing for a CP is only possible 12 times per year, as it relates to the CHMP meetings. This route of authorisation is mandatory for medicinal products to treat HIV/AIDS, cancer, diabetes, neurodegenerative disorders as well as biotechnology derived products and designated orphan[3] medicinal products. It is optional for innovative products (including all NCEs). As opposed to the MRP or DP, it is for the CHMP at the EMEA to decide whether or not to grant a MA. Thus, there is one filing/dossier and one pan-European assessment leading to one central approval, which means one MAH, one trademark, one PIL and labelling (including the EFTA states NO, IS, LI). Compared to total amount for all CMS within MRP, there are less fees to be paid.

Conduction of a CP requires sufficient logistic capacity (e.g., to prepare texts in 20 + 2 languages in time). However, under the prerequisite of a positive outcome, the CP should allow a shorter time to market: to have just one central assessment should be faster in comparison to the total time needed for a RMS approval plus subsequent MRP (a CP „clock stop" even included). Moreover, also the post approval/maintenance phase shall be easier to handle, as for instance all variations may again be handled in one procedure. Another advantage will vanish: 10 years of data exclusivity for each CP product.

[3]As laid down in Regulation 141/2000, an application for orphan drug status must be made prior to the application for the marketing authorisation. It is assessed by the COMP. The applicant must show that a) the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EU at the time the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU will generate sufficient return to justify the necessary investment, and b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the EU or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.
The major advantage of orphan drug status is that it provides a ten year period of market exclusivity within the EU. This means that the regulatory authorities within the EU will not grant another MA or accept an application to extend an existing MA to cover the same therapeutic indication. This ten year period may be reduced to six years at the end of the fifth year if it is established that the requirements for orphan drug status are no longer satisfied.

As regards the disadvantages of the quite inflexible CP, it is to be mentioned that co-promotion is impossible and co-marketing requires a further MA (only granted in exceptional circumstances). Also, the aforesaid 20 + 2 languages need to be addressed always, independent of the actual interests in markets.

With the revised pharmaceutical legislation coming into force, the total procedure time of this route of authorisation will be reduced to 277 days (instead of effectively more than 300 days previously). The latter is yielded by accelerating the final decision making process, thereby enabling an overall shorter time to market. What is more, fast track authorisation procedures are foreseen for medicinal products of major interest to public health (by shortening the time period to reach a CHMP opinion from 210 days to 150 days). Also, in case of a specific patient need, there will be a conditional licence, valid for one year.

2.3.8.3 Decentralised Procedure (DP)

Based on the concept of the MRP, the idea of the DP was to reach two actually contradictory goals at the same time: 1) to increase the evaluation time for the CMS, thereby improving protection of public health and 2) to reduce the overall time of the registration process. Thus, instead of having the RMS assessed the dossier first, as of autumn 2005, the registration file is to be submitted simultaneously in RMS and CMS. As with the MRP, the applicant, who must not have submitted the dossier in any EU Member State, has to decide upfront which involved country shall act as RMS.

The RMS will have 120 days to prepare a draft assessment report, including drafts for SmPC, PIL and labelling, all to be forwarded to the CMS. Thereafter, with the CMS having started to evaluate the dossier in parallel, a 90 days procedure similar to the MRP is to follow. The CMS can either approve the product or the application will be referred to the EMEA for arbitration under Article 29 of Directive 2001/83/EC (as amended).

Before this will happen, the new legislation provides 60 days for the coordination group[4 (see next page)] to reach a compromise, i.e. arbitration would take place only if the coordination group fails in this respect. However, the arbitration process as such shall be simplified and accelerated (faster final decision process, see CP).

The faster time to market will be paid for by risking a negative RMS opinion on the file, which would hardly support the submission in such case. Further, it is to be decided at a comparatively early stage in which countries to apply for a MA. This puts Business Development departments under pressure to contract their application partners sooner than under the MRP. Nonetheless, co-marketing/co-promotion, different trademarks or MA-transfers are possible evenly to the MRP.

