

DUE DILIGENCE OF R&D PROJECTS – A GUIDELINE FOR EVALUATING REGULATORY ASPECTS

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LIST OF ABBREVIATIONS

AE	Adverse Event
API	Active Pharmaceutical Ingredient
CA	Competent Authority
CFR	US Code of Federal Regulation
CL	Contract Laboratory
CMC	Chemistry, Manufacturing and Control
CMO	Contract Manufacturing Organisation
COG	Cost of Good
CQA	Critical Quality Attributes
CRO	Contract Research Association
CTA	Clinical Trial Application
DP	Drug Product
DS	Drug Substance
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
IB	Investigators' Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IPC	In-Process Control
KOL	Key Opinion Leader
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MOA	Mode of Action
NCE	New Chemical Entity
NDA	New Drug Application
NPV	Net Present Value
OECD	Organisation for Economic Co-Operation and Development
PIP	Paediatric Investigation Plan
ROI	Return on Investment

QA	Quality Assurance
QP	Qualified Person
QTPP	Quality Target Product Profile
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPC	Supplemental Protection Certificate
TMF	Trial Master File
TPP	Target Product Profile

1 EXECUTIVE SUMMARY

This master's thesis is a guide on all regulatory aspects which need to be taken into account when performing a due diligence of a pharmaceutical research and development project for the purpose of reaching a decision as to whether the project offered is worth licensing in. Since the final acceptance of a project by regulatory authorities, i.e. its marketing authorisation, is the basis for revenues, it is recommended that the evaluation of the project in question should be headed by a regulatory expert supported by technical, pre-clinical, clinical, quality and marketing specialists. It is described in detail how to assess the acceptability by competent authorities, the scientific value, the market and development potential, the fit to the company's product portfolio and available resources, the net present value and the risk/benefit profile. The description of this thorough evaluation is followed by a guidance on how to come to a well considered decision on whether to license in a project or not. This is substantiated by a detailed model case exemplifying a decision analysis on whether to licence in a Phase III project.

2 INTRODUCTION

The licensing of research and development products is a common business strategy in the pharmaceutical industry. It is a process during which the developer of a drug (licensor) makes its technology available to a collaboration partner (licensee) who will take on the further development. The decision to out-license may be based on numerous reasons; a few examples are listed below⁽¹⁾:

- Forming alliances with partners with manufacturing capability.
The licensor may only have the resources to fully develop a drug but needs to partner with another company that has the capability to manufacture the product for the market.
- Progression of the development of the technology to take the product to market.
The licensor might be restricted in resources and must partner to take its product through later development phases and into the market.
- Exploitation in a different field of application.
The licensor may have the expertise of exploiting a certain development field, e.g. single indications or diagnostic applications, but might not have the capability or interest to exploit another field.
- No commercial capability.
The licensor may be a research institute or a university which does not have the capability to exploit the project commercially at all and needs to partner with an organisation that does have that capability.

The legal agreements which lay down the collaboration structure contain 1) a description on how the licensee may exploit the technology, 2) how the licensor is compensated (usually financially) for the grant of those rights and 3) the respective rights, duties and obligations of both parties that will govern their legal relationship.

The possible deal structures which result of one of the above mentioned motives can be described as one of the following:

1. Exclusive license:⁽¹⁾ In the pharmaceutical sector, most licenses are granted on an exclusive basis where the licensee can exploit the intellectual property (IP) to the exclusion of all other developers, including the licensor. The licensor may however limit the license to specific fields (e.g. indications or marketing territories) to maximise his benefits anticipated from commercialisation, taking into account the licensee's particular expertise, market position,

existing product range, and marketing and distribution networks. A licensor might also consider retaining the right to exploit in its own field of capability, e.g. diagnostic applications, and to license out the rights in fields of exploitation where the licensor has no resources, capability, or marketing networks, such as all human applications other than diagnostic.

2. Co-development agreement / strategic alliance: In this strategic alliance, the IP is licensed to the licensee and both the licensor and the licensee participate in the further development of the licensed compound. The development risks and the expertise of both companies as well as the later revenues are shared. Hereby the licensor's financial remuneration is generally greater compared to a deal where the licensee takes over all risks and costs of the further development.

The manner in which the responsibilities are split up between the licensor and the licensee can be manifold. For example, one party might take over the production of the drug whilst the other party takes care of the preclinical and clinical studies. Alternatively the co-development could be focused only on the clinical development, where the companies split the work by e.g. territories or indications. Either the parties' contributions can focus on their respective area of expertise, or the collaboration could be aimed at broadening the expertise of a partner in a specific field by participating in the specific sector of development.

3. Co-marketing/co-promotion collaboration: In such a collaboration, the IP is licensed to the licensee (either in an exclusive or co-development agreement); additionally both the licensor and the licensee jointly market (i.e. individual trade names) or co-promote (i.e. identical trade name) the drug in question. Hereby the licensor is also able to add value to the project, by accessing his marketing networks and resources to jointly market the drug with the licensee. The co-promotion or co-marketing can be subdivided into separate territories (e.g. based on relevant expertise or available resources such as subsidiaries) or focus on identical territories, creating a competitive situation.
4. Acquisition: Strictly speaking, the acquisition of a project is not a collaboration since all the rights and risks (!) of the project in question are assigned to the acquiring party which then can independently develop the drug in question or even take the decision to license it out. This deal structure however is not that common in the pharmaceutical sector, since the probability of a scientific, clinical, regulatory and market failure need to be taken into consideration when determining the price of the project, thereby minimizing its profitability⁽¹⁾.

A deed of assignment cannot be terminated (in contrast to a license), i.e. the IP cannot be reverted to the original owner, although – in exceptional circumstances – provisions can be met if certain obligations are not met.

The deal values constitute 1) upfront payments, which are paid upon the signing of the license, 2) milestone payments, which are paid as particular milestones along the development, clinical and regulatory pathway are reached, and 3) royalties, once there is a product in the marketplace. The amounts of these components may change, but theoretically, the total deal value should remain the same⁽¹⁾.

Since the potential licensee should carefully analyse the value of an offered project before investing in any collaboration or acquisition, this master thesis gives guidance on the evaluation of the regulatory aspects of pharmaceutical research and development projects which are offered for licensing. The quality of the work performed by the licensor, the development potential, the scientific benefit, the business case, legal aspect and also possible development gaps and risks of the product in question are taken into account, thereby providing assistance in generating a recommendation on the value of the project. As a support, examples of EU and US laws and regulations are given as these are most relevant for the development of pharmaceuticals since

these markets make up the major share of the world pharmaceutical market ⁽²⁾. However, the requirements dictated by other countries' laws need to be assessed by the potential licensee on a case-by-case basis if it is intended to develop the product there.

Based on such an analysis the pharmaceutical company interested in acquiring a relevant project will be able to make a qualified strategic decision regarding the potential deal. Guidance is given on how such a decision making process is best approached. This is also exemplified by a detailed model case which assesses whether or not to sign an exclusive license for a Phase III project.

For the sake of simplicity Marketing Authorisations will be termed MAs throughout this document, irrespective of how it is named in the territory it is filed in; the according application of a MA is termed marketing authorisation application (MAA).

3 ASSESSMENT OF TARGET – GENERAL ASPECTS

3.1 DEFINITION OF A LICENSING GOAL

For a structured approach of identifying potential licensing targets, the basic conditions/parameters of the new project should be clearly defined. Apart from the scientific aspects which will be discussed further on, the business strategy and the available resources (human and financial) are important factors to be considered during the due diligence process.

The fit of the licensing candidate to the product portfolio of the interested company should be assessed. Is it complementary or rather similar to the available products? With similar products, the company already has substantial expertise in the respective indication; however, the failure of one compound might have a strong impact on the success rate of other, similar compounds. Complementary products might mitigate the risk of the whole product portfolio, but a broader spectrum of expertise is necessary for the development.

Regarding the similarity of the products, not only the indication should be considered; the chemistry of the drug also needs to be taken into account. Is the candidate a New Chemical Entity (NCE) or a biopharmaceutical product? Developing a biologic medicinal product brings with it much more developmental hurdles than a NCE (high molecular complexity, and sensitivity to manufacturing process changes). Does the interested company have the resources and the expertise to develop such a product?

The risk/benefit policy of the company should also be taken into account. Is the company willing to develop risky, first-in-class products which promise a high return on investment, or would the company rather like to invest in lower-risk, me-too products for which the proof of concept and marketability has already been demonstrated, which however will not be able to generate such a high profit margin?

The magnitude of risk of a product is also influenced by the amount of research data available, i.e. the development step it is in. As assessed by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in 2007, of every 5,000 molecules tested, only 250 promising new substances enter preclinical testing; 10 enter clinical development and only one will be approved by the regulatory authorities and make it to the market ⁽³⁾. Since the risk is inversely proportional to the price tag of a product, it should be carefully weighed whether the developmental or the financial burden should be taken.

All in all the decision whether to in-license a specific target is made through the tightly linked interplay of a number of different disciplines, making it a multi expert task.

3.2 ANALYSING THE LICENSOR

Apart from assessing the acquiring company's disposition to licence a developmental drug, it is also recommendable to identify the licensor's motivation for rendering the project and also to understand the deal structure which is envisioned.

The size of the company may play a considerable role in the grounds for licensing out. For instance a big pharmaceutical company might be more interested in developing blockbuster drugs and might license out or sell compounds identified during their discovery research which do not promise a return on investment above a set target. Such projected income would be based on the potential market size of the envisaged indication which is strongly influenced by the competitive environment, the determined advantages of the product in question and the available preclinical and clinical data supporting or not confirming the assumptions made. In contrast to big pharmaceutical companies the potential turnover might however be considered lucrative for a start-up company.

During the profiling of a drug, research results might reveal a compound to be suitable for an indication which is not part of the company's product portfolio or expertise. This might be a reason to consider the licensing out of such a product to a company which is experienced or specialised in developing such drugs. Although the rendering company might not have the expertise on the indication for which the compound shows potential, it might also consider broadening their own product portfolio. Entering a collaboration with a company experienced on the field in question would profit the licensee with regard to risk-sharing and gaining of expertise.

