Global Generic Business: Regulatory oriented Analysis of Development versus Licensing

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vorgelegt von

Annika Weyand

aus Bonn-Duisdorf

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Betreuer und 1. Referent:	Herbert A. Jopp
2. Referent:	Dr. Josef Hofer

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List of Abbreviations

API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
ATC	Anatomic Therapeutic Chemical (Code)
AUC	Area under the curve
BE	Bioequivalence
BPI	Bundesverband der Pharmazeutischen Industrie
CEE	Central and Eastern Europe
C_{max}	Maximal Concentration
CMS	Concerned Member State
CP	Centralised Procedure
CRO	Contract Research Organisation
CTD	Common Technical Document
DA	Decision Analysis
DCP	Decentralized Procedure
DMF	Drug Master File
DP	Decentralised Procedure
DRA	Drug Regulatory Affairs
EMEA	Europen Medicines Agency
EPO	European Patent Office
EU	European Union
FDA	Food and Drug Administration
FDF	Finished Dosage Form
GMP	Good Manufacturing Practice
GxP	Good Practices
ICH	International Conference on Harmonisation
IHD	In-house Development
IL	In-Licensing
IT	Information Technology
LoE	Loss of Exclusivity
MA	Marketing Authorization
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
MS	Member State
PA	Problem Analysis
Ph. Eur.	European Pharmacopoeia
PPA	Potential Problem Analysis
R&D	Research and Development
RMS	Reference Member State
SA	Situation Appraisal
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPC	Supplementary Protection Certificate
UAE	Unexpected Adverse Events
US	United States
USP	Unique Selling Proposition
WTO	World Trade Organisation

EXECUTIVE SUMMARY

Pharmaceutical companies in general and generic companies in particular have to regularly decide whether to develop medicinal products by themselves or whether it is more beneficial to in-license such products.

Several pharmaceutical companies feel impelled through the persistent cost pressure, causing them to concentrate more on their key competences by divesting business units or functions which on a medium term are deemed not to be competitive any longer. Thereby, diverse services are shifted to external providers, such as product development or production. Thus, pharmaceutical companies have to decide whether to further perform own product development and to keep their manufacturing facilities or if it is more profitable to in-license and/or to sell their production unit and to outsource to contract manufacturers. In reaction to the increasing pressure on margins, the industry approaches low cost countries such as India, China or CEE countries on the purpose of regaining shrunken profitability.

Along the analyses within this thesis, certain trends could be identified, which all exert significant impacts on the activities of the pharmaceutical industry. Amongst those are

- Consolidation through mergers and acquisitions
- Alliances and cooperations (in particular in the R&D sector)
- (further) globalization and internationalisation
- Specialization and focus on niche products
- Fierce patent litigations
- Increasingly more own patent claims by generic companies
- Integration of further value added steps into the (generic) value chain
- Outsourcing
- Increasing regulatory requirements

This Masterthesis shall evaluate the factors relevant to decide between In-Licensing as opposed to in-house development, but will also assess potential options for development and production: India or – exemplary for CEE countries - Poland. For

each of these options, all determining factors identified will be subject to a detailed decision analysis.

The decision in-house development versus in-licensing is exemplarily appraised for a specific business case: a fictive mid-sized company with own R&D and manufacturing facilities. The analysis reveals that despite the general advantages of in-house development, the current business model (about two thirds of the products are developed and manufactured in-house) should be changed in favour of less costly and risky in-licensing activities. Further, it is proposed that the production unit should specialize in modified release products and engage in contract manufacturing. Nevertheless, it evaporates that the recommendation which option to go for will depend on the individual case.

The second decision analysis addresses the current trend to relocate or outsource development and production facilities to low cost countries. Strengths and weaknesses of both Poland (representing the CEE region) and India are analysed in order to identify the best possible option. The outcome of the analysis indicates that both locations offer different pros and cons, but are overall of no significant difference. Hence, individual decisions are to be taken. However, especially with the recent change of the patent legislation, India has lost a significant advantage for generic companies as a preferred place to perform pharmaceutical development programs.

Finally, with a view to the future, proposals are made how to optimize a pharmaceutical value chain, how to arrange for a global marketing authorisation and how to create a more marketing oriented role of DRA-managers, in order to support a sustainable profitability in a changing global business environment.

1 INTRODUCTION

Throughout the world, healthcare systems are under enormous budgetary pressures. Primary causes are the demographic development and an increase of chronic diseases as well as cardiovascular diseases. Politicians appear to not yet have found the right answers. However, realising that the use of generic drugs leads to significant cost-savings, such imitations of originator drugs gained more and more importance within the growing pharmaceutical market during the last decades. Consequently, European Governments strengthen generic companies by creating a favourable legislative environment (e.g., through introduction of the Bolar-Roche-provision [see 4.5.1]).

The pharmaceutical quality and therapeutic equivalence of generic medicines (to the respective reference product) are meanwhile well established in most European markets. Quality and efficacy of the generic medicinal product, as evidenced by the grant of marketing authorisations, are assured by years of experience with the corresponding reference product by the originator. Generic companies could offer their medicinal products at cheaper prices, as (usually) no costs for preclinical tests and in particular for the extremely expensive (phase III) clinical studies arise.

Some European governments (e.g. United Kingdom, Germany, the Netherlands and Denmark) explicitly support generic drugs as a cost-saving instrument. Contrastingly, member states with lower price levels for medicinal drugs (e.g. Italy, Spain, France and Greece) are less favorable towards generics. Nonetheless even in some of these countries a slow-going process of rethinking takes place. Medical doctors who have contract based commitments to sick funds are to prescribe economically, including a certain percentage of generics (e.g. France). In 2005 the generic market in (Western and Eastern) Europe adds up to 33 billion Euros whereas the global generic market totalled to estimated 88 billion Euro.

The governmental pressure on prices of medicinal products leads to decreasing margins of the pharmaceutical industry (most pronounced in Great Britain). This hurts generic companies even more than their originator equivalents as generic margins are comparatively lower anyway. Hence a trend of consolidation and

specialization could be observed within the generic industry. Others consider integration of more value-added steps as a mean to increase their profitability.

Facing increasing competition of e.g. low cost Asian manufacturers, in particular smaller and mid sized pharmaceutical companies have to review their business models: could they still afford costly (and more risky) own development activities or are they better off with in-licensing? Alternative options for creating synergies between established pharmaceutical players and generic players shall be presented, too.

Based upon the aforesaid, this master thesis aims to examine strategies as to when to choose in-house development and when to prefer in-licensing. The relevant parameters and criteria shall be scrutinized within a specific business case.

Part I addresses important considerations that pharmaceutical companies have to reflect on in their decision process about internal or external development. These issues will thereafter be evaluated within the scope of a detailed decision analysis in Part II.

Furthermore, the current trend in generic business to relocate production to low cost countries shall be examined in Part III, where two considerable options, Eastern Europe (along the case of Poland) and Asia, will be compared with each other.

PART I

2 PLAYERS AND TRENDS IN THE GENERIC MARKET

The analysis of currently established players in the generic market basically reveals business models ranging from pure API[1] supply, contract development, contract manufacturing, selling of registration dossiers to pure marketing companies (for instance late entrance generic companies with focus on low-price segment such as AAA-Pharma, Accedo or AxiCorp Pharm). The various offered pharmaceutical services such as performing registration procedures, conducting stability or bioequivalence studies or analytical testing shall not be addressed in deeper detail.

When it comes to integration along the pharmaceutical value chain, the following types of companies can be distinguished:

1. **Vertically integrated** generic companies (e.g. Teva/IVAX, Pliva, Hexal/Sandoz);

2. **Backwards integrated** dossier developers and sellers (e.g. Siegfried, Synthon, Cimex)

3. **Virtually backwards** integrated dossier developers and sellers (e.g. Midas, A.E. Tiefenbacher, Kohne Pharma)

In view of fierce competition and the governmental demand for further price reductions, companies look for strategies to consolidate or even increase their profits. As one result, a trend towards strategies of integration of further value added steps of the generic value chain could be observed.

For instance the **virtually backwards integrated** dossier developer and seller Alfred E. Tiefenbacher used to be an API trader in the past, established later virtual (i.e. advising development companies) development of finished dosage forms with partners and regulatory services in-house for outlicensing activities. Taking it

[1] See abbreviations list

further, Tiefenbacher recently constructs the development and production site "Medicon" in Hyderabad for also offering products from own production.

Pharmathen, a **backwards integrated** dossier developer and seller, started with development and production of finished dosage forms for out-licensing activities. The Greek company recently established further backwards towards autonomous development by including in-house synthesis of niche APIs.

Within the pharmaceutical market place, mergers and acquisitions amongst the diverse players create an environment of consolidation and increasingly powerful competitors. In particular **vertically integrated** companies take advantage of acquisitions as thereby foreign markets can be conquered most rapidly.

Besides the trend to move development and production to low cost Asian countries, merging of pure marketing players with Asian developers/producers is also to be observed. Such could even mean that European or US companies integrate Asian sites and vice versa. In the recent past, especially Asian companies try to thereby improve on infrastructure and gain further pharmaceutical know-how. Indian and Chinese companies are traditionally strong with regard to API supply but more and more also in terms of finished dosage form development and production. A few big generic players have already established development centres and production sites in India. Vice versa, large Indian production companies purchase European generic companies. An example for an Indian producer acquiring a European registration service provider would be Jubilant Organysos, who bought PSI in Belgium. Examples for acquired European marketing companies by Indian companies are Esparma (Wockhardt), Basics (Ranbaxy), Heumann (Torrent) and betapharm (Dr. Reddy's).