However, it needs mentioning that there will be no withdrawal of CMS possible. In case of divergent opinions in between the involved Member States, a compulsory arbitration will always result, though marketing is permitted in those CMS, which assessed the registration file positively.

It becomes evident that the new multi-national registration procedure provides benefits and risks at the same time, the final appraisal of which remains to be established.

2.4 Criteria: cooperation partners in general

Licensing activities as well as change of manufacturing sources require some thoughts about decisive factors when looking for new partnerships. At first, some general criteria shall be examined.

2.4.1 Expertise

Co-operations in the pharmaceutical industry are aiming at creating value for each involved party by causing synergies (also) in terms of expertise. In order to assess how a company applies its knowledge, the number of successful projects may serve as a useful measure. Likewise, the experience and the qualification of its employees provide valuable indications.

[4]The coordination group represents the successor of the MRFG (Mutual Recognition Facilitation Group), which was originally established as an informal group by the heads of the competent European Health authorities. The coordination group, which has its legal basis in article 27 of Dir. 2001/83, shall coordinate and facilitate MRP's and DP's by translating legal interpretations into rather practical recommendations. For a renewable period of 3 years, each EU member state assigns a representative, which may be accompanied by an additional expert.

2.4.2 Costs

Almost superfluous to mention, but often forgotten in practice: when talking about costs, short term and long term costs need to be taken into account evenly. When having discovered a cheap source at first sight, which as such might indeed be low cost, consequential expenses are to be considered, too. For instance, a company might perform manufacturing well, but much worse when it comes to document properly what has been done. This in turn necessitates additional efforts, i.e., time and capacity, by the Regulatory Affairs team trying to overcome the lack of adequately presented data.

Further, extra transportation, customs or insurance costs may arise. In case one company produces only the bulk form and second company in another country performs batch release and packaging - a situation quite often taking place in practice - shipment in between three countries is required before the product reaches its destination.

Lastly, it causes a difference if a manufacturer is directly dealt with or if an agent is involved, who will charge commission for his service. Still, many agents offer a regulatory capacity, which might be necessary in case the internal capacity is currently not sufficient.

2.4.3 Strategic alliances

Once companies identify an above average mutual benefit from co-operating, it may be worth considering a long term partnership. Part of such could be making use of the other party's business network. There may be options to work with people, who would otherwise not have bothered without being introduced by the new contact.

When it comes to strategic alliances, the conditions and terms of intended contracts need to be given a closer look, as both parties are about to bind themselves for a longer period. It needs questioning whether there will be a fair sharing of risk and profit or enough flexibility when needed. What about liability and mutual warranties? In case reality does not match with high expectations, it should be contemplated at what conditions the contract may be terminated.

A further important aspect of a potential long term alliance is the respective partner's validity and soundness as an ongoing profitable company, i.e., each partner has to be financially able to fulfil all his obligations and duties. Nowadays, with an increasing number of mergers

and acquisitions, it has to be carefully reflected whether to co-operate on a long terms basis with a company that is in the hands of investors, whose strategy is unknown. However, strategic alliance may also mean agreement on a "basket" of e.g. ten products, which will be developed by one company and marketed be a partner company. Such deal could easily extend more than 10 years of co-operation. Here, the capacity savings and the calculability are to be balanced against the risk of failing developments or a change in ownership (affecting the business strategy).

2.4.4 Reliability & reputation

Reliability, or the manner of keeping promises, is a key to a fruitful partnership. No one wants to persistently experience delays in delivery of goods or service, not to mention the need for an ongoing high level of product/service quality.

Ideally both partners should benefit from the counter part's reputation. However, as it happens, reputation might evenly be at risk through that co-operation, e.g., if a bad press of the partner radiates onto the other company.

2.4.5 Confidentiality

Know-how may be well converted into money. Thus, every company will cautiously examine who to disclose the company's intellectual property to. Even on a more general level, such as certain particulars of the Business model, might be worth to protect from transpiring to competitors. Therefore, in case of the slightest doubt on maintaining confidentiality, it may prove wise not to engage in a certain co-operation.