Apart from the above mentioned reasons, companies could also be interested in mitigating the risk and lowering the expenses of developing a promising compound. This is especially of interest for start-up companies which need to secure the financing of e.g. clinical trials or production of medicinal product.

As can be seen, the reason for out-licensing a product can be manifold and should be identified during due diligence processes since it might give hints to how the licensee assesses the scientific value and the market potential of the product. However, the communicated reason should also be questioned. The manner of how the project is appraised by the licensor and also his attitude during the due diligence process might possibly reveal a hidden agenda. How, for example, does the potential licensor react to questions with regard to identified inconsistencies of the project documentation? A reluctance to explain the problem in detail or effort to disguise the problem might hint to a weakness of the project which might have been concealed, hoping to achieve a higher deal price. For this reason people skills and common sense should be part of the toolkit used when performing a due diligence.

4 DRUG REGULATORY AFFAIRS

As the final acceptance of a project by regulatory authorities, i.e. its MA, is the basis for revenues, it is recommended that the evaluation of the project in question should be headed by a regulatory expert supported by CMC (Chemistry, Manufacturing and Control), pre-clinical, clinical, quality, marketing and legal specialists. The detailed analysis of the regulatory and scientific viability of a drug should enable the due diligence team to establish a recommended development strategy which is the basis for the final decision on whether to license the product or not.

Since the key success factor of a drug is its acceptability by the Competent Authorities (CAs) which finally grant the MAs, this should be the starting point for assessing the value of a project during a due diligence process. The review of prior discussions with or evaluations performed by CAs (if any) should serve as a good basis to assess the acceptability of the available scientific data on the drug in question. For this it needs to be identified which interactions have already taken place with the regulatory bodies (e.g. EU: national or European Medicines Agency (EMA) scientific advice or hearings during Clinical Trial Applications (CTAs) or even MAA procedures; US: pre-Investigational New Drug (pre-IND) meeting, end-of-Phase II meeting or scientific advice). The results of these meetings should indicate whether concerns were raised.

In particular it should be investigated whether common questions regarding the development of a drug have already been addressed with one or more CAs. Examples of topics which need to be addressed with the CAs during the course of drug development are:

- Adequacy of the toxicology program (i.e. subchronic, chronic, reproduction and carcinogenicity studies);
- Adequacy of characterisation of the range of safe and effective doses and the dose interval;
- Confirmation on the suitability of the Ph II clinical study design and statistical methodology to document efficacy;
- Verification of appropriateness of the clinical endpoints;
- Acceptability of clinical data obtained outside of the concerned region as supporting data in the MAA;
- Adequacy of the tentative package insert;
- Adequacy of data and planned additional studies to support labelling in special patient populations;
- Determination of the length of therapy necessary to support long-term safety;
- Acceptability of the Phase III world-wide clinical development plan and protocols; or
- Requirement of any additional information which is necessary to support the MAA.

Should the CA(s) have raised any issues on these or similar topics, it needs to be investigated, whether this has already been mitigated or addressed by the licensor. The involvement of the CMC, preclinical and clinical experts should help to assess the quality and appropriateness of the mitigation work and the existing risk of not meeting the authority's demand. It is also worthwhile investigating the completeness of the documentation to ensure all authority objections are identified (in the case of correspondence with the FDA, all submitted documents should contain a serial number which can easily be checked for completeness).

Furthermore it should be investigated, whether part of the documentation could contain orphan drug applications or even MAAs. The information regarding the submission, grant or denial of orphan drug applications is useful for assessing the further development options including costs and timelines (refer to Section 11 for more details). Details on a failed MAA procedure – either based on the rejection by the authority or a withdrawal by the applicant – should reveal the best information on the issues authorities have with the project. Since such information has a major negative impact on the value of a project, the licensor might try to conceal such documents during a due-diligence process. As a precaution the regulatory expert should have a look at authority websites (e.g. <http://www.emea.europa.eu/htms/human/withdraw/withdraw.htm> or <http://www.emea.europa.eu/htms/human/refusals/list.htm>) which might also contain information on failed procedures (the provision of such information is mandatory for the EMA⁽⁵⁶⁾).

After having gained an impression with regard to the authority view of the project in question, the likelihood of the success of gaining a MA should be evaluated. For this, the detailed analysis of scientific success of the project by the CMC, preclinical, clinical and quality experts described in Sections 5-8 should be taken into account. In case a fair chance is seen, the further development plan of the project should be established as described in the Section 11, further taking marketing and legal aspects into consideration (described in Sections 9 and 10 respectively).

The generation of such an all encompassing view on the potential project is of essence for the final decision analysis. Since the further development is dictated by the available regulations, it is recommended that the regulatory expert should coordinate the whole due diligence process.

5 CHEMISTRY, MANUFACTURING AND CONTROLS

The basis for preclinical and clinical development to assess the safety and efficacy of a potential new drug is the availability of Investigational Medicinal Product (IMP). Its chemical/biological structure should be well analysed. The manufacturing process and the purity and quality of the produced compound should (as far as possible) be consistent to ensure ongoing safety levels for treated animals, volunteers and patients and to warrant the validity of the single studies which contribute to the overall picture on the safety and efficacy of the drug, being the basis for a MA.

Results of studies performed with IMP of different quality or composition cannot be considered complementary; at most they could be considered supportive. Therefore, when assessing the CMC of a compound, the overall quality of the manufacturing process, the Drug Substance (DS), the final Drug Product (DP) and its appropriateness for the use in humans should be investigated in order to identify:

- 1) Its inherent risks;
- 2) Steps to mitigate these risks (further optimisation of the manufacturing process) and
- 3) Further work which still needs to be performed in order to establish a process which is acceptable for CAs when applying for a MA.

For a profitable project these additional development steps should not negatively affect the business case too much.

5.1 MANUFACTURING PROCESS

The robustness of the manufacturing process as well as the knowledge about and quality of the drug usually grows with an increase of experimental knowledge and adequate adjustments during the development process and might still continue beyond the marketing of the drug. Depending on the stage of development of the product, the amount of data available to assess the quality of the drug produced and the value of its manufacturing process varies.

In case the drug has already been tested in clinical trials, the information and data required to support the quality of the IMP for the use in humans is for example contained in the Investigational Medicinal Product Dossier (IMPD) which is part of the CTA in Europe⁽¹⁷⁾ or in the US IND dossier which is required for the use of unauthorised drugs to be tested in humans⁽¹⁸⁾. These regulatory documents are a good basis to get an overview of the manufacturing work performed and whether the work has been conducted under a valid manufacturer's license.

After gaining a general understanding of the process, the quality of all manufacturing steps – including the characterisation work – should be assessed. In general, the currently quality guidelines available from the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) listed in Annex 3 are applicable for all production steps (if at all relevant for the particular drug) which lead to the IMP which will be used in clinical trials or as market material.

These guidelines have partly been integrated into relevant legislations, e.g. the Good Manufacturing Practices (GMP) described in the ICH Q7 guideline which includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of Active Pharmaceutical Ingredients (APIs) and the related controls have been implemented in the EU Commission Directive 2003/94/EC and Parts 210-266 of the US 21 Code of Federal Regulations (CFR). A statement that the manufacturing site works in compliance with GMP, signed by the relevant Qualified Person (QP), should be contained in the IMPD⁽¹⁷⁾ and the IND. In general, assessing whether the recommendations given in the ICH Q8, Q9 and Q10 Guidelines have been implemented should additionally provide a good understanding regarding the quality of the work performed. A description of the quality management system of the organisation should be available in the Quality Manual⁽¹⁹⁾.

These examinations should be performed irrespective of whether the manufacturing work is performed directly by the licensor or by a Contract Manufacturing Organisation (CMO) or a Contract Laboratory (CL) / Contract Research Organisation (CRO). Possibly it would also be worthwhile to make enquiries regarding the reputation of the involved contractors and the QP(s) to assess the quality of the work and how stringent the quality checks were performed. Helpful for this assessment is a review of possible reports of audits performed by the contractor. Do these reveal any audit findings? If yes, have these findings been resolved in the meanwhile? In case no audit report should be available for a certain contractor, the reason for not having performed an audit should be questioned. The support of a quality assurance expert or of the licensee's own QP in this quality assessment might be considered.

Apart from the quality of the manufacturing steps, it should be assessed in detail how well the manufacturing process is understood, how robust it is and which weaknesses it might have which still need attention during the further development. For this, it should be analysed whether the manufacturing process is based on established methods or whether it is innovative (according to the Annex of the ICH Q8 Guideline, an appropriate manufacturing process should be identified). In both cases the acceptability by authorities should be investigated; an expert in the field should preferably be consulted for support. The acceptability of a method can be assessed by performing a literature search or reviewing assessment reports prepared previously by CAs upon granting MAs for products which were produced with similar methods (e.g. EU: European Public Assessment Report (EPAR); US: product approval information available on the website of the US Food and Drug Administration (FDA)). In case potential new processes have not yet been discussed with CAs in the scope of a scientific advice or CTAs which could have revealed authority opinions regarding the methods applied, an expert on the field might be able to determine how the process might be judged by CAs. In the EU the CPMP/QWP/848/96 Guideline (Note for Guidance on Process Validation) should also be taken into account.

The safety and environmental aspects of the compounds, the synthetic processes and the final product might also play a role in the acceptability of the process. An application for a MA needs to contain an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment⁽²⁰⁾. Although these requirements only relate to those environmental risks arising from use, storage and disposal of medicinal products and not for risks arising from the synthesis or manufacture of medicinal products, it might be worth examining the present process

for any components or sub-steps which might have an adverse effect on the environment either during the production process or once the product is distributed for clinical research or market use.