Along with the efforts of generic pharmaceutical companies to work on their profitability, a trend away from commodity products becomes apparent. Pharmaceutical companies currently are inclined to focus on niche products and so called "generics plus" (generics with a small additional benefit such as the introduction a strength not marketed before). In particular smaller, but also mid-sized companies see their future within specialisation. This might be illustrated by the example of the German company Dr. Rentschler, which has recently sold their

marketing unit on the purpose of concentrating on development and production of modified released products (Rentschler Pharma) and biotechnology (Rentschler Biotechnology).

It could be speculated that due to the ongoing erosion of margins, the high prices hitherto paid for launching earlier than the loss of exclusivity date to gain additional market share, might become too costly for generic companies. This in turn might lead to a trend towards comparatively more affordable co-marketing or co-promotion models as means to increase reputation and sales.

Moreover, new and amended legislation (nationally as well as on a European level) impose further challenges to the industry, but also provide additional options, such as new route of registration, the Decentralised Procedure (DCP).

Lastly, patent claims and challenges become a more and more important battle field within the pharmaceutical industry, as the cost for proceedings are very high but marginal in comparison to sales lost or gained. These rather complex issues will be addressed in more detail in 4.5.1.

3 IN-HOUSE DEVELOPMENT VERSUS IN-LICENSING: PROS & CONS

3.1 In-house Development

In these days companies with production facilities frequently discuss measures to reduce their expenditures by e.g. shifting development and production to low-cost countries. For instance due to lower labor costs (combined with well trained people) India belongs to the most attractive regions in the world for dislocation of pharmaceutical production. European generic companies or dossier vendors without own production sites take advantage of alliances and strategic cooperations with Asian developers and manufacturers.

Within the scope of this thesis, virtual in-house development shall be understood as development of finished dosage forms in collaboration with an external manufacturing site. Regarding documentation, Asian companies are still not at

Western standard and could thereby benefit from working with European companies. Baring in mind that Western authorities continuously enhance the demanded documentation standards, Asian companies could get even more out of such co-development. Thus, European regulatory expertise and structured approach complement e.g. with comparatively inexpensive, but highly qualified Asian work-force in order to ensure that the requirements and standards of the European market are met.

In the following, the general advantages and disadvantages of developing in-house shall be presented in a key word format:

PROS:

- Increased margins through integration of more value-added steps
- Full control/transparency of cost, risks, timing, supply chain (in particular API sources), regulatory strategy, products as such (strengths, break-lines, colour, shape, etc.)
- less dependency on external suppliers
- No need to audit own plant(s), (but need to audit raw material suppliers)
- Opportunity for submission of company-owned patents
- Outsourcing opportunities

CONS:

- High development cost, leading to a long pay back period (plus money spent on development is no longer available for marketing)
- Higher fixed cost (assets & Human Resources)
- Critical size is needed
- Development risks (patent infringement, failure of bio- or stability studies, etc.)
- Risk of non-profitable production cost in case of market price erosion
- Need for early decision whether to develop a certain product or not
- Promising acquisitions are rare (more than 50% of acquisitions are below expectations)
- Requirement of dedicated facilities for the production of speciality pharmaceuticals such as biotechnology/hormons/oncology products

- Responsibility for quality of API, although not being involved in manufacturing

3.2 In-Licensing

The term "Licensing" stams from the words "License" and "Marketing" and stands for commercialization of licenses. In the pharmaceutical industry, in-licensing is numerously used to strenghten the portfolio, e.g. if there is no internal development department or simply to add on to the pipeline. Other motivations for in-licensing or outsourcing of development activities are increased needs to manage complex synthesis processes, specialisation in key technologies in demand (soft-gel capsules, sterile formulations, special drug delivery etc.) and abilities to handle high potency drugs with dedicated equipment. In case a company is not able to conduct certain activities - be it due to a lack of capacity or expertise -, external services become valuable.

Similar to what has been listed above for internal development, the general advantages and disadvantages of licensing in are pointed out as follows:

PROS:

- Flexibility (e.g. allows later decision making and freedom of choice in between different regulatory or supply options)
- Taking advantage of external expertise and capacity (e.g. regulatory and patent service, audits, development and production, logistics and supply chain management as such)
- Benefits from economies of scale
- Less risk (failure of development, investment in production facilities etc.)
- Time to market (choosing the fastest registration route)
- More than one API source and site of manufacture

CONS:

- Poor transparency and less control (regarding quality)
- Higher supplier dependency
- Less individual solutions (strengths, shape, breakline, colour etc)

- Exclusivity has to be paid for
- Supply prices are compartively higher than own production costs

Furthermore, in-licensing can strategically be used as a bridging solution, if the internal development fails or is running late. (Not only) in the generic business, time correlates to money. In the end, the loss of market share due to a delayed launch is more expensive than the purchase of an external license. Again, a brief overview shall point out the advantages and disadvantages of in-licensing as a bridging solution.

PROS:

- Enables launch in time with the loss of exclusivity date
- Hedging of risk

CONS:

- More expensive than choosing a single route of development and application for marketing authorisation (e.g. multiple regulatory fees)
- Two or more suppliers for the same product might lead to difficulties in closing contract with the second source (which might insist on exclusive production)

4 POINTS FOR CONSIDERATION

4.1 Costs

Development costs:

During development of finished dosage forms, costs accrue unequally distributed in various steps. In the following, the process of generic product development is outlined along the significant milesstones.

1. API qualification
2. Formulation trials up to the intended formulation
3. Manufacture of pilot batches
4. Stability program
5. Bioequivalence studies

6. Dossier compilation
7. Submission to regulatory authorities (thereby initiating the registration process)

Development costs also depend on:

1. Properties of the API
2. Cost of formulation trials
3. Individual requirements for certain dosage forms (e.g. three BE-studies for modified release products)
4. Development of methods (unless a monograph in the Ph. Eur. exists)
5. Validation of methods
6. Development of process and validation of process
7. Failing batches
8. Pilot batches
9. Cost of production staff and equipment
10. Maintenance of production site(s)

Usually bioequivalence studies are the most expensive integral part of the development process, followed by the stability program. To quantify dimensions, a regular single dose bioequivalence study (oral solids) totals about 180.000 €. Often immediate release solid dosage forms are comparatively less expensive. Modified release products require three bioequivalence studies (single dose fasted, single dose fed and multiple dose), adding up to about 500.000 €. The pricing depends on the study design, number of volunteers, the pharmacologic active components (and potential metabolites), etc. For regular stability studies about 1000€ have to be calculated per testing point. In the majority of cases, stability studies amount to around 100.000€.

As generic products are developed many years later than the original product, enhanced technology often makes generic medicines even superior. Roughly for the whole development process including all milesstones a generic company may calculate about 1mio. € plus/minus 500.000€ depending on the degree of difficulty of development.

Further factors contribute to development cost of generic drugs:

- Cost for additional batch release testing ("EU re-analysis")
- Comprehensive patent evaluation (covering manufacturing & marketing territories), cost of failed/delayed developments
- Logistic cost
- Currency risks
- Stock piling due to hedging suppliers risks

In-Licensing costs

The down payment demanded by the developing company is lower and less risky than the cost of own development, the latter often made up for by out-licensing such development. However, in typical licensing deals, the following payments are charged:

- Upfront-/down payments (as a compensation of the development costs)
- Supply prices (e.g. calculated as percentage of the buyers price to the wholesaler; discounts on samples are common as they contribute in yielding a higher market share– useful for both parties; further, often transfer prices which are later to be settled against the actual supply prices are agreed on)
- Floor prices represent the minimum supply price viable for the manufacturer
- License fees for using the associated intellectual property
- Regulatory fees charged by authorities and for management of the registration process

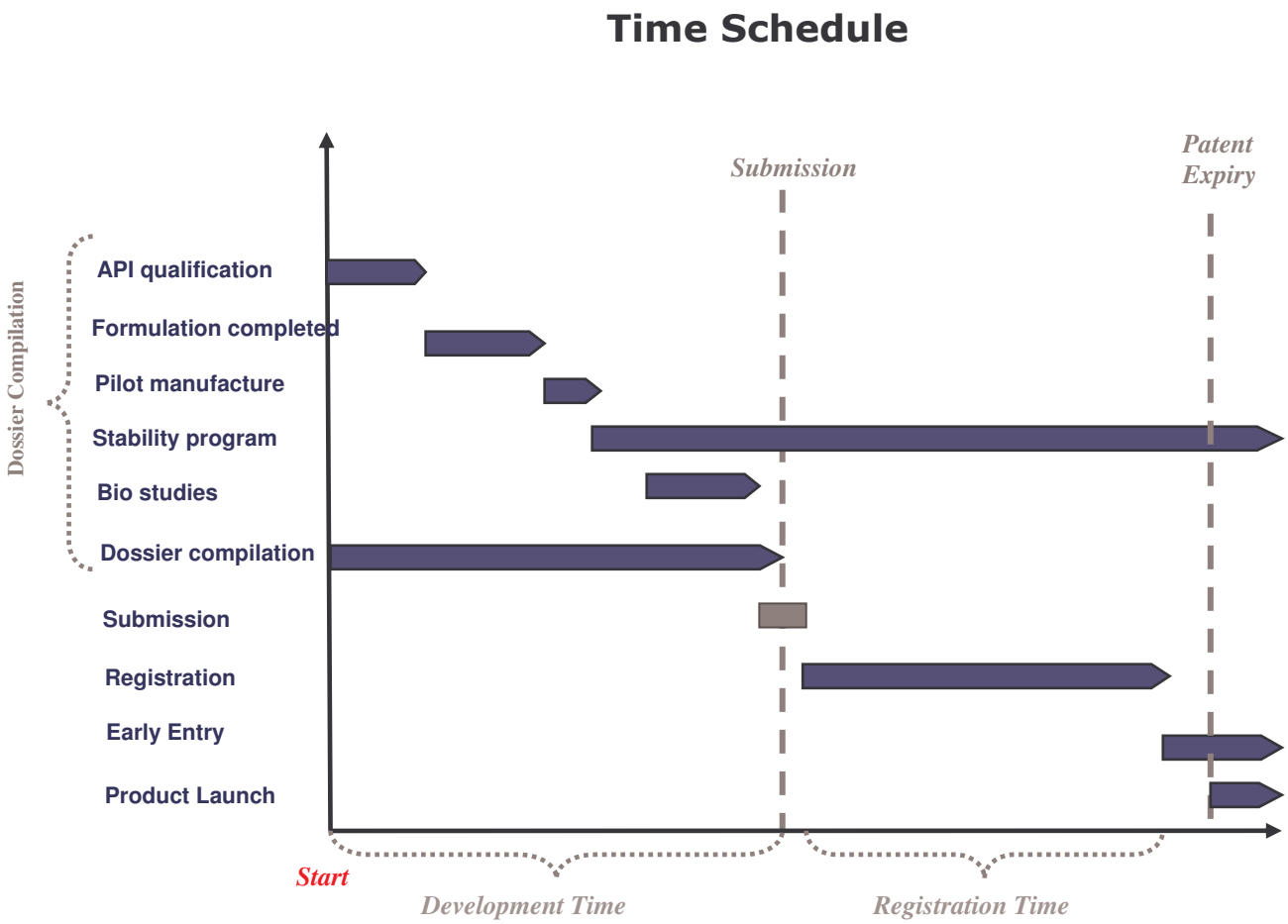
Table 1 Outline Costs of virtual in-house development vs. in-licensing