2.4.6 Capacity

Straightforward, but often a limiting factor, is the question of capacity. For all equipment, staff or space required, it needs to be ensured that the task can actually be performed. In this respect, it is important to take into account the capacities made available for other customers. Hence, it might well be that a manufacturer (in theory) has the capacity to e.g. produce a certain tablet quantity, but if half of the staff is tied up with other duties, there is not much use to make thereof.

2.4.7 Language & culture

Pharmaceutical issues often tend to be rather complex. Therefore, it is to be ensured that both partners share the same understanding of what is required. Especially when it comes to trouble shooting, it is important to exchange information efficiently. Cultural differences frequently contribute to misunderstandings. A popular example of such is the question whether "yes" means indeed "yes", since in some cultures politeness (e.g. the British) or non admittance of failure (e.g. in some Asian countries) causes signals to come across different to German traditions.

2.5 Criteria: manufacturers in general

2.5.1 Product and dossier development

Apart from the general capabilities and quality standards of a manufacturer, such as the quality of materials (API, excipients) and equipment used, which in turn, much depends on the quality of the suppliers, a sound understanding of what matters in EU is essential. It shall be borne in mind that manufacturers often serve different markets, i.e., the EU and the United States, which implies different necessities. For instance, the U.S. pharmacopoeia might foresee different excipients or test methods, requiring different equipments, than the European pharmacopoeia.

Even if the quality of the product or documentation is adequate, there is still a proper documentation to be prepared. Both tasks require sufficient understanding of and adherence to the applicable guidelines.

All above issues determine the date of submission of the registration file.

2.5.2 Service during registration process

However, not only the time needed pre-submission is decisive for the time to market, but also the service provided during the ongoing registration process. Once the competent authority issues the first deficiency letter, a fast reaction time is indispensable. The time needed to respond does not only depend on the regulatory performance "in the office", but probably even more on the time it takes to generate additional data in the laboratory.

2.5.3 EU vs. non-EU manufacturers

With a view to cost of goods and service, it is to be expected that on average, non-EU sources provide a more attractive pricing than their competitors in the EU. However, the situation within Europe needs to be seen with from a differentiated perspective. Due to their comparatively low cost of labour, Eastern European countries are usually cheaper than for instance Germany.

It is to the favour of non-EU manufacturers that they are not hampered by a patent legislation enforceable in Europe. Thus, from an EU perspective, they may be regarded as "patent-free" countries allowing development and manufacture of medicinal products without any patent restrictions. This of course, will drastically change once the new pharmaceutical legislation comes into force, allowing most of formerly patent infringing operations to take place (except manufacturing of commercial batches). On the whole, the former necessity to turn to non-EU manufacturers will revolutionize upon introduction of the revised EU legislation. A further issue to be considered is the fact that, as opposed to manufacturing within the EU, import from a non-EU country requires an EU import licence, which might take quite some time to be issued.

Non-EU production further necessitates an additional EU-batch releasing site, even if the product has undergone full analytical testing already. The additional costs and time needed for this extra step will have to be taken into account when receiving low cost offers from e.g. Asian countries. With some non-EU countries, such as Canada or New Zealand, a Mutual Recognition Agreement (MRA) is in place. For those, no additional EU-batch release is required, since it has been agreed that their standards of analytical testing are comparable to their European counterparts. A MRA also entails the GMP certification of the manufacturing site in question. Contrastingly, non-EU manufacturers not falling under a MRA will have to be inspected and approved by an EU authority.
Depending on the actual distance to be covered, shipping costs could be expected to be generally lower within EU. However, in case of air freight, the question is whether these differences are actually significant.

The issue of language and culture was already raised, but within Europe one should generally expect to find a greater likelihood of a common understanding than with entirely different cultures. In particular it needs to be taken into account that a business deal which was closed on a high management level, i.e., by people who are often travelling and used to

converse in foreign languages, will soon come down to people having to put this into a day to day practice, which raises the question of the corresponding qualification of lower level staff.