In further detail, the value and the safety of the established manufacturing process should be ascertained by looking at the (enantiomeric) purity of the DS produced. Is the product quantity and quality satisfactory and is it measurable and reproducible on a batch-to-batch basis (quality aspects are discussed in further detail in Section 5.2 below)? Further, it should be examined whether all In-Process Controls (IPCs) and analytical assays to verify the quality of the product have already been established, are sufficient to monitor the quality and the identity of the product and whether these have been validated according to the ICH Q2(R1) guideline. The extent to which specifications have been established should also be assessed. The quantity of data (amount of batches of the relevant dosage form) should be analysed to assess whether these allow meaningful specifications to be set. These specifications are usually summarised in a product specification file and should be based on the ICH Q6A or Q6B guidelines as appropriate (exceptions may be made in case the product is still in an early phase of development and only little experience has been gathered on the manufacturing process).

The economy of the production scale should also be taken into account when evaluating the project from a CMC perspective. Usually only small amounts of DP are produced for development purposes as only limited amounts are necessary and to keep development costs at a minimum (pilot scale). This is especially the case for biotechnologically derived products which are often very expensive to produce and often only render a small yield. Large scale manufacturing is however inevitable for a reduction of the Cost of Goods (COGs), which is necessary to establish a profitable process for a marketable product, and to also meet the market demands from a quantitative aspect. The CMC expert should hence investigate whether a scale-up of the current production process is technically feasible (Are there difficulties and critical points of the manufacturing process which might hinder a scale up? Are the apparatus and the methods appropriate for a large-scale production?) and whether the expected demand of material and COGs are realistic.

Once all the above mentioned aspects have been considered, practical aspects for the potential further development should be taken into account. Together with the preclinical and clinical experts it should be assessed what the substance need is for the further clinical development and whether these amounts are currently available. Should material be available, possible import restrictions should be assessed (e.g. the narcotics act in Germany ⁽²¹⁾). In case no drug is available for research use, timelines of producing such material should be determined, which might have a great impact on the overall development timelines, which in turn effects the time point at which the product might attain its MA – both milestones possibly significantly influencing the business case (together with the additional expenditures required).

The timelines for producing additional material should also include considerations regarding a technology transfer of the manufacturing process in case it is not intended that the licensor or the current CMO continues to be the manufacturer of the drug (this possibly includes the selection of new CMOs/CLs or the transferral of contracts from CMOs/CLs as well as the performance of audits). Such a technology transfer needs to include several (normally three) consecutive batches ⁽²²⁾ to evaluate the consistency of the process at the new site and possibly also additional in vitro or in vivo studies (e.g. for proof of bioequivalence ^{(23), (24)}, or requirements given for biotechnologically derived products ⁽²⁵⁾) to serve as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the DP.

In addition to the technical complexity, the risks of transferring the manufacturing process should be evaluated, since slight changes to the process can impact the quality of the product (e.g. interaction of a surfactant with a protein⁽²⁶⁾).

5.2 IMP QUALITY & STABILITY

Ancillary to assessing the quality and validity of the production process itself, the quality of the intermediates, DS, DP and excipients should be analysed. An initial step for this evaluation could again be to review the physicochemical characterisation data collated in the IMPD or IND (provided such a document is available). In general, a rigorous proof of the structure of the DS should be established and the degradation process⁽²⁷⁾ as well as all possible impurities^(28; 29; 30) identified and characterised as a basis for developing and validating suitable analytical procedures for the evaluation of the safety of the drug. As it is stated in the Annex to the ICH Q8 guideline, the pharmaceutical development should include (amongst others):

- Defining the Quality Target Product Profile (QTPP) as it relates to quality, safety and efficacy, considering e.g. the route of administration, dosage form, bioavailability, strength and stability;
- Identifying the potential Critical Quality Attributes (CQAs) of the DP, so that those product characteristics having an impact on product quality can be studied and controlled;
- Determining the critical quality attributes of the DS, excipients etc. and selecting the type and amount of excipients to deliver DP of the desired quality;
- Defining a control strategy.

Optionally, by applying an enhanced quality by design approach, a systemic evaluation, understanding and refining the formulation and manufacturing process could be performed, including:

- Identifying, through e.g. prior knowledge, experimentation and risk assessment, the material attributes and process parameters that can have an effect on the product CQAs;
- Determining the functional relationships that link material attributes and process parameters to product CQAs⁽³¹⁾.

The extent to which previous work performed by the licensor has been performed to meet these standards should be assessed during the due diligence process. Sources of variability that can impact the product quality should have been (or still need to be) identified, appropriately understood and subsequently controlled⁽³²⁾.

An integral part of the product quality is its stability; hence there is a need to provide evidence on how the quality of a DS or DP carries with time under the influence of a variety of environmental factors such as temperature, humidity and light⁽³³⁾. Stability studies should include testing of those attributes of the DS that are susceptible to change during storage and are likely to influence the quality, safety and/or efficacy⁽²⁷⁾. The testing should cover (as appropriate) the physical, chemical, biological and microbiological attributes; validated stability-indicating analytical procedures should be applied⁽²⁷⁾. For the final goal of receiving a MA for the drug in question, the stability studies should conform with the ICH Q1A(R2), Q1B, Q1C, Q1D, Q1E and Q5C guidelines, as appropriate.

The stability work performed to date on the drug in question should correlate to the stage of development it is in. Based on the guidelines mentioned above, it should be assessed, whether a

stability testing assay has been initiated for the dosage form or formulation which is currently used in clinical development (these data are meant to be part of the IMPD⁽¹⁷⁾ / IND⁽¹⁸⁾). The current status of stability results, stress/accelerated studies, stability-indicating methods for the intermediate, DS and the DP should be evaluated in order to assess whether it can be expected to be sufficiently stable. Preferably, information should be available on the container closure system.

By evaluating the available analytical stability-indicating data, it should be identified whether there are critical stability issues which still need to be addressed for the successful development of the drug.

5.3 DOSAGE FORM AND FORMULATION

The unvarying quality of the manufacturing process and the resulting product is an essential requirement for the development of a drug, supporting its safety and efficacy. The formulation and the dosage form however also play a major role with regard to the safety and efficacy and need to be taken into account when developing the drug in order to generate a product which is not only technically mature, but also suitable for the adequate treatment of patients.

Not only from a CMC perspective this aspect also needs to be regarded during a due diligence process to be able to identify the potentially required resources for the development of a suitable formulation and possible technical hurdles. The support of clinical and pharmacological experts is recommendable for this assessment.

In case the drug in question is an early development product, it should be assessed whether the identified physicochemical properties indicate that a feasible dosage form with acceptable bioavailability/ pharmacological effect can be developed with minimal technical difficulties to meet the proposed indication. Potential critical dosage and formulation issues which need to be addressed for the successful development of the drug should be ascertained.

For drugs for which selected preclinical and clinical studies have already been performed, one should investigate whether changes in the formulation were already introduced during the development. Such changes may impact the validity of the (pre-) clinical data supporting the MA application, since the required safety and efficacy data need to describe the attributes of the drug which is to be marketed. Data on developmental predecessors may only be regarded as supportive, unless bioequivalence studies were performed successfully^(24; 34). Not only previous changes in the formulation, but also the potential necessity of introducing a (further) change in the composition of the dosage form during the future clinical development should be identified.

Apart from the technical feasibility of formulations and dosages, the potential need for future development should be analysed. The interaction with clinical and pharmacological experts should reveal whether the envisioned patient population might be divided into sub-populations, requiring more than one dosage or dosage form necessary. The mandatory paediatric development^(35; 36), for example, would necessitate such additional work. Possible medicinal practice among key countries might also indicate the need for more than one formulation or dosages (influenced by intrinsic or extrinsic ethnic factors)⁽³⁷⁾.

6 PRECLINICAL

To ensure that the rights, safety and well-being of clinical trial subjects are protected, (amongst others) preclinical data are required to be adequate to support a clinical trial^(38; 39; 40). The results of pharmaceutical (physico-chemical, biological or microbiological) and preclinical (toxicological and pharmacological) tests are also to be submitted as part of the MAA for a pharmaceutical product⁽⁴¹⁾. Thus, when performing due diligence on preclinical data the quality and completeness of the available data needs to be assessed, the safety and efficacy of the compound in question should be evaluated and potential development risks and opportunities should be identified.

6.1 COMPLETENESS OF DATA

In case the drug candidate has not yet been tested in humans, the single preclinical study reports need to be assessed to get an impression of the amount of preclinical work which already has been completed. Provided the development of the drug candidate has already advanced to the clinical stage, a summary of the preclinical work performed will be available in the Investigator's Brochure (IB)⁽⁴²⁾. This is a good starting point of assessing whether the relevant safety studies recommended to support human clinical trials of a given scope or duration as well as the MA of NCEs described in the ICH M3(R2) guideline have been performed (safety pharmacology studies, repeated dose toxicity studies, toxicokinetic and preclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies and, for drugs that have special cause for concerns or are intended for a long duration of use, an assessment of carcinogenic potential; other preclinical studies are to be conducted on a case-by-case basis). This guideline also takes regional differences into consideration. For biotechnology-derived products the ICH M3(R2) guideline only provides a general insight with regard to timing of the preclinical studies relevant to the clinical development stage⁽⁴³⁾. The types of safety studies to be performed for such products should be in accordance with the ICH guideline for biotechnology-derived products (ICH S6).

A further exception to the ICH M3(R2) guideline exists for pharmaceuticals under development for indications in life threatening or serious diseases (e.g. advanced cancer, resistant HIV infection and congenital enzyme deficiency disease) without a current effective therapy. Here it might also be feasible to perform a case-by-case approach regarding the toxicological evaluation and the clinical development to optimise and expedite the drug development. In these cases, for products using innovative therapeutic modalities (e.g. siRNA) and for vaccine adjuvants, particular studies can/might be abbreviated, deferred, omitted or added⁽⁴³⁾.

It should be assessed whether all performed studies have been included in the IB. In case selected studies have not been included, the reason for not doing so should be identified. Reasons for not having included a study in the IB might be:

- 1) A study has not been considered relevant to be included;
- 2) New preclinical data is available, however an up-to-date version has not yet been prepared (necessary periodically⁽⁴⁴⁾/annually⁽⁴⁵⁾ in case a clinical trial is ongoing); or
- 3) The study has been wilfully omitted, possibly to suppress unfavourable results.