COST	
Cost of virtual in-house development	Cost of in-licensing
▫ Personnel (Regulatory affairs), material and equipment cost ▫ Cost of failed/delayed developments (incl. patent infringement)	Down-payment
Fixed cost for development site	Rather rare: royalties
Overhead cost	Cost for unwanted changes
Regulatory fees	Regulatory fees (usually included in down-payments)
Possibly lower supply price	Higher supply price
Cost of comprehensive patent evaluation (for manufacturing sites as well as marketing sites)	
Cost of stability and bioequivalence studies	

4.2 Time

"Time to market" is crucial (not only) within the generic pharmaceutical industry. Once a patent/SPC of an innovator drug expires, the market is segmented very soon. Early generic product launches ensure a long term high market share for such product. Hence generic companies aim to launch on the first day after patent/SPC expiry. A few financially sound companies disburse to the innovator sizable sums of money for so-called "early entries", for allowing them to launch even beforehand the patent expiry. Early entries aim to ensure even higher market shares. The fact that companies pay such high sums for early entries indicate the important role of time within the generic business, which directly correlates to money.

Figure 1 Time schedule



In former times own development of a standard generic product (with a simple galenic) for multiple markets had to be started at least five years before patent/SPC expiry. A rough calculation included two years for the formulation development, stability and bioequivalence studies and further three years for a national procedure with a subsequent MRP. By adoption of the new decentralized procedure the registration time has been accelerated: the total time required until grant of a market authorization is condensed to at least four years prior to the targeted loss of exclusivity date. Hence, GMP-certified API sources have to be selected well in advance.

In-Licensing

Contrary to time necessary for development, in-licensing can basically be started almost anytime before the relevant launch date. The appropriate regulatory strategy, fast internal processes in general and in particular artwork and logistics are factors with significant impact on the lead time. Furthermore, in-licensing can be strategically used to bridge the gap until the own product is approved.

Table 2 Outline Time needed for In-house development vs. In-licensing

TIME	
In-house development	In-licensing
Start > 4 years prior to patent expiry (time until a decision is needed)	Start (almost) anytime before LoE

4.3 Regulatory Strategy

Regulatory strategy adopts a key role which is to be considered well in advance of the targeted launch date – whether early in the development process or before any in-licensing activity takes place. Regulatory decisions depend on desired territories for marketing. Potential procedure options such as national application (with subsequent MRP to follow) versus DCP or CP need to be balanced carefully.

Formerly regulatory submission in RMS used to be requisite three years before patent expiry or before the desired launch date in multiple markets was scheduled, beforehand the new decentral registration procedure came into force. Since November 2005, companies may calculate about two years for the complete registration process. The determined time of more than two years for the registration process is a conservative time dimension, during which multinational applications for marketing authorisations ought to be approved. Companies development strategy and early licensing activities offer a freedom of choice between different regulatory strategies.

The current legal situation allows innovator companies in the EU to enjoy a data exclusivity of eight years during which the regulatory authorities are not allowing

generic companies to make reference to the originator's pre-clinical and clinical data. Additional two years of market exclusivity endow the innovator further time to recoup their R&D investment. Moreover, an additional year of market exclusivity is gained for a new indication, which was clinically tested for during the first eight years of data exclusivity. This "8+2+1" provision needs to be considered for the regulatory strategy of generic products.

Further, it might be adjuvant for the regulatory strategy to conduct a SmPC-comparison for gaining the best options of member states combined in one procedure. Main regulatory objectives are to achieve as many indications as possible, clinical substitution status to the brand product (fundamental in some member states), reimbursement status for prescription only medicines etc.

4.3.1 In-house development and regulatory strategy

Miscellaneous issues will arise during the drug development phase that also affects the regulatory strategy. It may turn out, that the medicinal product is not stable under conditions defined from ICH, the breakscore does not work properly or the bitter taste cannot be masked. All such issues observed during drug development process need thorough evaluation and are to be assessed for their possible regulatory consequences. The (global) development plan should consider different scenarios and also include the corresponding regulatory strategies. It should be regarded a living document modified in accordance with various issues that may come up during the development process.

For example the design of bioequivalence studies may influence the regulatory strategy regarding choice of potential MS intended for the registration procedure. A couple of regulatory authorities require lower limits for certain substances, than common acceptance criteria of 80-125%. An example of the Danish authority is given in the table displaying alternative acceptance limits below.

Table 3 Acceptance limits of the Danish authority

Substance	ATC	Acceptance limits for AUC and C_{max}	
		MA	Generic range
Aminophylline/ Theophylline	R03DA05 R03DA04 R03DB04 R03DA54 R03DA74		90-111%
Lithium	N05AN01		90-111%
Thyroxine	H03AA		90-111%
Wafarin	B01AA03		90-111%
Antiepileptics apart from benzodiazepines	N03 (NOT N03AE)		90-111%
Immunosuppressives	L04	90-111%	90-111%
Antiarrhythmics	C01B		90-111%
Centrally acting anorectics	A08A		90-111%
Tricyclic antidepressiva	N06AA		90-111%

(http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=6437)

Summary of criteria that could influence regulatory strategies:

- Quality of product (e.g. stability, impurities, specifications…)
- Bioequivalence-study (design, conduct, data assessment….)
- Patent situation (API, finished product)
- Time to market (incl. *regulatory strategy*)
- Pharmaceutical form & strengths
- Product appearance (bulk [incl. breakability if applicable], packaging)
- Competitors and their strategy

4.3.2 In-Licensing and regulatory strategy

Thorough preparations of Dossier audits are key factors for success of any in-licensing activity. Experienced regulatory professionals and taking advantage of well written SOPs regarding audit procedures are relevant for a successful dossier audit.

Reimbursement status and a thorough country-based SmPC comparison are of great importance for the regulatory strategy.

Using external regulatory services, unfavourable results due to subordination of individual applicants into overall regulatory strategies may occur. Therefore the individual flexibility is limited.

Along with licensing activities beneficial services of complete after sales regulatory assistance are often provided. Questions of maintenance support are important to raise. Regulatory service agreements may be applicable in case of a lack of regulatory capacities in house.

Table 4 Outline Regulatory Affairs issues in IHD vs. IL

REGULATORY AFFAIRS	
In-house development	In-licensing
Regulatory submission in RMS > 2 years before patent expiry or the desired launch date in multiple markets	Complete after sales regulatory assistance
Freedom of choice in between offered regulatory strategies	External regulatory services often results in subordination of individual applicants into overall regulatory strategies

4.4 Quality

Quality aspects of generic products have to be considered of high importance independent whether concerning proprietary developments or in-licensed products. Despite quality being an indispensable criterion, a certain minimum quality standard could be assumed to be achieved by successfully passing the registration process of the regulatory authorities. The higher the quality of a product (and its corresponding registration documentation), the more likely is a fast completion of the registration procedure.

When comparing generic products with their respective originator reference product, sometimes the variations between different batches of the originator products are even higher than the average difference between the generic batches (e.g. in dissolution tests). Such findings indicate the differences in assessment over the time in between the originators registration and the corresponding generic application.

In reaction to increasing quality standards (in-house as well as demanded by the regulatory authorities) pharmaceutical companies audit own production sites as well as external manufacturers and suppliers more frequently and more detailed to improve and assure product quality.

4.5 Risk factors

4.5.1 Infringements of patents

Since the 1980s, patent protection activities for pharmaceutical products have increased substantially. In fact, the EU currently provides the highest level of market protection for pharmaceuticals in the world. A validity period of 20 year for product patents applies since the early 1990s. The invention must have a practical purpose. Patents are registrable nationally as well as with the European Patent Office (EPO). However, the patents granted by the EPO represent only a bundle of national patents. No EU-wide single patent system exists to date, although the Community Patent (supposedly) is in the final stages of enactment. Generally, the

Patent registration provides the patentee with the right to prevent anyone producing, using, dealing with or importing the invention for 20 years. This 20-year protection can now be increased by up to 5 more years through a Supplementary Protection Certificate (SPC). However, the sum of remaining patent period and SPC shall not be more than 15 years. SPCs were introduced in 1992 to compensate originator companies for the time and cost of developing until product launch.