Even nowadays with long distances actually easy to bypass, there is, at times, still a psychological aspect to be found with "far away countries", where some "black sheeps" might fell being less controlled. Thus, it needs to be reflected how much control of the partner is needed (and possible). On average, EU partners are probably less inclined in this respect.

2.5.4 Supply

When it comes to the supply of the approved medicinal product, three fundamental issues are of relevance for as long as the underlying contract is valid: a) is the quality as per specifications? b) will the product be supplied in-time? c) is the complete ordered quantity delivered or only a part of it?

2.6 Alternative manufacturers: points for consideration

When contemplating whether or not to include alternative manufacturing sites, there are basically two options to go for:

1. purchase of marketing authorisations/dossiers to replace existing marketing authorisations
2. transfer of the approved technology of existing marketing authorisations/dossiers to alternative manufacturing sources

Baring this in mind, the following issues ought to be thoroughly reflected on:

- With a view to timing: what are the capacity, expertise and technical equipment of the alternative manufacturing site (including production, analytical testing and documentation of both)?
- The patient should not recognise the product familiar to him as being sourced from an alternative manufacturer.
- The costs, time and capacity needed for the technical and/or know how transfer, which also concern necessary audits, Regulatory Affairs and, at a later stage, logistics.
- Regulatory Affairs: the costs, time and capacity necessary to get the new site approved.
- Will the resulting product quality of product be comparable to or worse than the "old" product (e.g. shelf life)?

3 FOCUS: DECISION PROCESS IN-LICENSING

The most important criteria for portfolio product candidates and potential co-operation partners were discussed in quite detail. However, it needs to be pointed out that in general, no decision should be made without weighing the criteria to be applied.

How much significance will be attached to the single criteria, depends on the respective situation and will usually result out of team discussions. Within these discussions, it appears likely that the involved departments will have different views as to how criteria should be weighed, which are at least to be divided into rather technical or more commercial perspectives. The respective weight of the criteria has to be handed in a flexible manner, as illustrated by the following situations: should an in-licensing offer come in very late (in relation to the intended launch date), time to market will play the key role and price concessions will have to be made. In case of a modified release product, the results of bioequivalence studies need to be taken more into account than for instance the shape of the tablet, i.e., a marketing aspect. Generally, different circumstances are to be addressed accordingly. In any case, it has to be ensured that divergent opinions about the significance of the respectively relevant criteria do not slow down or even block the necessary decision process.

In the following, the steps to be undertaken for in-licensing of new medicinal products shall be outlined. First of all, the opportunities offered need to be evaluated against what is actually looked for. Product wishes as well as product offers should be entered into a common database, which may serve as a basis for the compilation of further information needed. In case of differences, it is to be reflected if the products not actually "set on search" are worth to be followed up, too. However, it always has to be considered that things might change over time, therefore a product which is currently not of interest should not be deleted from the database.

3.1 Information needed for identification of product candidates

3.1.1 History of sales and volume

As generics always refer to an originator product, there should be sales data to analyse. Here, not only the sales in the market of interest, but also revenues in other markets, in particular with a view to corresponding growth rates, should be given a closer look. Are sales still rising, do they remain on a plateau or are the already going considerably downwards?

Is the tendency the same in all market places or are there differences and if so, what could be the reasons behind? Is the therapeutic principle still state of the art or are there already better alternatives available (be it through reduced adverse effects or through a superior efficacy)?

Is it a high volume product (many dosage units) or are the impressive sales merely a result of a high price level? How has the originator product price developed over time and what would this mean for the generic company's own possible launch pricing? Likewise, the number of expected competitors has to be considered for evaluating the appropriate price level. However, the flexibility in pricing is evidently limited by the costs of manufacturing.

3.1.2 Market feedback

The sales force is in direct contact with the health care professionals and hence represents an invaluable source of information about the market. The feedback they receive - be it passive or actively asked for - will be put into the context of other products in the same therapeutic field by the product management. Ideally, the results of these market observations should answer questions such as: what kind physician groups and how many doctors are likely to prescribe the medicinal product of interest? What do health care professionals think about the product in question? What do they believe do their patient really need? What does the patient feel or believe would help him best? What are his concerns? What could be USP's?