Beyond the assessment of which studies have been performed by the licensor, it should be considered to identify the additional work required for the completion of the clinical development and for the MA. This rather formalistic approach based on the aforementioned ICH M3(R2) guideline should also be complemented by the critical assessment of the quality and the scientific value of the data, which is described below.

6.2 QUALITY OF DATA

A preclinical expert should be asked to assess the quality of the studies performed. In general, the recommendations given in the currently available ICH Safety guidelines (S1-S8) listed in Appendix 2 should have been followed for the relevant studies, as applicable.

Since guidelines always leave room for interpretation, the preclinical expert should assess the value of the performed studies to support CTAs and/or a MAA using his scientific expertise and experience with CAs. Hereby it should be ascertained whether the studies have been performed correctly or adequately, whether the data has been interpreted correctly or whether the studies have been designed to only reveal favourable results. In detail: it might be investigated whether the sample sizes chosen are appropriate; whether the studies have been performed in the most appropriate species (with the most human-like response); whether there are questionable findings (based e.g. on a mix-up of samples or a lack of understanding about the Mechanisms Of Action (MOA) of the compound in question); whether the compound is sufficiently pure to provide valid toxicological findings; whether the route of administration employed is representative for the use in humans; whether the dosages used were adequate to assess the safety (or rather its toxicity) of the compound and whether the duration of the treatment/study was adequate to support clinical studies. Preclinical trials performed for other similar products and their “regulatory success” could also be taken into account. For this, a literature search or review of assessment reports prepared by CAs upon MA of products (e.g. EU: EPAR; US: product approval information available on FDA’s website) could be performed.

In addition to the choice and setup of the studies performed, the principles of Good Laboratory Practice (GLP) which has been defined by the Organisation for Economic Co-Operation and Development (OECD) and which has been implemented into several legislations, e.g. in the US and the EU ^(46, 47), should have been taken into account for all preclinical safety studies, i.e. those studies recommended to be performed by the ICH in the M3(R2) guideline (described above). The relevant GLP statements should be contained in the analytical reports. One exception can be made here: acute toxicity data may be obtained from non-GLP studies if the clinical administration is supported by appropriate GLP repeated dose toxicity studies ⁽⁴⁸⁾. This is not the case in some specific situations (e.g. micro-dose studies) where acute toxicity or single dose studies are the primary support for single dose studies in humans; these studies should be performed in compliance with GLP ⁽⁴⁸⁾.

6.3 SAFETY AND EFFICACY

Apart from determining the scientific value of the preclinical trials performed, which is rather a technical evaluation, the preclinical expert is the key person to assess the safety and efficacy of the drug candidate in question as a basis for the risk/benefit assessment of the project. For this purpose it is very beneficial to receive transparent data to assess how well the MOA of the drug is understood and whether it is important or relevant for the diagnosis, prevention or treatment of the targeted disease. Possibly there is already scientific data available documenting that the mechanism may not be relevant for the indication in question.

Besides evaluating the results of the mandatory scope of preclinical studies performed, common scientific knowledge should be taken into account. Are the drug class, the (prevalent) impurities or metabolites generally known to have toxic/mutagenic potential based on their structural features? Is the determined therapeutic index acceptable? What are the probable advantages and disadvantages of the current drug candidate compared to other lead compounds that were evaluated during the development? In case no human data is available yet: do the findings from

initial, repeated-dose studies (with blood concentration measurements) suggest that the candidate would be safe at the expected human exposure or do they rather suggest potential toxicological difficulties and hence a developmental risk? In case safety issues have already been identified, how were these dealt with? Have all issues/open questions been addressed? What issues still need to be clarified by additional experiments (beyond the mandatory scope) to ascertain the efficacy and particularly the safety of the compound; what additional resources would be required to generate sufficient data to support the CTA of the next clinical trial(s) and the MA respectively?

6.4 DEVELOPMENT RISKS AND OPPORTUNITIES

In addition to the evaluation of the safety and efficacy of a compound, its risk/benefit ratio is also influenced by its positioning in relation to other, competitive products. Although it is the main task of the marketing experts to evaluate the competitive environment, the preclinical expert is needed to contribute to the assessment of the market value of the compound in question.

Possibly the effect seen in the preclinical studies – safety as well as efficacy aspects – might not be as advantageous as that of already marketed products. This should be a clear sign that it is not worth while developing the drug any further – at least for the intended indication.

In general, the preclinical expert should also assess the drug's potential in indications where it possibly could act comparable or even superior to available competitive products, which would add a significant value to the project.

7 CLINICAL DEVELOPMENT

The clinical development of a drug can only be initiated once satisfactory information has been gathered on the quality of the product and its preclinical safety⁽⁴⁹⁾. This clinical testing is finally essential to demonstrate its benefit/risk ratio for a certain indication in which it is to be marketed and is hence also critically assessed by the CAs when applying for a MA. Similarly critically, the review of the available clinical data should be performed during a due diligence process (provided however, the development of the drug in question has already advanced to the clinical stage).

7.1 AVAILABILITY AND QUALITY OF DATA

As an initial step, a look at the IB will provide an overview of the clinical development work performed to date⁽⁴²⁾. It should be assessed whether all studies have been included in the IB. In case selected studies have not been included, the reason for not doing so should be identified. Reasons for not having included a clinical study in the IB might be:

- 1) New clinical data is available, however an up-to-date version has not yet been prepared (necessary periodically⁽⁴⁴⁾/ annually⁽⁴⁵⁾ in case a clinical trial is ongoing); or
- 2) The study has been wilfully omitted, possibly to suppress unfavourable results.

Similar to the CMC and preclinical assessments, the quality of the work performed needs to be evaluated. With regard to clinical studies, the international quality standards are described in the ICH E6(R1) guideline ("Good Clinical Practice: Consolidated Guideline") which has also been implemented in (supra-) national laws in the EU^(50; 51) as well as in the US⁽⁵²⁾. A good vantage point to gain insight with regard to the technical quality of a clinical trial one can take a look at the

Trial Master File (TMF) which should include all essential documents of a trial as listed in Section 8 of the ICH E6(R1) guideline.

In general, the other ICH efficacy guidelines should also have been regarded during the performance of the clinical trials, as appropriate. A complete list of the currently available guidelines is available in Appendix 3.

Apart from assessing the quality of the work performed by having a detailed look at the essential documents generated, one might also consider identifying the reputation of the CRO (if any such was engaged for the work). This could possibly be based on own experience.

The extent to which Quality Assurance (QA) experts were involved in the studies should also be assessed. This could be done by looking at the kind and amount of audits which were performed. In the case of audit findings, one should assess how these were dealt with. Were they fully addressed and risks mitigated, or were there any recurrent findings?

Beyond the analysis of the technical quality of the work performed, also the value of the strategy of the clinical development should be assessed. The development of medicinal products for the paediatric population, which is encouraged in the ICH E11 guideline, should be highlighted here, since this recently has become a mandatory prerequisite for a MA of a drug in the EU (unless the paediatric development has been waived or deferred by the authority)^(35; 53). During the due diligence process it should be investigated what paediatric work has been performed, whether a PIP has been set up and whether this PIP has already been discussed with and accepted, waived or deferred by the Paediatric Committee of the EMEA^(35; 53).

In furtherance to the ICH guidelines which are applicable in the ICH regions (Europe, Japan and the United States), often local guidelines are available which describe how drug classes or drugs for certain indications are best developed. For example, the clinical and safety guidelines developed by the different working groups of the EMEA are available under: <http://www.emea.europa.eu/htms/human/humanguidelines/efficacy.htm>. Guidance documents issued by the FDA are available under: <http://www.fda.gov/cder/guidance/>. Hence it needs to be assessed whether there is a special guideline available for the drug or indication under development in the respective region and whether this has been adhered to by the licensor (as far as applicable to the stage of development of the product). In case there is no guideline available by the relevant CAs, current treatment guidelines prepared and issued by expert associations might also be considered for the product under development (e.g. the Practice Guidelines from the American Heart Association⁽⁵⁴⁾). The consultation of experts in the field might turn out supportive here.

Apart from this reconciliation of the available guidelines and the development strategy the licensor has pursued, possible interactions with CAs discussing the proposed strategy are very valuable for assessing the CA(s) acceptance of the work performed or proposed for the further development. Have possible recommendations by the CA(s) been implemented? Is the proposed development plan considered sufficient for filing a MA (provided the results are favourable)? – These questions are important, since ultimately the CAs are the “customers” which need to be satisfied and convinced of the safety and efficacy of the product which is to be brought to the market.

7.2 DRUG SAFETY

The quality of the clinical trials performed plays a major role in the assessment of the trustworthiness and hence the value of the generated results, however, the results themselves reveal information on the value of the drug for the patient in the sense of its efficacy and – most importantly – its safety.

The safety profile of a drug should be closely assessed during a due diligence process to ensure that all pertinent risks – as far as the available data are able to reveal these – are understood. Here, once again, the IB is a good starting point to get an understanding of the available data, since this document should contain all Adverse Events (AEs) detected in patients during clinical trials⁽⁴²⁾. Since it is mandatory to list all AEs in the IB so that the treating physicians are able to make their own safety assessment of the drug used in the clinical trial they are participating in, it is also worthwhile verifying the completeness of AEs listed in the IB.

In case selected AEs have not been included in the IB, the reason for not doing so should be identified. Reasons for not having included an AE in the IB might be:

- 1) An AE has not been considered relevant to be included (although this is mandatory for all AEs so that the investigator is able to make his own safety assessment of the drug);
- 2) New safety data is available, however an up-to-date version has not yet been prepared (necessary periodically⁽⁴⁴⁾/annually⁽⁴⁵⁾ in case a clinical trial is ongoing, although information which might have an impact on the safety of trial subjects needs to be communicated to and approved by the relevant authorities⁽⁵⁵⁾); or
- 3) AE(s) has/have been wilfully omitted, possibly to conceal an unfavourable safety profile.