Further patents for varying periods are regularly granted to pharmaceutical companies for new uses, indications, dosages and changes in formulation, colour or markings in addition to this 25-year protection. Once granted, these patents provide extra years of market monopoly for often insignificant changes, providing little or no added therapeutic value to patients (provided that no circumvention of such patents has been identified).

Patent landscape becomes increasingly complex. On the one hand it is current practice of innovator companies to maximise lifecycle by seeking to obtain as many patents as possible during the development and marketing cycle and to apply for new uses of established products or to add on to the time-lag between patent grant and public health approval. Likewise, originators are willing to invest substantial capital to sue any generic company copying their product. Even in cases where it is unlikely that they will be successful in court proceedings they will almost always chose to turn to the next instance, just to go on challenging the "copy cat". On the other hand, generic companies claim more and patents by themselves as they found out that this represents an elegant way to keep competitors "off their back" (switch from the former reactive to a proactive approach).

In order to exemplify the numerous aspects of patent claims around a single product, some relevant issues are listed below:

- Formulation
- Aspects of drug delivery
- Processes and intermediates
- Packaging

- Method of treatment (including different dosing, new use of known excipients, and combination therapies)
- Polymorphism: different crystalline structures
- Screening Methods
- Gene-markers (showing response to drug therapy)

The extent of coverage of pharmaceutical patents and their complex evaluation introduce considerable risks of infringement, which causes professional legal and scientific advice to be essential. Due to increasing patent claims, the business risk of patent infringement arises in any pharmaceutical drug development. In case of patent litigation, the advantage of combined forces with other concerned companies is usually taken into consideration.

As of November 2005 the "Bolar-Roche" provision (refers to the U.S. patent case of Roche Products, Inc. vs Bolar Pharmaceutical Co., Inc.) is in force within the EU. This provision permits all activities necessary to achieve a marketing authorisation at any competent European authority. This leaves the production of commercial batches as the main patent infringing activity within the EU.

4.5.2 Failure of Bioequivalence-study

A generic medicine is defined as being identical to a branded drug in terms of active principle, and having the same pharmaceutical form, safety level, and therapeutic effectiveness.

Hence, generics (lawfully referring to original (pre-)clinical data after expiry of the exclusivity phase), are being developed to display a dissolution profile of no significant difference to the originator's reference product (risk minimising in-vitro testing). Thereafter, the vital question is whether the product is bioequivalent with the reference product or not (in vivo studies). Bioequivalence studies are one of the major cost factors within generic drug development, wherefore a negative result is extremely disappointing to the ambitious generic company. Besides the generic product, a careful selection of a CRO of particular experience with this type of

product is strongly recommended. Further a thorough preparation of the study design is also a factor for success of the study.

4.5.3 Current therapeutic principle(s)

A partial risk factor persists for the therapeutic principle of "older" drugs in general. Despite careful investigations prior to generic drug development, it occurs that new therapeutic principles prove to be superior. Market shares for former drug principles decrease and the estimated profits do not justify anymore for numerous generic distributors. This instance is peculiar severe, if the own development phase for the older principle is well advanced and various investments have already been made.

4.5.4 Developments may fail...

As with any pharmaceutical research and developement, there will always be projects that will have to be canceled (even in the very last stages) e.g. due to severe stability problems or bioequivalence may be evidenced, but study participants may suffer from e.g. serious rash.

4.5.5 Competitors

It might be the case that what was once expected to be a rather exclusive development turns out to be copied by others. Likewise a certain time advantage once held might melt down due to unforeseen development problems. Evenly, a competitor might have achived an exclusive supply for a difficult to produce API or claim own patents, thereby blocking the only profitable way to circumvent a certain originator process patent. Therefore, the question might arise whether it is still reasonable to follow up with the concerned development project or whether it might be more useful to assign capacity and capital to other more promising projects.

4.5.6 Macro-environment

Besides the general risk of a therapeutic principle no longer being current state of the art, further macro-environmental changes might have a significant impact on the development/licensing activities. For instance, the reviewed pharmaceutical legislation in the EU provided a new route of registration, the DCP, which theoretically allows submitting the registration file a later stage than before. To name a negative example, there might be a governmental initiative to cut prices as recently happened in Germany. Expensive developments might be forced to be stopped due to the enforced reduction of potential margin.

Table 5 Outline Risk factors in In-house development vs. In-licensing

RISK FACTORS	
In-house development	In-licensing
Patent infringement / litigation (cost, expertise, complete failure, combined forces)	Patent infringement / litigation (cost, expertise, complete failure, combined forces)
Failure of bio and/or stability studies	Failure of bio and/or stability studies – corresponding exit paragraphs to be included in supply agreement
Therapeutic principle may no longer be state of the art	Conflicting activities of competitors
Developments may fail in the very last stages	Developments may fail in the very last stages
Market/regulatory situation may change during development phase	

PART II

5 DECISION ANALYSIS I

IN-LICENSING VS. IN-HOUSE-DEVELOPMENT

5.1 Situation Appraisal (SA) I

World Generics presents itself as a 15 year-old, mid-sized, vertically integrated generic company, with two development and production sites in Germany. Its Headquarter is situated near Cologne. Currently the marketing focus is limited to a few European markets, but further markets like US and Japan are planned to be entered into on a medium-term basis.

The current quarterly management review requires a strategic decision whether to further increase the number of in-licensed products or to maintain the number of development projects. Momentarily about 65% of the World Generics products marketed are developed in-house and about 35% are licensed in. Specialities are more difficult to be developed and produced in-house, as special equipment and conditions besides particular competences are required, which are therefore typical products from external sources. World Generics has already concentrated on in-licensing activities regarding specialized products e.g. oncology products or hormones. The product portfolio consists currently of 200 products whereof 15 products have sales > 10 batches per year, about 35 products have sales between 3 to 10 batches per year, about 50 products have sales between 1 and 3 batches per year and about 100 products have sales < 1 batch per year. Especially the large number of small products with comparatively high manufacture costs forces to reconsider the current business strategy.

Facing decreasing profitability due to high production costs and significant maintenance cost of the owned development and production facilities, the management board is looking for alternatives and cost-saving strategies. Hence, the Head of Business Development was asked to present a detailed analysis to the management board, whether it is more beneficial for World Generics to develop

products still in-house or to in-license new products. Strategic considerations as well as economic and regulatory factors have to be thoroughly taken into account.

The complex situation of the pharmaceutical market – especially in Germany - and the high cost pressure force pharmaceutical companies (including World Generics) to re-consider their business model.

5.2 Structuring of concerns I

Potential reasons for shrinking profits and high development and production cost of World Generics:

- Development projects failed
- Development projects were delayed (resulting in late launches)
- Decreasing market shares
- In-balance between profit and cost
- Competitors can offer their products at lower prices
- Decreasing market prices

What changes are anticipated to create threats or opportunities?

Threats:

1. Fierce competition due to low cost Asian manufacturers.
2. Further political pressure on prices
3. Sinking market reputation
4. Trend towards niche products, which cannot be produced with available equipment and experience

Opportunities:

Company owned production sites would give the opportunities to out-license

What areas should be improved?

Development times and production cost are to be reduced. Costly investments in R&D capacity are required.

What decisions need to be made?

A decision between further support of the own development and production site and a turn to pure in-licensing activities has to be made.

What actions do need to be taken?

If World Generics prefers to stick with the current business model, cost could be reduced with a relocation of the production site to a low cost country and also by means of co-development. If in-licensing activities shall turn out to be the new business model, the production site will have to be sold.

5.3 Assignment of priorities I

5.3.1 Seriousness

Failed or delayed development may have dramatic negative impact on market shares as well as the company's reputation. Missed product launches contribute to lower growth rates. Cost saving programs need to be set up. Further, risk comes up due to investments in development capacities.

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5.3.2 Urgency

Action is quickly needed during a set period of three to five years. Liquidity will cover the forthcoming year in which reduction of cost needs to be achieved. Further time reducing strategies for development projects are to be defined as soon as possible.

5.3.3 Growth

Due to the high ambitions of (mainly Asian) competitors, World Generics is to accomplish the necessary turnaround soonest, as the global competition will hardly wait for them to be ready for it.

5.4 Location of suitable process: differentiation between PA, DA & PPA I

Problem Analysis (PA)

Higher production cost compared to (Asian) competitors lead to higher market prices. High cost for failed development reduce profitability. Delays of developments lead to a late market entry and low market shares. World Generics is bearing the development risk and solely responsible for the appropriate risk management.

Decision Analysis (DA)

The board of World Generics has to decide whether to maintain the cost-intensive production site, or to move production site in a low cost country (CEE, Asia) or to sell the production facilities and to fully concentrate on licensing in future.

Potential Problem Analysis (PPA)

Moving the production site to low cost countries could lead to a reduction of jobs in Germany. Difficulties with works committee and trade union are likely.

Selling production facilities and to rely to 100% to in-licensing activities demands to strengthen the business development unit. Maybe not all products intended for future launches are available to be licensed in.

5.5 Decision Statement I

Purpose of decision:

To evaluate if a company own development and production facility is still profitable in a changing environment for a midsized generic company or if a review of the business model is required. Outsourcing opportunities could be a second option to regain investments. The alternative business model focuses on in-licensing activities to enlarge the product portfolio. In the latter case World Generics would concentrate on its marketing and distribution competences.