3.1.3 Exclusivity data

It is vital for a generic company to know when it will be authorised (and able) to market the product of interest. The market exclusivity of the originator depends on granted patents and the protection of the pharmacological and toxicological as well as clinical data.

At first the patent situation is to be evaluated. It needs to be found out how many and what kind of patents are claimed or already granted. What are the expected costs of challenging those? From a tactical point of view, a challenge together with a partner might be taken into consideration in order to reduce the related legal costs (through attorneys and court cases).

Further, it needs to be investigated whether it is possible to circumvent the identified patents and if the answer is "yes", what the related costs would sum up to. Also, it should be examined if own patents could be claimed. In order to predict what will happen in the market(s) of interest, the originator's strategy as well as the trends in other countries should be known. It should be always checked whether a corresponding SPC has been claimed, thereby adding up to five extra years of market exclusivity.

In contrast to patents or SPCs, data exclusivity is looked after by the regulatory authorities. Due to the current difference between the 6 and the 10 year countries, the knowledge of the period of protection of the originator's pre- and clinical data impacts the regulatory strategy to be chosen. Depending on the case it might be worth considering how much time and human as well as financial resources would need to be spent on bridging data.

3.1.4 Regulatory / strategic options

As outlined under 2.3., from November 2005 onwards, there will be three multinational regulatory procedures within Europe. For all of these, the Regulatory Affairs team will have to evaluate specific issues, though MRP and DP are of course closely related to each other. In general, the intention of co-promotion or co-marketing would speak against a CP.

3.1.4.1 MRP

For a successful MRP (and DP), the SmPC's of all Member States intended to be involved are to be compared in terms of their potential for harmonisation. Will it be possible to include all CMS in one procedure or are two (or more) waves required? Until the new legislation has not been implemented in all Member States, the different periods of data exclusivity as well as the risk of arbitration need to be carefully considered, too. Lastly, the patent situation in each involved Member State is to be examined.

3.1.4.2 DP

As regards the DP, the choice of the RMS is deemed to be highly important. Therefore, the reputation, expertise and capacity of the intended RMS should be reflected. What is the medical school in the RMS like? Will the RMS be able to fulfil the desired leading role? With a view to the CMS, the respective future market situation will have to be assessed, too.

3.1.4.3 CP

Depending on the technology used or the therapeutic area addressed, there might not be much of a choice (see 2.3.8.2). Regulatory capacity, timing and costs have to be thoroughly contemplated. In case of free choice of the route of authorisation, one should reflect whether the quantity of markets of interests indeed justify a CP. Likewise, there has to be either a sales force in the markets of interest or co-marketing is foreseen, the latter of which being rather rare.

3.2 Appraisal of a dossier / marketing authorisation offer

3.2.1 Role of involved departments/teams and flow of information

The following scenario is assumed: the Business Development team is actively searching for a certain product licence. The identified API source discloses three FDF manufacturers, all of which have a spare licence and are willing to sell it. All FDF offers encompass different regulatory strategies and different overall costs. Moreover, different likelihoods of matching the desired time line (i.e., to enter into the market straight after the originator's loss of exclusivity), thereby resulting in different sales expectations, are to be assumed. It is deemed likely that competitors are evenly interested in (some of) those opportunities. All in all, fast decisions need to be made, necessitating a smooth flow of information and work.

Within a fictitious company, the following departments/teams are involved in the decision process whether or not to spend money on a product offered to be in-licensed:

- Sales force
- Product management
- Drug information department
- External patent attorney
- Regulatory Affairs
- Audit expert
- Logistics/supply chain
- Business Development team
- Controlling department
- External lawyer
- Top Management/Managing board

3.2.1.1 Sales force

As described in detail under 3.1.2, the sales force seeks for the opinion of patients and health care professionals about potential products and reports the outcome to the Product management Team.

3.2.1.2 Product management

The product management forwards the aforesaid feedback to the Business Development team. It calculates expected sales figures and volumes of the product for the first years.