The review of all available safety data should allow the clinical expert to identify whether there are critical safety issues which still need to be addressed for the successful development of the drug or which might even endanger its marketability. The support of a preclinical expert is recommendable for this assessment, since the animal data already should contain several safety relevant signs (see Section 6.3). In comparison to the drug in question, available safety information on other drugs of the same substance class or drugs/therapies which target the same indication (if already defined) should be drawn on. Possibly the same MOA could indicate similar safety concerns, however, a different MOA could also promise an improvement to the current therapy.

7.3 DEVELOPMENT RISKS AND OPPORTUNITIES

After surveying the available clinical data and having a good overview of the safety and efficacy profile of the drug in question, its development risks and opportunities should be assessed by the clinical expert, thereby contributing to the overall evaluation of the project.

Starting off with assessing the risks and the potential of the indication(s) the drug is currently being developed for (i.e. the work performed by the licensor) and moving on to potential other indications for which the drug might prove to be beneficial, the clinical expert should assess what kind of competitive treatments are available. The research or market experience gathered with these competitors should be analysed, by e.g. performing literature reviews or consulting Key Opinion Leaders (KOLs) in the field, to identify the most likely factors why this drug might not be successful. In addition to the common/predictable problems with regard to the current therapy for the targeted/potential disease, the unmet medical need(s) should be discerned.

Apart from this rather scientific approach to analysing the risks and potential of the drug in question, the overall market situation should be reviewed. Section 9.1 provides more detail to this process.

8 QUALITY ASSURANCE

As described in previous sections, the scope and the quality of the development work performed should be closely assessed during the due diligence process to verify whether relevant regulations and guidelines have been taken into account, which not only contributes to the value of the project, but also to the regulatory acceptance of the data generated. In furtherance to this rather scientific assessment which is best primarily performed by the respective expert (CMC, preclinical, clinical and regulatory), the quality assurance expert needs to review the overall scope of measures which have been applied by the potential licensor to ensure qualitative work and to mitigate risks in order to get a general view on the value of the existing pharmaceutical quality system, which is stipulated in the ICH Q10 guideline.

As a starting point – in case the licensor has already been inspected by a CA – the inspection report will provide information on the quality of the work and the company's compliance to the rules and regulations.

An independent assessment of the quality system in the scope of a due diligence process should include the identification of the available Standard Operating Procedures (SOPs) – as required by Section 5.1 of the ICH E6(R1) guideline – and the level of detail to which the procedures are described. This provides a good overview to whether processes are handled rather strictly, i.e. leaving little/no room for interpretation, or whether there is much leeway which could lead to inconsistencies in the work performed. As a further step, it should be investigated whether all relevant guidelines and regulations have been taken into consideration in the SOPs and whether development work was performed in compliance with the available SOPs.

It might be considered to review audit reports which might be available in case part of the development work (preclinical, CMC or clinical) was performed by CLs, CMOs or CROs. The rate of compliance with the SOPs should have been assessed during the audits and the reports might hint to the quality of the performed work. Determining the diligence of the mitigation and pursuit of possible audit findings ought to complete the picture about the quality standard of the potential licensor.

9 MARKETING / MARKET PLANNING

Investing in the development of a scientifically very valuable drug is rather futile if the product proves not to be at least cost-effective once placed on the market. For this reason its market potential also needs to be assessed during a due diligence process. This is best coordinated by a marketing expert, supported by the scientific expertise of the development colleagues involved in the process. The following subsections explain in detail how the competitive environment and the market risks and potentials are best assessed.

9.1 COMPETITIVE ENVIRONMENT

As already touched upon in Sections 6.4 and 7.3 above, the competitive environment of the drug candidate needs to be assessed. At first the currently available therapies for the targeted disease

should be identified, analysing how well these satisfy the medical need(s). Furthermore the extent of the sales of the current products should be determined, also ascertaining potential market problems with the current therapy. In addition to these available therapies, competitive products/technologies which are currently being developed should be identified, together with the stage of development they are in. The question to be posed is whether the stage of development of the competitor is relevant to the development of the drug in question. Possibly this could impact e.g.:

- The design of future clinical trials if the competitor is close to a MA and thereafter would need to be considered as a comparator drug in the so far placebo controlled studies (a placebo comparator should only be used in case no marketed comparator is available/suitable⁽⁷⁰⁾);
- The speed of recruitment in clinical trials could be decreased if a competitor targets a similar patient population in the same territory; or
- The final market share (the own drug could be second in line in case the competitor is marketed earlier, however, it could also benefit if the competitor confirms the treatment action).

If possible, it might also be supportive to assess the capacities/ resources the competing companies have to develop their product or the priority they give the product, i.e. how likely is a rapid and successful development?

Based on this assessment, the market risks and potentials of the drug in question can be evaluated.

9.2 MARKET RISKS AND POTENTIALS

Although the assessment of market risks and potentials is a rather technical assessment, the support by the scientific and regulatory experts is essential to evaluate the business case of the drug candidate. To understand the positioning in the market which the licensor envisions, the proposed SmPC should be analysed. It needs to be assessed whether the generated scientific data (CMC, preclinical and clinical) and the outstanding studies are sufficient to support the filing of a MAA with the targeted SmPC. The comparison to data available on competitor products by reviewing literature or assessment reports prepared previously by CAs upon granting MAs for products (e.g. EU: EPAR; US: product approval information available on FDA's website) supports this analysis.

In case no draft SmPC has been prepared yet or the available SmPC is not considered appropriate, the due diligence team should establish their own proposal. Here it should be reflected which improvement(s) over current therapies would present a significant improvement and what characteristics the drug in question possesses which could be expected to produce advantages over current therapies and/or a differentiation from competitor candidates which are still in development. The marketing expert(s) should define what the minimum acceptable characteristics would be to make the candidate a leading player in the marketplace at the estimated time of commercial availability.

Whilst assessing the potential market by also obtaining the opinions of KOLs on the specific therapeutic area and on the characteristics of the respective drug in particular potentially critical market issues might be identified which need to be addressed for successful development of the drug (e.g. the need for a treatment guideline in a disease with a high unmet medical need). Potential market advantages or difficulties could also be identified when asking clinicians to assess a (blinded) portfolio of the drug in question.

Once the market potential has been understood, its magnitude for the envisioned indication(s) needs to be determined by calculating the potential size of the patient population which is to be treated (i.e. incidence and prevalence) and considering whether this population could be expanded by marketing activities. Of course also other demographic or epidemiological trends need to be taken into account which could affect the magnitude of the market. Possibly also a sub-population of patients could be identified which could be targeted early to allow a rapid progress to market with limited claims.

Concerning very limited market sizes (i.e. a prevalence of $\leq 5/10,000$ persons in the EU Community ⁽⁷¹⁾ at the time of submission or if the condition affects fewer than 200,000 people in the US ⁽⁷²⁾), it might be considered to apply for an orphan medicinal product designation which would then be entitled to CA incentives for the research, development and placing on the market ^(73; 74).

To determine the potential revenues, the factors need to be identified:

- Price of current therapies (if available),
- The therapeutic class of the drug (used as therapeutic reference pricing by Health Technology Assessments (HTAs) when determining the price of a drug), and
- The pricing environment which could be expected at the time of approval (e.g. taking into account that current competitor products might be available generically).

Based on the expected price and the potential market size, the magnitude of revenues of the drug in question might generate should be calculated. The determination of the NPV naturally needs to take the costs of licensing in the product be taken into account (including all milestone payments and royalties).

Together with the diligent scientific evaluation, this careful approximation of estimated revenues composes the risk/benefit assessment of a project. Consolidating all aspects should render a sound basis for the business decision whether the target should be licensed in or not.

10 INTELLECTUAL PROPERTY

Crucial for the value of a project is 1) the protection of the IP to bar competitors from commercially exploiting a product before the originator has had the chance to (fully) profit from the investments made and 2) to ensure that other IP rights do not limit the envisaged development.

There are two means to protect IP: by filing patents and by protecting data. A patent is the right granted to an inventor by a state, or by a regional office acting for several states, which allows the inventor to exclude anyone else from commercially exploiting his invention for a limited period of time, generally 20 years ⁽⁴⁾. For medicinal products this patent term can be expanded in the EU by a patent-like Supplementary Protection Certificate (SPC) ⁽⁵⁾ or in the US by a patent term restoration ⁽⁶⁾, which were both introduced to compensate for the long time needed to obtain regulatory approval of such products ^(5; 6). The SPC has a maximum life time of 5 years and enters into force after the corresponding patent has expired (provided the patent expires after bringing the product to market); the patent term of a marketed product and the SPC in sum may not exceed 15 years ⁽⁵⁾. The designated term of the SPC can however be prolonged by 6 months in case the MAA contains data which was generated according to the approved Paediatric Investigation Plan (PIP) ⁽⁷⁾.

Based on the Hatch-Waxman Act of 1984, the US patent term restoration similarly has a maximum life time of 5 years, however, the total patent life for the product with the patent extension cannot exceed 14 years from the product's approval date^(8; 9). A prolongation on the basis of the availability of study data in the paediatric population is not possible, which is however compensated by the grant of an additional data protection period (see below).

Data protection can be considered as an incentive to the originator of a drug by protecting him from direct competition during the first years on the market. Since unnecessary research on animals or humans should be prevented for ethical reasons, applicants for the MA of generic medical products may directly refer to the data of preclinical tests and clinical trials performed by the originator if it can be demonstrated that the medical product is a generic of the reference medical product. This however can only be done after the data exclusivity period of 8 years after the authorisation of the reference product in an EU Member State or in the EU Community⁽¹⁰⁾. The authorisation for a generic medical product may then only be issued after a 10 year market exclusivity period for the reference product. This market exclusivity period may be prolonged once by 1 year in case one or more new therapeutic indications are authorised for the product in question within the 8 year data exclusivity period, provided they are considered to bring significant clinical benefit in comparison to existing therapies⁽¹⁰⁾. An extension of the period to 12 years in total is also possible, if the requirement for data on the use in the paediatric population is fully met⁽¹¹⁾. Further, in case the drug is eligible to be classified and finally marketed as an orphan medicinal product, a 10 year market exclusivity period may be granted (however, only limited to the licensed indication), provided the product is licensed in every single EU member state⁽¹²⁾. This period may be shortened to 6 years in case the designation criteria do not apply any longer after the fifth market year; however, it may also once be extended by one year in case a MA is granted for another indication of the same drug within 8 years of the first approval⁽¹³⁾.