Results to be achieved:

1. Increase sales and profitability of World Generics.
2. Extend product portfolio

3. Product launches immediately after patent expiry to save market shares
4. Early entries (as an opportunity to increase market share beyond the scenario of launching straight after the loss of exclusivity date)

5.6 Objectives and criteria I

Objectives of World Generics:

1. High profitability
2. Early entry or at least a launch straight after the loss of exclusivity date
3. Little risk
4. High flexibility
5. Low dependency
6. Excellent reputation

Criteria:

1. Marketing Authorisation(s) in time (MA includes Bioequivalence with reference product & sufficient product quality (e.g. stability))
2. No patent infringement
3. High units and sales of reference product by the innovator company
4. Low development and manufacturing (or supply) costs
5. Exclusivity or at least weak competition
6. GxP conformity of all involved manufacturers (where applicable)
7. Sufficient production capacities
8. Product appearance fulfils World Generics marketing requirements

5.7 Classification of objectives and criteria I

5.7.1 Musts I

1. Marketing authorisation(s) granted (includes expiration of data exclusivity)
2. No patent infringement
3. Bioequivalence to reference product
4. Launch straight after loss of exclusivity of reference product
5. No quality problems (e.g. stability)

6. Reasonable development costs (up to a maximum for each individualproduct)
7. Viable Production cost
8. Suppliers of API (and intermediates) have to be GMP certified.
9. Minimum market share
10. Minimum units sales
11. Approved shelf life of at least 24 months

5.7.2 Wants I

For the subsequent list of "wants", the assignment of respective weights shall be as follows:

- Very important (4)
- Important (3)
- Preferred option (2)
- Nice to have (1)

1. Early entry in order to yield additional market share (2)
2. Gaining highest possible market shares (4)
3. lowest possible development and production cost (4)
4. Transparency/Control (cost, timelines, etc.) (2)
5. high flexibility (different regulatory options, change of order sizes, etc.) (2)
6. lowest possible dependency on third parties (1)
7. alternative API sources in dossier (3)
8. longest possible shelf life (3)
9. little risk (3)
10. Outsourcing opportunities (2)
11. Submission of own patents (3)
12. USP (3)

6 ADDITIONAL ALTERNATIVES I

To strengthen the company's portfolio, there are two main options discussed in detail within this thesis ("In-house development" or "In-licensing"). What could be potential alternatives to IHD or IL?
Alternatively in order to launch the product in time, World Generics could use in-licensing as a bridging solution if the own development fails or runs late. Another cost-saving alternative regarding in-house development would be to take advantage of a co-development model in collaboration with an adequate partner.

Given a certain minimum market share, other options for a generic company could be co-marketing or co-promotion of new products. The co-marketing alliance – though rather common for originator companies - avoids product development cost and may potentially increase the reputation of such generic company, which later may prove useful when it comes to negotiate for an early entry opportunity.
Co-promotion means that based on a respective individual marketing authorisation, two companies are marketing the same product under its respective brand name; whereas co-marketing indicates that two companies are marketing the same product under different brand names.

6.1 Comparison of additional alternatives against objectives and criteria I

The comparison of the above alternatives with the defined objectives and criteria shows that there are conceivable alternatives to all intents and purposes. In-Licensing as a bridging solution presents a redeeming option in case that the own product development is delayed. As main disadvantage of this alternative are the associated additional costs.
Co-development is a financially rewarding alternative which has to be seriously considered for future projects. The essential disadvantage of co-development is the associated semi-exclusivity in the later marketing of the product. In consideration of the fact that numerous companies aim to launch promising products anyway, the potential weakness of semi-exclusivity is not considered to be significant. Co-promotion and co-marketing win over almost no present risk factors. World Generics, as a beneficiary of a contract would make its sales force available to the

original company. However, these options are highly cost-intensive and do therefore not actually fit into a cost-saving strategy.

Table 6 Comparison of In-Licensing, Co-Development and joint marketing

Objectives and criteria	**In-Licensing (as bridging solution)**	**Co-Development**	**Co-promotion & Co-marketing**
High profitability	**-**	**+**	**-**
Early entry or at least launch straight after loss of exclusivity date	**+/-**	**+/-**	**+/-**
Excellent reputation	**-**	**+/-**	**+**
Low risks	**+**	**-**	**+**
High flexibility	**+**	**-**	**+/-**
Low dependency	**+/-**	**-**	**-**
Low dev. & manuf. (or supply) cost	**-**	**+**	**-**
Marketing Authorisation(s) in time (incl. BE study & prod. quality)	**+/-**	**+/-**	**+/-**
No patent infringement	**+**	**-**	**+**
Exclusivity or at least weak competition	**-**	**+**	**+**
High units and sales of reference product by the innovator company	**+**	**+**	**+**
GXP conformity	**+**	**+**	**+**
Sufficient production capacities	**+**	**+**	**+**
Product appearance fulfils World Generics marketing requirements	**+**	**+**	**-**

+ = applies ; - = does not apply

Additional alternatives are assessed irrespective of the main options IHD or IL.

7 POTENTIAL PROBLEM ANALYSIS (PPA) I

7.1 Risks and Consequences I

Table 7 Risks and potential consequences of In-house Development

Risks	Consequences
Patent infringement	Patent litigation (cost, expertise, complete failure, payment of damages)
Failure of bio and/or stability studies	Delay of development, loss of capital expenditure
Therapeutic principle may no longer be state of the art	Low market share, product can not regain investments
Developments may too costly, too risky, be too late or fail in the very last stages	Loss of capital expenditure, reformulation leads to further delay
Market/regulatory situation may change during development phase	Additional tests to be performed, complex registration process, market share not as high as expected

Table 8 Risks and (contractual) consequences of In-Licensing

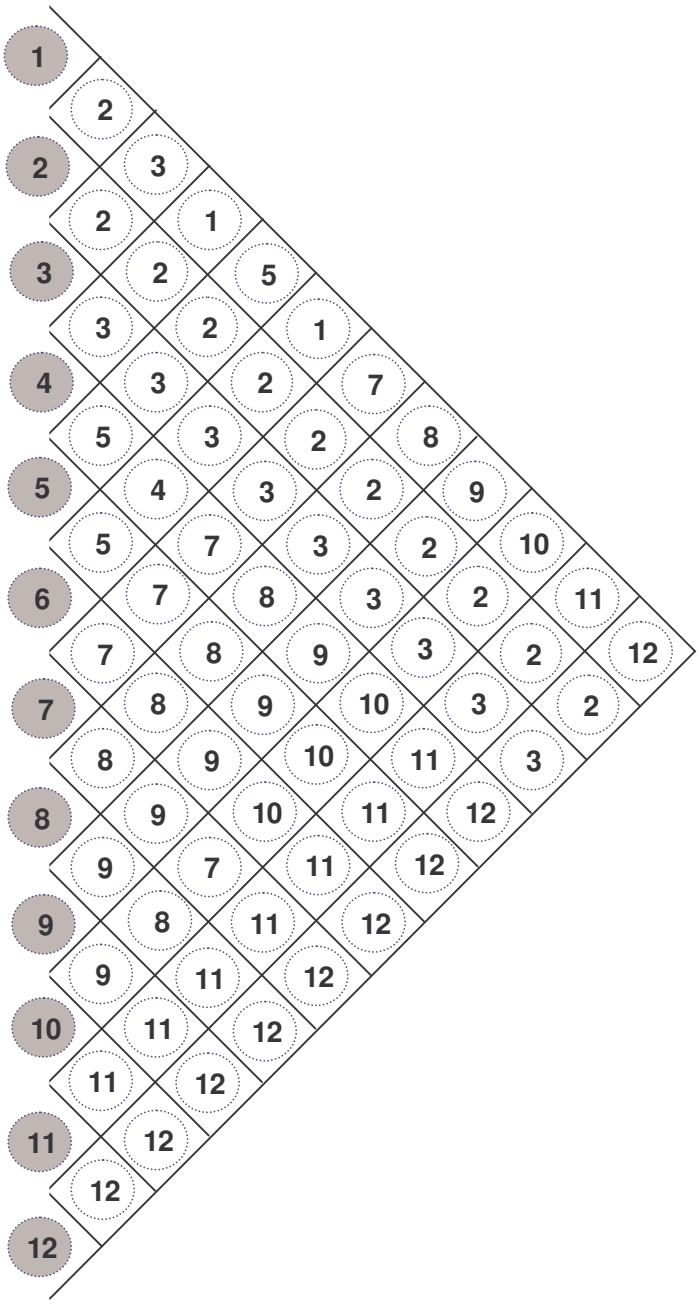
Risks	(Contractual) Consequences
Patent infringement	Patent litigation (cost, expertise of outlicensing company often provided, complete failure); alternative sourcing depends on availability and contractual situation
Failure of bio and/or stability studies	Corresponding contractual exit clauses are to be included in the supply agreement; (ideally) allowance of alternative sources, too.
Developments may fail in the very last stages	Corresponding contractual exit clauses are to be included in the supply agreement; (ideally) allowance of alternative sources, too.

8 DECISION I

8.1 Best Balanced Choice I

8.1.1 Decision Matrix for World Generics ("Wants")

Figure 2 Decision Matrix (IHD or IL)



Numbers in Matrix	
1	2x
2	11x
3	10x
4	1x
5	3x
6	0x
7	5x
8	6x
9	7x
10	4x
11	8x
12	9x

Table 9 Appraisal of Results ("Wants" of World Generics)

Results					
Want No.	**No. in Matrix (Weight)**	**Factor IHD**	**Factor IL**	**Results IHD**	**Results IL**
1	2	1	1	2	2
2	11	1	1	11	11
3	10	2	1	20	10
4	1	2	1	2	1
5	3	1	2	3	6
6	0*	2	1	0	0
7	5	1	1	5	5
8	6	1	2	6	12
9	7	0	2	0	14
10	4	2	0	8	0
11	8	2	0	16	0
12	9	2	1	18	9
Total				**91**	**70**

0= does not apply; 1= does partly apply; 2= does strongly apply (except 0*, which only refers to the matrix no.)