3.2.1.3 Drug information department

The drug information team checks whether the molecule and/or its corresponding pharmaceutical form still represents state of the art from a medical and pharmaceutical point of view. An assessment of the therapeutic principle as well as a search for any new safety topics will be performed, both aiming to identify if the original risk benefit ratio has worsened meanwhile.

3.2.1.4 Regulatory Affairs

The RA team evaluates the different regulatory options, estimates the associated internal capacities and recommends the best regulatory strategy.

Once a confidentiality agreement has been signed, RA will conduct a detailed due diligence procedure. Thereafter, RA will be able to assess whether the product is difficult to produce and/or to test, with an estimation of the respective cost of manufacturing to follow. The RA team also liaises with the external patent lawyer, who evaluates the related patent situation.

3.2.1.5 Audit expert

Besides the thorough evaluation of the documentation, the premises, the equipment used and related SOP's as well as its operating staff will have to be audited. Such audit allows a comparison between what is theoretically done and how the reality looks like. Furthermore, one gets a general impression as to whether a manufacturer indeed has full control of all processes.

At the same time, useful business information may be derived, such as how many and which other clients the manufacturer serves (i.e., the potential competitors). Likewise, by assessing the capacity already occupied, it becomes clear how much a manufacturer needs the deal and whether there might be problems in terms of prioritisation (not all customers could be assigned a favoured customer status).

3.2.1.6 Logistics/Supply chain

The logistics team provides its input concerning the related supply agreements and respectively checks what would have to be organised logistically.

3.2.1.7 Business Development Team

The BD team analyses the originator's product history of volume and sales and receives a detailed report of the PM about the market situation for the product offered. Together with the RA team, they perform a non-confidential (e.g. preliminary) evaluation of the opportunities.

The BD department would subsequently execute a confidentiality agreement on the purpose of conducting a full evaluation of the respective opportunity value (due diligence). In case of interest, BD would initialise negotiations, in the beginning by trying to reach agreement on the commercial key terms. The progress of such term sheet would be closely followed up by the management board, which would also be responsible for finally signing all related contracts. At the end, BD would hand over for implementation to the logistics and RA teams.

3.2.1.8 Controlling Department

The controlling department would support the BD team by comparing the offered terms with the real outcome of existing contract conditions. In case of economically complicated contractual issues, it would calculate financial models in order to evaluate the best possible deal structure.

3.2.1.9 Top Management

The managing board sets financial targets and is involved in contractual issues. The final decision how much and where to invest is reserved for the managing directors.

3.2.1.10 Legal advice

Legal advice is sought outside the company in form of a regular co-operation with a specialised lawyer.

3.2.2 Proposal for an efficient decision process

When reflecting the different tasks to be performed on the purpose of being able to decide based on facts rather than on "gut feel" (though the latter is definitely not to be underestimated), it becomes obvious that as many as possible should be undertaken in parallel. Otherwise the whole decision process would take too long and valuable opportunities would likely be missed. The goal is to rapidly decide which option to go for (with a fall back) and to define how much one is willing to pay respectively.

In particular when activities have to be undertaken very quickly to ensure success, the process needs to be well coordinated. As to be derived from the duties of the involved teams and departments, the data to be processed may be roughly classified into more technical and into rather commercial information. Hence, it is deemed justified to let two teams take the lead within such process: RA and BD. They should set up a common task force, which needs to organise for the requested information and has to follow up that all matters are completed in time. The latter is of great importance, since one department could not work without receiving the information from the other teams.

At first, it should be enquired at the drug information department whether the therapeutic principle is still state of the art or if current safety data speaks much against the drug looked for. In case of a negative feedback, there is obviously nothing more to follow up.

As it takes some days to receive the opinions from the involved sales representatives, another early thing to be organised for is an up to date market feedback. Offered opportunities (e.g. an alleged USP) unlikely to be successful in the market could be cancelled straight, thereby releasing extra capacity within the involved departments. Whilst the current market situation is about to be obtained, BD and RA should preliminarily evaluate the three opportunities based on all information accessible on a non-confidential level. Once the results of the market observations become available and provided they are positive, PM has to calculate a forecast. A confidentiality agreement needs to be quickly executed in order to receive more detailed information.