Similar data protection mechanisms are available in the US, where however the protection periods are shorter. A data protection period lasts for 4 years after approval of the originating medicinal product; the market exclusivity period initially runs for 5 years but can be prolonged by 3 years for each significant innovation which is authorised⁽⁸⁾. An additional option for prolonging the data exclusivity period by 6 months (in total: 5.5 years) is the filing of paediatric study data⁽¹⁴⁾. This is not possible in the EU where – with a similar effect – the SPC is prolonged by the same timeframe. The approval of an orphan drug secures a 7-year US market exclusivity⁽¹⁵⁾.

These methods of protecting IP should be considered when performing due diligence on a product of interest since they have a strong impact on the market exclusivity period and hence the potential market value of a project. It should be analysed closely what data has been patented, in which region this patent protection is available and whether the patent term would exceed the expected marketing date in order to be eligible to apply for an EU SPC, US patent term restoration or similar protection in other countries. In addition it should be assessed whether there are additional patentable data to prolong the patent protection period; here it should be ensured that the novel ideas/data can still be considered as such and have not yet been published or otherwise disclosed.

Apart from assessing the available and potential IP protection of a project, the freedom to operate should also be analysed to determine whether the envisaged development can be performed without infringing valid IP rights of others⁽¹⁶⁾ (e.g. with regard to the manufacturing process or treatment regimes).

Additionally it should also be checked which IP will be transferred when signing the license agreement – possibly the licensor has another license agreement permitting them to use e.g. a

production method or developmental data, however this would not be transferred in the deal. This might also apply to clinical data if these were generated in investigator initiated trials where often the investigator has the rights to the results and not the drug developing company.

Due to this complexity, it is advisable to perform the assessment of the IP situation of a product of interest with the support of a patent attorney as an expert in this field.

11 DEVELOPMENT STRATEGY

During the due diligence process the regulatory expert needs to ensure that the regulatory strategy for bringing the drug in question to market is plausible in order to be able to determine the development costs which are needed for the calculation of the project's net present value (NPV). At first, the available development strategy of the licensor needs to be assessed for its feasibility. For this, it should be assessed whether there are specific country governances, guidelines, points to consider or best practice guides available which impact or guide the drug development process and whether these have been taken into account during the previous development. The rules and regulations in the separate development territories need to be assessed to identify the requirements and scope of the documents necessary for the MAA process (in the ICH regions the requirements of the Common Technical Document is described in the ICH M4 guideline). Possibly also draft rules, regulations or guidelines might currently be in discussion which might influence the development of the product in future. White papers might also be available which have been prepared by experts in the indication of interest to influence the development paradigm in case new research insights have not yet been translated into appropriate guidelines.

Further, inasmuch as such documents are available, the Core Company Data Sheet, the Target Product Profile (TPP) or the draft Summary of Product Characteristics (SmPC), should be reviewed for plausibility, especially assessing whether the development plan supports the proposed package insert. For the determination of the scientific likelihood of such a SmPC, the CMC, preclinical and clinical experts should support this examination. Should there be any unique preclinical, technical or clinical issues with the drug (or its class), these could be detected by performing a thorough review of minutes of regulatory meetings performed by the licensor (see Section **Fehler! Verweisquelle konnte nicht gefunden werden.**), literature or trade press, SmPCs of marketed products, regulatory guidelines, summaries of regulatory industry conferences or reports prepared previously by CAs upon granting MAs for similar drugs (e.g. EU: EPAR; US: product approval information available on FDA's website) or by resorting to prior own experience with the particular reviewers at the CAs (in case similar drugs have already been discussed).

Possibly there are also regulatory strategy documents available which have been prepared by the licensor in discussions on the development strategy. Internal minutes of the licensor or minutes of meetings performed with regulatory affairs consultants could also be reviewed (inasmuch as these are made available during the due diligence process) to understand the complexity of the project and to detect possible challenging topics.

Apart from the risks, also the opportunities should be identified. It should be questioned whether there are mechanisms available to expedite the development timelines and the final regulatory approval. If the MAA is filed with the EMEA, the EU legislation for example allows for the following alternatives which enable an early market entry:

1. Conditional approvals: A MA can be granted earlier for medicines that satisfy an 'unmet medical need' on the basis of incomplete data which indicate that the medicine's benefits outweigh its risks. The MA holder needs to fulfil obligations (e.g. performance of further studies) and to renew the approval on a yearly basis. The approval is converted from a conditional approval to a normal approval once all obligations have been fulfilled and the additional data support the original risk/benefit assessment^(57; 58).
2. Approvals under exceptional circumstances: Such a MA can be granted in case the applicant can show that it is impossible to provide comprehensive data on the efficacy and safety of the drug in question, due to the rarity of the condition it is intended for (i.e. orphan medicinal products), limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of such data. With such an approval the applicant is given obligations to fulfil, relating in particular to the safety of the medicine concerned. These are re-assessed every year until such time as the approval can be converted into a normal one^(57; 58).
3. Accelerated approvals: When an application is submitted for a MA for drugs which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure (150 instead of 210 days for the opinion of the Committee for Medicinal Products for Human Use)⁽⁵⁷⁾.

In the US the following mechanisms are possible to facilitate an earlier market entry:

1. Accelerated approval: This MA is similar to the European approval under exceptional circumstances or the conditional approval. Such an approval may be granted if incomplete data indicate a positive risk/benefit ratio of a drug for life threatening diseases. This approval is however also subject to the requirement that the applicant performs further studies to verify and describe its clinical benefit⁽⁵⁹⁾.
2. Priority designation: A priority designation is intended to direct overall attention and resources to the evaluation of applications for DPs that have the potential for providing a significant improvement in the treatment, prevention, or diagnosis of a disease when compared to standard applications⁽⁶⁰⁾. The applicant cannot influence whether his application is designated a priority review (this is at the sole discretion of the FDA), however one might assess the likelihood of this being the case by reviewing prior cases.
3. Fast Track: The benefits of this mechanism include scheduled meetings to seek FDA input into development plans, the option of submitting a MAA in sections rather than all components simultaneously (Rolling New Drug Application (NDA)) and the option of requesting evaluation of studies using surrogate endpoints (accelerated approval)⁽⁶¹⁾. The Fast Track designation is intended for the combination of a product and a claim that addresses an unmet medical need, but does not necessarily lead to a priority review or accelerated approval. However the rolling NDA submission has proven to accelerate the review period, enabling a faster time to market⁽⁶²⁾.

Surely it would also be beneficial for the NPV if market exclusivity could be assured. Please refer to Section 10 for a detailed overview of possibilities to gain a SPC / supplementary patent protection, market exclusivities or data protection periods.

The project development costs can also be reduced by taking advantage of reducing the costs payable to authorities. In the EU for example, smaller company can apply for the so-called Small

and Medium-Sized Enterprise (SME) Status (awarded by the EMEA) which facilitates administrative and procedural assistance (e.g. translations), fee exemptions for certain administrative services, fee reductions for certain procedures or also deferrals of fees for MAAs or inspections⁽⁶³⁾. As an example the current fee exemptions as of February 2009 are⁽⁶⁴⁾:

- Full (100%) reduction for protocol assistance and follow-up
- Full (100%) reduction for pre-authorisation inspections
- 50% reduction for new applications for MAs to applicants other than SMEs
- Full (100%) reduction for new applications for MA only to SMEs
- Full (100%) reduction for post authorisation activities including annual fees only to SMEs in the first year after granting a MA.

Licensing fees can also be reduced for orphan medicinal products. Since such products fall within the mandatory scope of the centralised procedure by the EMEA⁽⁶⁵⁾ and are only rewarded their 10-year market exclusivity in case they are marketed in all EU member states⁽¹²⁾, the overall MAA procedure is less resource consuming (time and costs) compared to MAAs filed by the mutual recognition or decentralised procedure. In addition, the fees payable to the EMEA may be reduced in part or in total⁽⁶⁶⁾.

In the US the financial support for the development of orphan drugs is structured differently. Apart from the 7-year market exclusivity post approval⁽¹⁵⁾, treatment use can be granted prior to approval⁽⁶⁷⁾, making the drug accessible earlier to patients in need for this treatment. In addition, the sponsors of clinical trials are encouraged to design their protocols in such a manner that they permit the addition of persons with the disease or condition who are in need for the drug since they cannot be satisfactorily treated by available alternative drugs⁽⁶⁸⁾. Grants to support the development can also be conceded by the FDA⁽⁶⁹⁾.

Once all these considerations have been taken into account, the regulatory expert – together with the scientific part of the due diligence team – should establish a project plan (including the estimated development costs) on how the drug would be developed best – from the scientific and the business angle. Development alternatives including potential additional indications should also be taken into account. Together with the marketing and business development experts a detailed decision analysis needs to be performed to assess whether the business case is still of interest (see Section 12 below).

12 DECISION ANALYSIS

The final decision on whether to license in a project or not should not just be based on a “gut feeling” or a simple voting procedure amongst the experts who were involved in the due diligence process. It should rather be a very analytical process which highlights all benefits and risks and takes their respective ranking order into account. Only if all aspects are taken into account, a substantiated decision can be made. This section will elaborate how best to perform the required decision analysis. This theoretical basis is then substantiated by a model case.

12.1 METHOD

The following recommendations on how to perform a detailed decision analysis is based on the guidance given by the Jopp & Wilkens Management Consulting Group.

Step 1: At first a decision statement needs to be defined. This is made to clarify the purpose and the extent of the decision which is to be made. Here the activity, the object and possible limitations should be identified. Further the level of the decision should be clarified.