9 CONCLUSION I

This decision analysis indicates in-house development to meet more of the set objectives and criteria. Consequently, it represents an advantageous option compared to a strategy based on pure in-licensing.

However, in view of the global competition and the therewith associated cost pressure, it is questionable whether a mid-sized company such as World Generics is able to further maintain own development and production sites, as these assets necessitate a critical company size to be able to indeed take advantage of economies of scale. Thus, each company has to individually assess how to best balance its case. The most important arguments pro company-owned production sites and internal development are increased margins through integration of more value added steps, full transparency of cost and control of the supply chain. Such

are contrasted by disadvantages like high risks and fixed costs as well as the need for early decisions. In particular the latter two caused the managing board of World Generics to strategically decide for in-licensing as preferred option in the future. They consider the favourability of in-licensing to be underpinned by its flexibility and in particular by its potential cost savings through external expertise-capacities, the latter of which the board believes to become more important due to growing cost pressure in the pharmaceutical market.

On the basis of these assumptions World Generics will focus more on in-licensing activities, deemed to be more beneficial for the company than following cost-intensive development strategies. Further, there seem to be little opportunities to realise economies of scale within their own production site. For commodity products a price competition between numerous providers leads to attractive commercial terms for potential licensees. The managing board of World Generics expects the payable sum out of accumulated supply prices and downpayment to be much lower than the costs associated with an own complete pharmaceutical development program (including the necessary investigation of bioequivalence) and subsequent production.

On the other hand, the top management decides to make best use of World Generics' development and production facilities by focusing on modified release products in future. Thereby, it intends to create a niche development company which shall take advantage of outsourcing opportunities to reassert the site. Additionally increased filing of own patents and contract manufacturing for specific niche products shall contribute to the bottom-line of World Generics' new strategy.

PART III

10 DECISION ANALYSIS II

DEVELOPMENT IN INDIA VS. IN CENTRAL AND EASTERN EUROPE

10.1 Situation Appraisal (SA) II

One typical feature of the pharmaceutical industry is the variety of its inter-company relationships, traditionally much greater than in other industries. It relies to a considerable degree on outsourcing: backwards in R&D through various licensing arrangements and contract manufacturing as well as forwards through joint marketing agreements. This is referred to as the cluster approach. Its major advantage is to allow for access to the broadest spectrum of physical and intellectual resources, combined with potentially greater operational flexibility than possible by integrating all activities into a single company.

As concluded in the preceding decision analysis, in-house development offers diverse advantages to generic companies. On the other hand, various smaller and even mid-sized generic companies struggle with the high costs of proprietary manufacturing sites and the risks associated with own pharmaceutical developments. These facts are strong drivers for relocation and outsourcing activities, but also to benefit from foreign know how and insufficient patent legislation in certain countries (protecting the originator's innovations).

Profitable opportunities are offered in low cost regions regarding mission oriented product development. The following analysis shall evaluate strengths and weaknesses of two low cost regions conceivable for outsourcing R&D activities. Within the scope of this thesis, India shall represent Asia and will be compared to Poland as an example for CEE countries which recently entered into the EU.

Overview India:

India disposes the highest number of FDA-certified manufacturing sites for pharmaceutical products beyond the US. Indian labor cost constitute about 10%-30% of the European cost for qualified employees and are therefore among the

lowest personnel cost in the world. However, low personnel cost do not mean by definition a low-cost production site. In modern manufacturing sites with a great automation level, labor cost contribute only around 10% of the total cost. Contrastingly, for pharmaceutical products with complex packaging requirements (at a lower automation level) labor costs up to 50% are not unusual. The more personal intensive a production works, the more cost-savings can be expected through a production transfer to India. Essential prerequisites such as availability of high end production or analytical equipment, engineering services or qualified suppliers in general have worthily evolved meanwhile, causing India to represent not only on of the most important API sources, but also becoming a location for demanding finished dosage forms. API prices do not have to be necessarily considered in a comparison of cost (production cost India vs. Europe), because irrespective production site it is anyway a general practice to procure API from sources throughout the world.

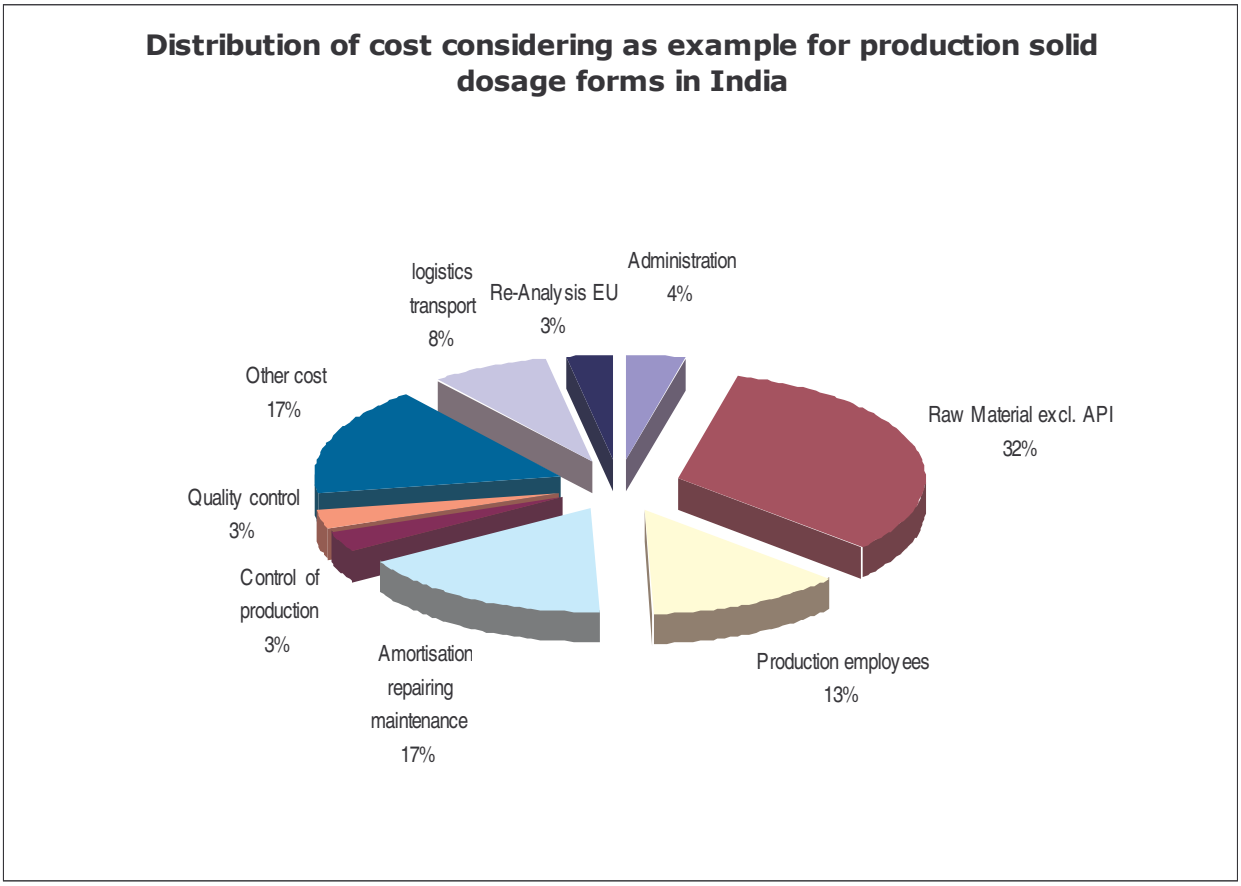
In comparison to (Western-)Europe and US, India provides the additional advantage of low expenses for premises and construction which is significantly related to lower labor cost. Moreover, most raw materials could be purchased locally and at lower cost than in Europe or US. In addition, some leading global manufacturers of equipment offer their products in India at discounted prices due to low price Korean and regional competition.

Due to the long distance to the key markets for pharmaceutical products – Europe and US – cost of transport and freight are partly reducing the aspired cost-savings.

The Indian Patent Act of 1970 allowed companies to focus on product development without having to fear being sanctioned. Consequently, their generic R&D skills increased, as did their corresponding pipelines. On the 1st of January 2005, India obliged itself to comply with the WTO trade-related requirements. Hence, beside procedure patents, also product patents are now recognized.

The following diagram displays the result of an analysis of averaged cost distribution for a solid dosage form in India (performed by the consulting company “Type Two”).

Figure 3 Distribution cost in India



Source: Pharm. Ind. 67,Nr. 1, 41-45 (2005)

Overview CEE countries

CEE countries are not clearly defined. In this thesis the term CEE is used as Central and Eastern European member states, which entered the EU in 2004: Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Slovak Republic and Slovenia.