Meetings with all three potential business partners have to take place soonest in order to fully evaluate the opportunity value (prioritised per most promising options). RA and BD should attend jointly, with RA thoroughly reviewing the dossier (due diligence) and interviewing the responsible RA manager(s) of the potential partner company. At the same time, BD should start to negotiate the heads of terms by exchanging the key commercial ideas and prerequisites with the business partners. It is essential to understand the needs and problems of the partner companies. Moreover, a respective audit procedure should be conducted in parallel.

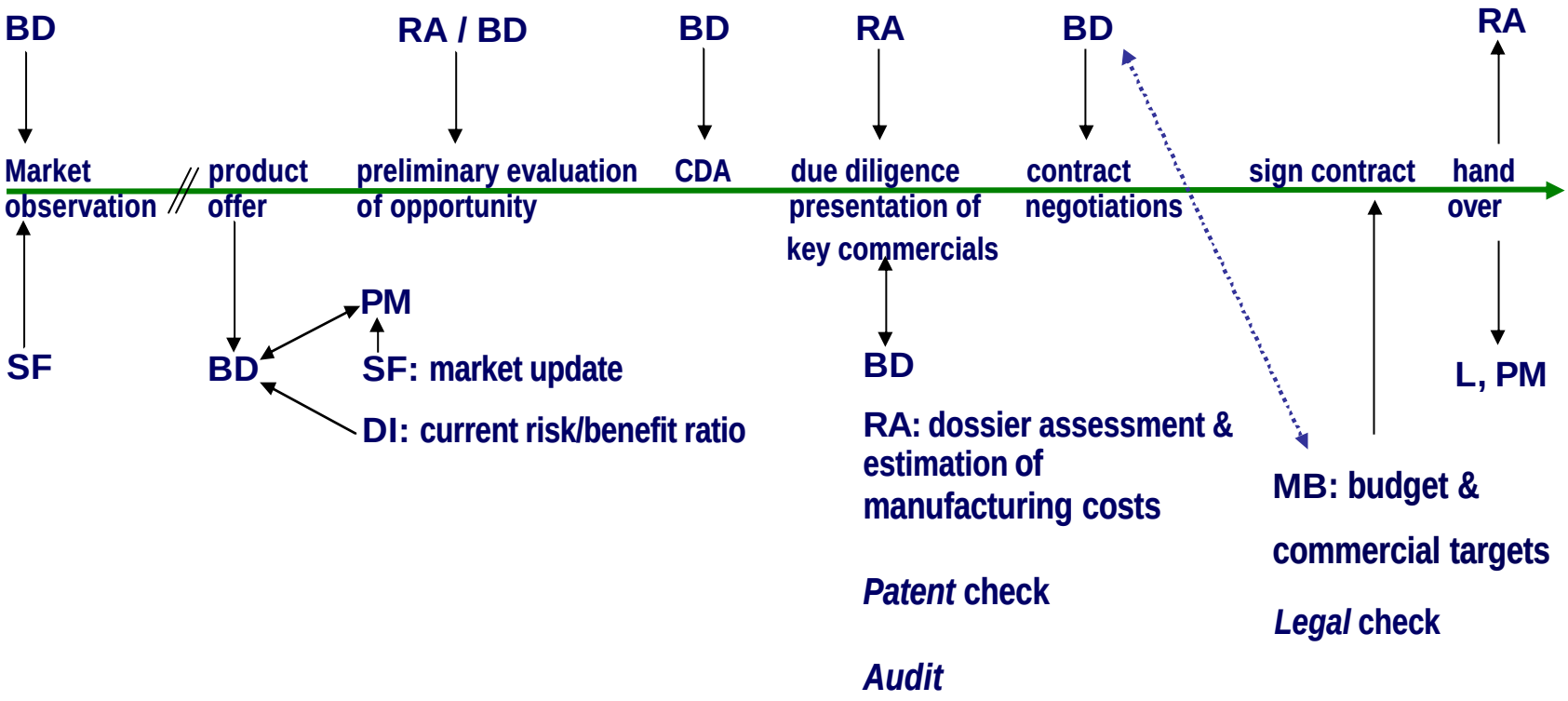
Subsequent to the respective due diligence procedure, RA should forward the relevant patent details to the patent attorney and estimate the costs of manufacturing. By comparing the different options form a regulatory point of view, RA will evaluate the preferable regulatory strategy. Meanwhile BD liaises with the logistics team to calculate the supply costs.