Step 2: An all-encompassing list of objectives/criteria should be compiled to ensure that every relevant aspect is taken into account when making the decision.

Step 3: As a next step all objectives/criteria should be classified as to whether they are “musts” or “wants”. “Musts” can immediately exclude impossible options, whereas the “wants” influence the priority of the remaining alternatives.

Step 4: The objectives/criteria need to be numbered according to their weight (highest number for highest priority). Here the “musts” should also be translated to “wants” so also these aspects can be taken into consideration.

Step 5: All possible decision alternatives which apply to the decision statement (Step 1) should be listed.

Step 6: Looking at the must criteria, alternatives which do not meet these should be excluded from further analysis. The remaining alternatives should be ranked using the listed objectives/criteria. This should reveal a ranking of the alternatives for each single objective. Easiest here is to generate a matrix listing all objectives/criteria as well as the alternatives which are not ruled out by the “must” criteria (see example). After ranking the alternatives per objective, a weighted score can be calculated by multiplying the relevant rank number with the weight which was defined in Step 4. The overall sum of the weighted score per alternative result in a first ranking of the alternatives.

Step 7: Prior to coming to a final decision, all potential risks should be listed per alternative, also identifying their likelihood and their seriousness.

Step 8: Balancing the evaluation of the alternatives (Step 6) with their risks/consequences the choice of the best balanced alternative can be made. The choice should now meet the objectives/criteria defined in Step 2 and have a manageable level of risks. In case the benefits are considered being too little or the risks being too great for all alternatives, the whole decision might need to be reconsidered (either new alternatives within the given frame or a totally new set of alternatives).

12.2 MODEL CASE

Current situation: The product Optimase, a plasminogen activator, has successfully been tested by PianoPharma in the indication of acute ischemic stroke in two similar Phase II studies with concurrent results, demonstrating favourable results in a dose-dependent efficacy profile. The Phase III program was initiated with a collaborator for the North-American market, EaglePharma. During the first pivotal Phase III trial an additional non-exclusive co-development agreement was signed by PianoPharma with the company DaisyPharm for the rest of the world territory. Unfortunately the Phase III trial, in which the inclusion criteria were similar to that of the Phase II trials, did not meet its primary objective, demonstrating Optimase to be equi-effective as placebo. An in-depth re-analysis showed that – despite of comparable inclusion criteria – the patient population differed to the patients recruited in the Phase II trials. The subpopulation of the Phase III trial which matches the patient population of the Phase II trials shows similar favourable results and thereby provides a rationale for the further development of Optimase by adjustment of the inclusion criteria in further clinical trials. A meta-analysis of the Phase II and Phase III trials support this view.

Despite of this retrospective analysis, EaglePharma has terminated its license agreement with PianoPharma; a new partner for the North-American market is sought for. DaisyPharm is closely assessing whether there still is a business case to continue the development or whether they should also cancel their development agreement with PianoPharma. The due diligence of the available data, the estimation of the inherent risks and potentials of Optimase should contribute to a detailed decision analysis on the way forward.

Decision Statement (Step 1): Identify DaisyPharm's best business development strategy for the development project Optimase.

Objectives/criteria (Step 2-4): Based on the current business situation of DaisyPharm, the due diligence team identified the following criteria (musts and wants) for the evaluation of the development options; the wants were weighted according to their importance.

Musts:

- The likelihood of regulatory success of Optimase (i.e. MA) should be greater than 80%
- The estimated revenues for DaisyPharm should not be less than € 400 million
- Human and financial resources for the further clinical development as well as for the marketing and distribution of the drug should be available

Wants:

- 1) Regulatory acceptability of clinical data
- 2) Regulatory acceptability of CMC data
- 3) Regulatory acceptability of preclinical data
- 4) Availability of IMP for further clinical development
- 5) Return on Investment (ROI) should be as high as possible
- 6) Availability of patent protection to maximise duration of market exclusivity
- 7) Development time to market should be as short as possible
- 8) Availability of human resources / sales force for marketing and distribution of the drug in the licensed territories
- 9) Availability of drug for market demand
- 10) Favourable competitive advantage on the respective markets
- 11) Investment as low as possible (including development and licensing costs)
- 12) Availability of human resources for further development of the drug

Alternatives (Step 5): The due diligence team identified four different options for the continuation of the collaboration with PianoPharma:

- 1) Continue the co-development with PianoPharma under the existing agreement
- 2) Extend the existing agreement to include the North-American territories
- 3) Expand the current co-development agreement to an exclusive license agreement in the current territories (no development support by PianoPharma)
- 4) Expand the current co-development agreement to an exclusive, worldwide license agreement (no development support by PianoPharma)

Comparing alternatives against objectives/criteria (Step 6): Applying the “must” criteria set above to the identified alternatives (see table below) reveals, that the first alternative needs to be excluded from the list since the expected revenue does not exceed the target of € 400 million.

	Alternative			
	1	2	3	4
	yes/no	yes/no	yes/no	yes/no
Likelihood of regulatory success > 80%	✓	✓	✓	✓
Estimated revenues for DaisyPharm > € 400 million	x	✓	✓	✓
Resources available for further development and marketing/ distribution	✓	✓	✓	✓

Ranking the alternatives for each “want” criteria and multiplying the relevant rank with the weight of each criterion results in a ranking of the alternatives (see table on the following page). This analysis revealed that the alternatives no. 3 and 4 are more favourable than alternative 2.

	Weight	Alternatives								
		2			3			4		
		Comment	Score	Weighted score	Comment	Score	Weighted score	Comment	Score	Weighted score
Clinical data acceptable	12	Inherent risk to prove efficacy	3	36	Inherent risk to prove efficacy	3	36	Inherent risk to prove efficacy	3	36
CMC data acceptable	11	Open issues with FDA	3	33	Positive feedback from selected CAs	4	44	Open issues with FDA	3	33
Preclinical data acceptable	10	Positive feedback from selected CAs	4	40	Positive feedback from selected CAs	4	40	Positive feedback from selected CAs	4	40
IMP available	9	IMP available for proposed studies	4	36	IMP available for proposed studies	4	36	IMP available for proposed studies	4	36
High ROI	8	Worldwide revenues; Piano share larger	2	16	Revenues ex US only	2	16	Worldwide revenues	4	32
Long IP protection available	7	IP protection 3 years longer in US	4	28		2	14	IP protection 3 years longer in US	4	28
Short development time	6	Possibly CMC questions to be addressed by a US Phase I	1	6	Performance faster without co-development	4	24	Possibly CMC questions to be addressed by a US Phase I	2	12
Sales force available	5	Use current sales force	4	20	Use current sales force	4	20	Use current sales force	4	20
Market material available	4	Larger territory; co-commercialisation	1	4	Smaller territory; no co-commercialisation	4	16	Larger territory; no co-commercialisation	2	8
Competitive advantage	3	Same competitors in all territories; worldwide availability of advantage	3	9	Same competitors in all territories	4	12	Same competitors in all territories; worldwide availability of advantage	3	9
Low investment costs	2	Larger territory; costs shared with PianoPharm	3	6	Smaller territory; 100% costs to be covered	2	4	Larger territory; 100% costs to be covered	1	2
Available human res. for dev.	1	US team has capacities for additional work	4	4	Current team could cont. working on project	4	4	US team has capacities for additional work	4	4
Total weighted score		241			266			260		

Risk analysis (Step 7): Since the alternatives no. 3 and 4 revealed to be almost equally favourable, a detailed risk analysis needs to be performed for both options.

Independent of the territory in which DaisyPharm intends to continue the development, a general risk is seen with the acceptability of the clinical data by CAs, especially due to the failure of the first Phase III trial. The re-analysis and the meta-analysis of the Phase II and Phase III data however provide a good rationale for a continued development. This theory is also supported by KOLs as well as contact to selected CAs. In order to ensure that the authorities are satisfied with the clinical data package delivered within the scope of the MAA (i.e. to minimise this risk), further scientific advices could be performed to discuss the data and to identify potential concerns which might be addressed during the Phase III development.

Also with regard to the clinical development, a competitive risk has been identified. It is quite likely that the sole competitor will expand its current license agreement to include patients which are part of Optimase's patient population (the Phase III program has recently been completed). This would on the one side influence the study design of the planned Phase III trials since these could no longer be placebo-controlled for the relevant sub-population (unethical), and on the other side the speed of recruitment and hence the time to market would be impacted due to the availability of a marketed drug for the according sub-population. DaisyPharm is however confident that the planned Phase III program will be almost completed once the competitor has received its extended license. Since the extended license will not affect the US, a very strong recruiting country, the recruitment of the relevant sub-population could be terminated in the relevant countries at that relevant point in time. The potential delay in development is still justifiable; the possible revenues are still convincing.

In furtherance to the clinical considerations, prior discussions with the FDA in the US have identified a risk that the current CMC data is insufficient for MAA purposes in this country. From these discussions however, necessary additional work has clearly been defined. Based on prior experience in the production of Optimase as well as analytical data, the risk that the data derived of this work will not address the FDA's requirements is considered as being rather low. To further reduce this risk, the generated requested data could be discussed within the scope of the scientific advice proposed for the discussion of the clinical issues.

Based on the identified additional CMC development steps, the development in the US might be delayed by a few months, however this is partly compensated by the longer patent protection in the US, which bars competitors from accessing the US market longer than in European countries. These additional revenues would compensate for the delayed market entry.

A further risk is seen with the availability of the market material. With alternative no. 4 far more material would be required in order to also address the need of the US market. The current production capacities would only allow market coverage for the first three years. However, further capacities are available and will be secured at the CMO to be able to meet the market demand. Since the same CMO will be addressing this need, there is no necessity (or inherent risk) of a technology transfer. The risk of a total loss of material by loss of a production site has already been addressed since the material already is being manufactured in separate sites and stored in separate depots.

Lastly, a major risk has been identified which cannot be ascribed to the Optimase project, but rather is a risk inherent in DaisyPharm's pipeline. Due to the fact that another Phase III project of DaisyPharm's pipeline has also failed to meet the clinical endpoint, however does not provide any rationale for further development, Optimase is DaisyPharm's next market candidate. In case this product is not brought to market, DaisyPharm's market value would decrease significantly and the company would need to restructure its operations to focus more on early stage projects. Especially the unit in the US would be dependent on the Optimase project.