Poland

As the CEE region comprises quite different regions regarding e.g. the size of the population, infrastructure, etc., it would be difficult to directly compare them as a whole with India. Therefore, Poland with the largest population of all CEE countries (almost 40 Mio inhabitants) has been chosen to represent the Eastern territory

within the scope of the decision analysis. Poland suffers from the highest rate of unemployment within the EU (18% in 2005). Germany is the most important trade partner of Poland (import and export amount to about a quarter of the respective total). The pharmaceutical industry and pharmaceutical manufacturers are well positioned and mostly specialised in the production of generic drugs. Before EU accession, the generic market benefited from a data exclusivity period of merely three years. Furthermore, SPC's were introduced in 2000 only. Consequently, the market share of generic medicines attained 60% by value and even 85% by volume (2005, respectively). In 2003, 183 pharmaceutical companies had its place of business in Poland, with their (regional) employees totaling ca. 25.000. The 15 companies formerly belonging to the Polfa-group are responsible for about two thirds of the production of pharmaceutical products in Poland. Nowadays, a significant part of Polish pharmaceutical industry is privatised, but many companies were taken over by foreign investors such as GlaxoSmithKline and IVAX (now belonging to the Teva group). Foreign companies such as GlaxoSmithKline, Schwarz Pharma, Lek Polska, Solco Basel and Rhone PoulencRorer set up own production sites in Poland. Currently, GlaxoSmithKline boasts the highest market share in Poland (followed by the local player Polpharma), but also other foreign companies such as Lek (Novartis), Krka, ICN, Merck&Co and Pliva are highly active within the Polish market. The states of the former Soviet Union represent the most important market for Polish pharmaceutical companies.

Low costs and tax advantages as an investment incentive

Central European and East European member states are attractive as research and production locations. Privatization of the pharmaceutical sector offers appealing investments to western groups, particularly as it is difficult for many Eastern European companies to comply with the stricter EU legal requirements for production at GMP standards and the protection of intellectual property.

A growing scientific and technological establishment is providing a cheaper source for research and clinical trials. Likewise driven by various tax incentives, manufacturers are moving towards the Eastern region. For instance in the Czech Republic, start-ups or joint-ventures of certain industries are not required to pay

any taxes during the first ten years (under certain conditions). In the free trade zones of Lithuania, investments of more than one million euros are exempted for six years from business tax. The regular business tax rate in the new member states varies from 15 percent in Latvia and Lithuania to 25 percent in Slovenia. Further, a biophysicist in Czech Republic earns monthly about 800 US dollars, i.e., only a fraction of the salary paid for an equivalently qualified person in US or Western Europe.

Patent protection in CEE

The EU-Enlargement of May 2004 has raised particular concerns amongst the originator pharmaceutical industry. Traditionally these countries had comparatively weak patent protection for pharmaceuticals, although all CEE countries introduced product patent protection for pharmaceuticals between 1991 and 1994 and diverse forms of pipeline protection for non-novel medicines. Therefore many products patented in the rest of Europe between 1976 and 1991 are not patented in CEE countries. This allows for generic competition and contributes significantly to the price differences between drugs in those Eastern regions and those in the current EU Member States.

10.2 Structuring of concerns II

India

Indian generics companies take pride in their highly qualified staff and their strong synthesis and production capabilities. In the following, the general situation of the pharmaceutical industry in India shall be highlighted.

Strengths:

- High quality of products
- Low cost manufacturing capabilities by low personnel cost (10%-30% of western markets) and through local sourcing opportunities of raw materials and equipment (at 20-30% lower costs)

- Strong chemistry and process engineering capabilities
- Highly qualified personnel

Weaknesses:

- Recent adoption of patent protection reduces attractiveness. In the past India, had only recognized process patents, but since January 2005, the country formally also recognizes product patents.
- Documentation not yet at western standards
- Focus on own manufacturing capability rather than on market demands

Poland (exemplary for CEE)

Eastern Europe generic companies have a stronger understanding regarding the European market and documentation standards, as pointed out in the brief description of the main characteristics associated with CEE countries.

Strengths:

- Good understanding of both western and eastern specific market needs
- Low manufacturing cost
- High product quality from certified manufacturers

Weaknesses:

- Few API production sites
- Numerous eastern European companies have a lack of R&D capacities and know-how.
- Shortage of regulatory capacity due to ongoing EU-harmonisation process.

10.3 Location of suitable process: differentiation between PA, DA & PPA II

Problem Analysis

High development costs significantly reduce profitability.

Decision Analysis

The following decision analysis balances WANT-arguments for outsourcing of development and manufacturing activities according to their significance. Within a second step a scoring system shall evaluate the best possible option – India or Poland.

Potential Problem Analysis II

Not openly communicating of failure or delays, e.g. due to cultural differences, will cause intransparency of the development progress and its associated time lines. In order to be prepared for potential problems along the supply chain, some companies increase the inventory kept in stock, thereby binding more capital. Furthermore, sourcing finished products from a non-EU country like India also requires additional re-analysis in for the country belonging to the European community.

10.4 Decision Analysis (DA) II

10.4.1 Decision Statement II

Is it more beneficial for generic companies to develop and manufacture products in India or in Poland?

10.5 Objectives and criteria II

Most objectives and criteria are identical with section 5.6.

Objectives:

1. High profitability

2. (Time lines allow for) Early entry or at least a launch straight after the loss of exclusivity date
3. High product quality
4. High flexibility
5. Pharmaceutical infrastructure (e.g. access to raw material sources, maintenance of equipment)

Criteria:

1. Marketing Authorisation(s) in time (MA includes Bioequivalence with reference product & sufficient product quality (e.g. stability))
2. No patent infringement
3. Low development and manufacturing (or supply) costs
4. Quality control and quality reliability
5. Exclusivity or at least weak competition
6. GxP conformity (where applicable)
7. Sufficient production capacities
8. Experience & competence

10.6 Classification of objectives and criteria II

10.6.1 Musts II

1. No patent infringement
2. Bioequivalence to reference product
3. Launch straight after loss of exclusivity of reference product
4. No quality problems (e.g. stability)
5. Reasonable development costs (up to a maximum for each individual product)
6. Viable production costs
7. Suppliers of API (and intermediates) have to be GMP certified.
8. ICH conform product development
9. Infrastructure (political stability, logistics, electricity etc.)

10.6.2 Wants II

For the subsequent list of "WANTS" the assignment of respective weights shall be as follows:

- Very important (4)
- Important (3)
- Preferred option (2)
- Nice to have (1)

1. Lowest possible development and production cost (4)
2. Transparency/Control (cost, timelines, etc.) (3)
3. R&D competences (3)
4. API & FDF from one source (1)
5. Alternative API sources in dossier (diversification of risks, costs etc.) (3)
6. Lack of patent protection / early product development (4)
7. Tax incentives (3)
8. Implementation of latest technologies and process improvements (3)
9. Short transport distances (1)
10. No EU re-analysis (2)
11. Cultural fit (2)
12. Monetary stability (3)
13. Lower payment of customs (1)
14. Highly qualified employees (3)
15. Quality control and quality reliability (3)
16. Delivery reliability (4)
17. Documentation according to EU standards (3)
18. Good understanding of EU market demands (2)

10.7 Additional alternatives II

What could be potential alternatives to India or Poland? Few Asian countries could be considered as an alternative to India. Overridingly, China belongs to the most interesting candidates, as well as Singapore. Whilst China is especially attractive due to its low wage costs and strategic relevance associated with the size of its

population, Singapore gains its importance through tax incentives offered to the pharmaceutical industry.

Another conceivable option is Malta as a European location for development and production sites. One reason for the significance of Malta in the generic industry is a lack of patent protection, providing the generic industry with more freedom to "copy" than in most Western European member states. Currently Malta is not a member of the EPO (European Patent Office), but this might change in the future as Malta is invited to accede.

10.8 Comparison of two main additional alternatives against objectives and criteria II

The above facts evidence that both, China and Malta, represent potential alternatives to India/Poland. In China, there is much room for improvement regarding infrastructure and (to a lesser extent) pharmaceutical know how, though much progress has already been made. China has gained its relevance through API synthesis, whereas manufacturing of FDF is still quite far from being at Western standards. Malta comes up with a good pharmaceutical infrastructure besides competences in both contract manufacturing and production of FDF. A comparison of China and Malta against objectives and criteria is presented in the table below.

Table 10 Alternatives to India/Poland: comparison of China and Malta

Objectives and criteria	**China**	**Malta**
High profitability	**+**	**+/-**
Early entry or at least a launch straight after the loss of exclusivity date	**+**	**+**
High product quality	**+/-**	**+**
High flexibility	**+**	**+**
Pharmaceutical infrastructure (e.g. access to raw material sources, maintenance and repair of equipment)	**-**	**+**
Marketing Authorisation(s) in time (MA includes Bioequivalence with reference product & sufficient product quality (e.g. stability))	**+/-**	**+**
No patent infringement	**+**	**+**
Low development and manufacturing (or supply) costs	**+**	**+/-**
Quality control and quality reliability	**+/-**	**+**
Exclusivity or at least weak competition	**-**	**+/-**
GxP conformity (where applicable)	**+/-**	**+**
Sufficient production capacities	**+**	**+/-**
Experience & competence	**-**	**+/-**

+ = applies ; - = does not apply

Additional alternatives are assessed irrespective of the main options India or Poland / CEE.

11 POTENTIAL PROBLEM ANALYSIS (PPA) II

11.1 Risks and Consequences II

Table 11 India: Risks and Consequences

Risks	**Consequences**
Recent adoption of patent protection. Since January 2005 India formally recognizes also product patents.	Reduced attractiveness for the generic industry.
Documentations are not yet at western standards	Experienced DRA-Manager with knowledge of EU requirements needed to support Indian colleagues.
Focus on own manufacturing capability rather than on market demands	Product attribute may not be important for marketing.