Based on the feedback of the patent attorney, it shall be exemplarily assumed that his opinion would lead to a negative decision against one of the formerly three options. The remaining two opportunities should be closely followed up in parallel. Taken into account the available commercial information, an agreement on key financial terms (such as down payments, cost of goods, samples, term, etc.) should be sought for by the BD team. The proceeding of the contract negotiations will have to be reported to the managing board, which will check if their target commercials are met. In case that an agreement could not be reached with one of the two remaining companies, this would leave one last company to close the deal with.

Once a final agreement has been yielded, it is for the lawyer to ensure that all legal issues have been adequately addressed. Thereafter, the board of directors may sign the contracts. Simply, but importantly, their availability needs to be ensured, as it would not have made any sense to reach a rapid decision, when the final signature is still missing. At last, the project needs to be handed over to the logistics team and RA for implementation. It is beneficial that both teams have already been involved in the process at a rather early stage.

The following graph shall illustrate the complex process and indicate where tasks ought to be performed concurrently.

Decision process in-licensing



BD: Business Development DI: Drug information L: Logistics/supply MB: Managing board RA: Regulatory Affairs
PM: Product management SF: Sales force

4 CONCLUSION

This thesis is meant to provide guidance along the various criteria relevant to development and licensing of generic pharmaceutical products. Among those, product quality, time to market, non-infringing of granted patents, bioequivalence to the originator product and of course the associated costs have been identified as indispensable.

In order to take full advantage of the expertise of the RA department, business decisions should carefully take into account the "regulatory opinion", as such feedback concerning e.g. the most promising regulatory strategy (strongly affecting to time to market), the eligibility of associated manufacturers (reflected in product quality and supply), production costs as well as patent issues (subsequent to the due diligence procedure, RA will be able to estimate the costs of goods and to support patent evaluation) will help to save time, capacity and money.

In particular with a view to strategic alliances, where the involved partners bind each other for a longer period, two further important aspects are to be borne in mind: firstly, the necessity for an ongoing financial capability of all involved parties to meet their obligations and secondly, in times of consolidation through mergers and acquisitions, the risk of altered business strategies due to a potential change in ownership.

Pharmaceutical development and licensing performances will substantially be affected by the revised pharmaceutical legislation in EU. Once the "Bolar provision" will come into force, a shift of development performances from Asian or other non-patent infringing territories to Europe could be expected, the precise extent of which cannot be foreseen at this stage. Similarly far-reaching, the new regulation of data exclusivity will allow generic companies to enter into the market at an earlier stage, resulting in accordingly adjusted submission and marketing strategies.

The strong linkage between commercial and technical aspects of the pharmaceutical business was illustrated through the example of in-licensing. Based on the different roles of the involved departments, the flow of respectively required information as well as of the work was outlined in detail.

Consequently, a "best practice" recommendation how to yield a fast and efficient decision process for products available for in-licensing was developed, the basis of which is primarily

formed by setting the right priorities and by performing activities in parallel wherever possible.

Evidently, the respective activities of the Regulatory Affairs and Business Development department mutually affect each other. Business decisions have to carefully consider the regulatory consequences, with the Regulatory Affairs team having to put those into practice.

It has been demonstrated that no strategic business decision should be made within the pharmaceutical industry without considering the expertise from the regulatory experts, who should be seen more as a profit center as opposed to the frequent perception as a cost factor.

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