Decision / best weighted choice: In summary it can be said that DaisyPharm depends on the development of Optimase, especially in the US, to maintain their current market value. Despite the risks inherent in the clinical development (acceptability of clinical and CMC data), it is recommended that DaisyPharm should extend its co-development agreement with PianoPharma to a full license agreement, also including the North-American market.

Comments on the procedure: This model case demonstrates that it is worthwhile identifying and weighting all criteria which need to be taken into account when considering to license in a project. This structured analysis should render a sound decision on how to proceed with an offered project.

13 SUMMARY

The licensing of research and development products, as a common business strategy in the pharmaceutical industry, allows collaborators to progress the development of the drug up to marketing. Reasons stretch from 1) limited resources of the licensor; 2) different development focuses of the licensor (rather research than development); 3) seeking alliances with partners with manufacturing capability; 4) exploiting different field(s) of application; or 5) the licensor's lack of commercial capability.

Once the wish of licensing in a product has been expressed, the licensing goal should be clearly identified. This should include the acceptability of the potential drug by competent authorities, its scientific value, its market and development potential, its fit to the licensee's product portfolio and its overall value for the company. The due diligence process which is necessary to assess the net present value and the risk/benefit profile of a drug in question should focus on whether these licensing goals can be met.

This thesis combines the detailed regulatory and scientific risk/benefit assessment of drug candidates with the evaluation of their market potential and market risks. This assessment work, which is performed by the close interaction of scientific (technical, preclinical and clinical), quality, regulatory and marketing experts, is best coordinated by a regulatory expert and provides the basis for the analysis for the final decision on whether or not the drug should be licensed in or not.

The regulatory expert should lead this assessment with his expertise on the legal requirements regarding the development of the drug. A close assessment of the feedback gained from authority interactions (e.g. national scientific advices, hearings during clinical trial applications, pre-IND or end-of-Phase-II meetings in the US, or even failed MAA procedures) reveals the acceptability of the generated data and proposed development by the authorities and identifies issues which still need to be addressed prior to filing a MAA and might constitute a project risk which needs to be factored in into the risk/benefit assessment of the project.

The scientific assessment of the drug candidate is best initiated by comprehending the status quo of the respective development areas (CMC, preclinical and clinical). Summaries of the work performed are often available in regulatory required documents such as the IB, IMPD or the IND (depending on their stage of development). The completeness of such summaries should be assessed to ensure that no unfavourable data is concealed.

By assessing which rules, regulations and guidelines apply to the development of the drug in question, the value of the development work already performed by the licensor as well as the work still required to bring the drug to market in the target indication can be assessed. This evaluation should not only be reduced to a technical gap-analysis, but also the scientific aspects of the drug should be taken into account. By assessing the results of the work performed, factors which might contribute to the project being unsuccessful, need to be identified. Such factors could

be safety risks inherent in the production process (e.g. inconsistent process; impure or unstable drug) or the physiological effects of the drug detected in either animal or human studies (e.g. toxicity, carcinogenicity or pharmacological side-effects), or even the insufficiency or lack of efficacy. Hence, the scientific risk/benefit profile should be carefully evaluated and be taken into account when identifying the additional work which is necessary to bring the drug to market. The risk/benefit assessment should however also include an evaluation as to which further potential the drug candidate may have in other indications.

In parallel to this scientific and regulatory assessment of the product in question, the marketing expert needs to assess the competitive market. This is best done by defining the targeted SmPC (with the help of the scientific and regulatory experts) and should include the identification of available competitive products (either in development or already on the market) and the impact they could have on the development (e.g. timelines or study designs) and market share of the product. The potential revenues should be estimated, also taking into consideration the costs of licensing the product (milestone and royalty payments).

The regulatory expert – in support of the scientific and marketing experts – should establish a project plan for the recommended further development of the drug, taking all risks, potentials and impacting factors into considerations. Possible legal provisions for either a faster way to market for drugs which address high medical needs (e.g. EU: conditional or accelerated approval or approval under exceptional circumstances; US: accelerated approval, fast track status or priority designation), or to reduce development costs (e.g. SME status awarded by the EMEA) should be considered.

In summary, all considerations made by the close interaction of the experts in the due diligence process should serve as a all encompassing basis for a detailed decision analysis using the methods described. This elaborate evaluation delivers a sound decision on whether a product is worth while to be licensed in or.

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31. Section 1 of Annex to ICH Q8(R1) Guideline.
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70. Section 2.1.3 of ICH E10 Guideline.
71. Article 3(1) of Regulation EC No. 141/2000.
72. 21 CFR Part 316 Section 20.
73. Article 6(1), 7(1-2) and 8 (1-3) of Regulation EC No. 141/2000.
74. 21 CFR Part 316 Section 2.

15 APPENDIX 1

The current ICH Quality Guidelines (Status 22 February 2009). Please consult the ICH web-page for possible updates: www.ich.org/

No.	Title	Released
Q1A(R2)	Stability Testing of New Drug Substances and Products (Second Revision)	Feb 2003
Q1B	Stability Testing: Photostability Testing of New Drug Substances and Products	Nov 1996
Q1C	Stability Testing for New Dosage Forms	Nov 1996
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	Feb 2002
Q1E	Evaluation for Stability Data	Feb 2003
Q2(R1)	Validation of Analytical Procedures: Text and Methodology	Oct 1994
Q3A(R2)	Impurities in New Drug Substances	Oct 2006
Q3B(R2)	Impurities in New Drug Products	Jun 2006
Q3C(R3)	Impurities: Guideline for Residual Solvents	Jul 1997
Q4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions	Nov 2007
Q4B Annex 1	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Residue on Ignition/Sulphated Ash General Chapter	Nov 2007
Q4B Annex 2	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Extractable Volume of Parenteral Preparations General Chapter	Jun 2008
Q4B Annex 3	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Particulate Contamination: Sub-Visible Particles General Chapter	Jun 2008
Q4B Annex 4A	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Microbial Enumerations Test General Chapter	Nov 2008
Q4B Annex 4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-organisms General Chapter	Nov 2008
Q4B Annex 4C	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter	Nov 2008
Q4B Annex 5	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Disintegration Test General Chapter	Jun 2008 (draft)
Q4B Annex 6	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Uniformity of Dosage Units General Chapter	Nov 2008 (draft)
Q4B Annex 7	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Dissolution Test General Chapter	Nov 2008 (draft)
Q4B Annex 8	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Sterility Test General Chapter	Nov 2008 (draft)
Q5A(R1)	Viral Safety Evaluation of Biotechnological Products Derived from Cell Lines of Human or Animal Origin	Sep 1999
Q5B	Quality of Biotechnological products: Analysis of the Expression Construct in Cells Used for the Production of r-DNA Derived Protein Products	Nov 1995
Q5C	Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products	Nov 1995
Q5D	Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products	Jul 1997

No.	Title	Released
Q5E	Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process	Nov 2004
Q6A	Specifications: Text procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances	Oct 1999
Q6B	Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products	Mar 1999
Q7	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	Nov 2000
Q8	Pharmaceutical Development	Nov 2005
Q9	Quality Risk Management	Nov 2005
Q10	Pharmaceutical Quality System	Jun 2008

16 APPENDIX 2

The current ICH Safety Guidelines (Status 22 February 2009). Please consult the ICH web-page for possible updates: www.ich.org/

No.	Title	Released
S1A	Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals	Nov 1995
S1B	Testing for Carcinogenicity of Pharmaceuticals	Jul 1997
S1C(R2)	Dose Selection for Carcinogenicity of Pharmaceuticals	Mar 2008
S2(R1)	Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use	Mar 2008 (draft)
S2A	Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (currently being revised in S2(R1))	Jul 1995
S2B	Genotoxicity: A Standard Battery for Genotoxicity Tests of Pharmaceuticals (currently being revised in S2(R1))	Jul 1997
S3A	Note for Guidance on Toxicogenetics: The Assessment of Systemic Exposure in Toxicity Studies	Oct 1994
S3B	Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies	Oct 1994
S4	Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)	Sep 1998
S5(R2)	Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility	Jun 1993
S6	Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals	Jul 1997
S7A	Safety Pharmacology Studies for Human Pharmaceuticals	Nov 2000
S7B	The Non-clinical Evaluation of the potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals	May 2005
S8	Immunotoxicity Studies for Human Pharmaceuticals	Sep 2005

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The current ICH Efficacy Guidelines (Status 22 February 2009). Please consult the ICH web-page for possible updates: www.ich.org/

No.	Title	Released
E1	The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions	Oct 1994
E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	Oct 1994
E2B(R3)	Revision of the E2B(R2) ICH Guideline on Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports	May 2005 (draft)
E2B(R2)	Maintenance of the Clinical Safety Data Management including Data Elements for Transmission of Individual Case Safety Reports	Feb 2001
E2C(R1)	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs	Nov 1996
E2D	Post-Approval Safety Data Management: Safety and Standards for Expedited Reporting	Nov 2003
E2E	Pharmacovigilance Planning	Nov 2004
E2F	Development Safety Update Report	Jun 2008 (draft)
E3	Structure and Content of Clinical Study Reports	Nov 1995
E4	Dose-Response Information to Support Drug Registration	Mar 1994
E5(R1)	Ethnic Factors in the Acceptability for Foreign Clinical Data	Mar 1998
E6(R1)	Good Clinical Practice: Consolidated Guideline	May 1996
E7	Studies in Support of Special Populations: Geriatrics	Jun 1993
E8	General Considerations for Clinical Trials	Jul 1997
E9	Statistical Principles for Clinical Trials	Feb 1998
E11	Clinical Investigation of Medical Products in the Pediatric Population	Jul 2000
E12	Principles for Clinical Evaluation of New Antihypertensive Drugs	Mar 2000
E14	The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	May 2005
E15	Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories	Nov 2007

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