Table 12 Poland (CEE): Risks and Consequences

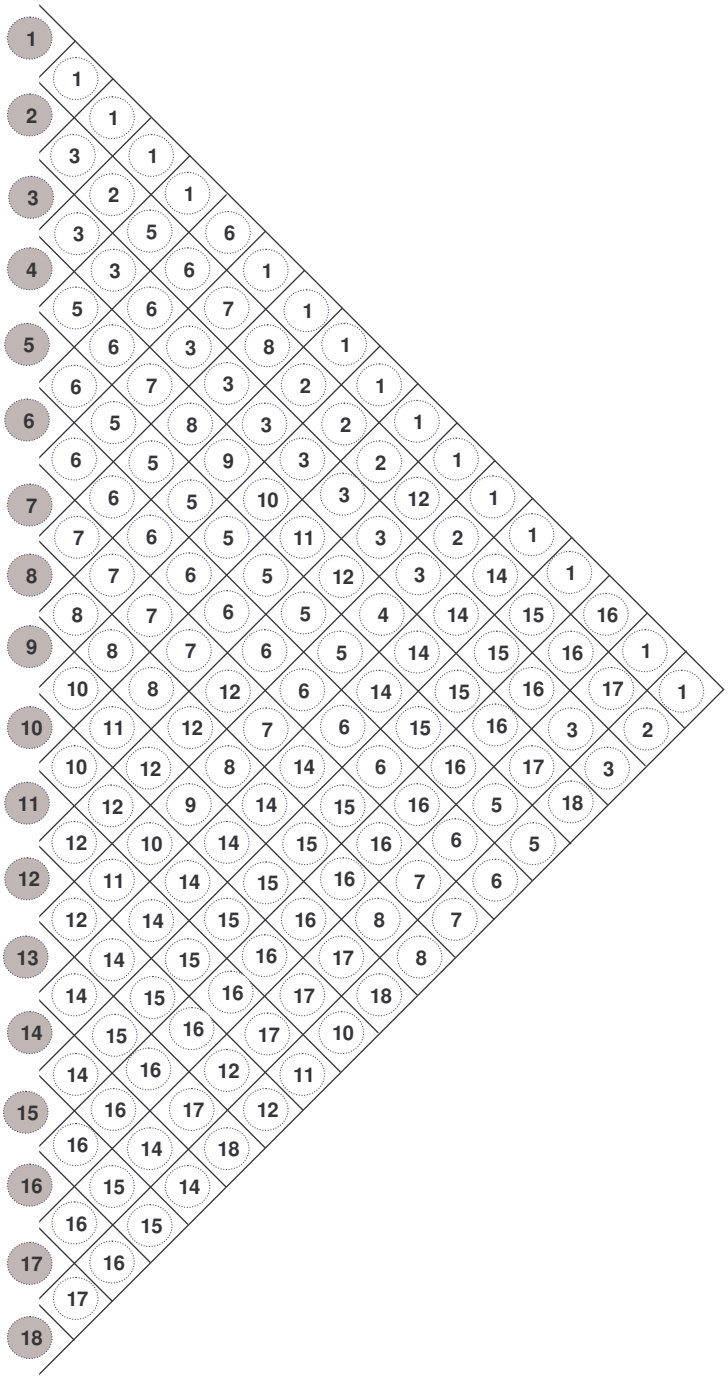
Risks	Consequences
Shortage of regulatory capacities due to ongoing EU-harmonisation process	Product launches out of CEE countries or rather Poland might be delayed.
Outsourcing of API supply	Little control and transparency with a view to ASMF (*former* DMF) changes, making it more difficult to evaluate for non patent infringement.
Little expertise in product development (numerous eastern European companies have a lack of R&D capacity/know-how)	Either partner with experienced companies (e.g. Pliva, Lek/Sandoz) or support with own professionals.

12 DECISION II

12.1 Best Balanced Choice II

12.1.1 Decision matrix „Wants" II

Figure 4 Decision matrix (India or Poland)



Numbers in Matrix			
1	15x	10	5x
2	6x	11	4x
3	12x	12	10x
4	1x	13	0x
5	11x	14	14x
6	16x	15	13x
7	9x	16	17x
8	8x	17	7x
9	2x	18	3x

Table 13 Appraisal of Results (Evaluation: R&D in India or Poland/CEE)

Results					
Argument No.	**Number in Matrix**	**Factor India**	**Factor Poland**	**Results India**	**Results Poland**
1	15	2	1	30	15
2	6	1	1	6	6
3	12	2	1	24	12
4	1	2	1	2	1
5	11	1	1	11	11
6	16	1	1	16	16
7	9	0	2	0	18
8	8	2	1	16	8
9	2	0	1	0	2
10	5	0	2	0	10
11	4	0	1	0	4
12	10	1	1	10	10
13	0*	0	2	0	0
14	14	2	1	28	14
15	13	1	1	13	13
16	17	1	1	17	17
17	7	1	2	7	14
18	3	1	2	3	6
Total				**183**	**177**

0= does not apply; 1= does partly apply; 2= does strongly apply (except 0*, which only refers to the matrix no.)

13 CONCLUSION II

It becomes obvious from the table of results that the differences between the two selected low cost options India and Poland / CEE are of little significance (though India often scores higher than Poland, e.g. regarding R&D competences).

With its commitment to the WTO to also recognize product patents, India sacrifices its long time advantage of allowing for product development of patented drugs. Thereupon the Indian pharmaceutical industry is forced to abandon their traditional business models. By taking advantage of India's low labour costs on the one hand and well trained staff on the other hand, contract manufacturing as well as contract research (clinical trial and drug discovery) have become promising opportunities for the Indian pharmaceutical industry.

Dr. Anji Reddy, the chairman of the second largest Indian pharmaceutical company Dr. Reddy's, goes even further, by declaring that he would like to see his company to be under the top ten pharmaceutical companies in the world, a goal which he believes can only be achieved by engaging in the discovery of new chemical entities, thereby leaving alleged "copy cat" strategies far behind.

In recent years the trend came up to invest in facilities in Central and Eastern Europe, both to stake a claim to an emerging market for pharmaceuticals as CEE states join the European Union, and to take advantage of the low labour, set-up and production costs of these countries. Besides the advantages of e.g. having a much better understanding of the EU market demands, in 2004 a joint report[2] from Cap Gemini and Ernst & Young found that Central and Eastern European countries, which offer lower clinical development costs, higher site productivity and less local regulations, could relieve some of the pricing pressures on pharmaceutical firms in Europe.

[2] Source: http://www.in-pharmatechnologist.com/news/news-NG.asp?id=50919&ip=1

14 OUTLOOK

Putting all aforesaid together, an optimized strategy for an European generic company can be developed along the value chain in order to allow for the most profitable option in combination with ensuring experience and know-how. The pharmaceutical development could basically take place all over the world, mainly following patent-, know-how-, infrastructure- and cost of labour considerations. A joint development strategy could lead to a maximisation of the development outcome. To advance most rapidly, the companies involved should ensure to work (e.g. linked via an IT-sharepoint solution) in two shifts à 10 hours within time zones of (ideally) 12 hour difference (three shifts à 8 hours would involve three parties and represent therefore a quite theoretical concept for a worldwide cooperation of independent companies). In particular for R&D purposes, establishment of so-called "collaborative knowledge networks" could be an option for sharing of information, thereby enhancing each company's performance by means of web-based approaches. The most profitable production of API is likely to take place in India or China; the low cost production of the corresponding FDF should include an Indian or CEE located source. The necessary bioequivalence studies could e.g. be conducted in South Africa or in CEE countries. Assuming that marketing is intended to happen within EU countries, the overall project management as well as all Regulatory Affairs activities (ideally performed by the same [group of] person[s]) should be organized by an experienced European company (service company or in-house, depending on the available expertise).

On the purpose of taking it even further, i.e. by striving for a worldwide marketing authorisation, a global regulatory procedure is needed for. By making best use of the CTD format, which may serve as a regulatory bracket for applications of registration of medicinal products throughout the world, considerations about a global regulatory procedure can be initiated. Based on the on the framework of the ICH guidelines and the CTD format, competent authorities could be named for each continent, e.g. FDA for America and EMEA for Europe, in order to establish one authority for worldwide evaluation of central international applications. Such global product might require clinical studies in all populations, stability studies for all

climatic conditions and creation of a worldwide valid SmPC text as well as e.g. mock-ups for each country.

A strategic move to strengthen the generic position in the field of research and to integrate generic expertise could be the creation of an advantageous situation between the established pharmaceutical industry and generic companies. For instance the generic industry could conduct research within the first eight years of data exclusivity in order to discover new indications or improve the galenic formulation of the finished dosage form. In return for a successful extension of the originators market exclusivity, the generic company could receive an early entry opportunity for the corresponding product.

Pharmaceutical companies could increasingly benefit of DRA-Managers as key personnel. For entering virgin markets or emerging big markets like India, regulatory accomplishment could become essential. It is therefore to consider whether DRA-manager could gain a kind of "pre-marketing" function in future by generally exploring new regions. DRA-managers could spearhead by collecting all necessary information for marketing products in new countries or regions. Responsibilities could switch from the marketing department to Regulatory Affairs by expanding the tasks of DRA-managers who already know a lot about the specifics of a certain country (e.g. specific requirements of the patient information leaflet or the lay-out of the carton box, which already reflect local characteristics). For example, if European generic companies decide to market products in India as one of the potent emerging markets, they have to be aware of the particular regulatory circumstances and requirements: as Indian authorities are not (yet?) committed to the ICH guidelines, Indian drug registration procedures still follow the "Drugs and cosmetic Act of 1940" and the "Drugs and cosmetic rules of 1945" in the revised version. Further, as for instance opposed to the German authority, Indian authorities are much more open for various combinations of active ingredients, with pharmaceutical companies not having to demonstrate the contribution of each component to the drug efficacy.

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