News in Nonclinical Evaluation of Anticancer Pharmaceuticals: ICH guideline S9 and beyond

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Abbreviations

ADME	Absorption, distribution, metabolism, externalization (excretion)
AUC	Area under the curve
C_{max}	Maximum plasma concentration
DLT	Dose limiting toxicity (of an anticancer drug)
EPAR	European public assessment report
EU	European Union
GLP	Good Laboratory Practices
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.v.	Intravenous
MAA	Marketing authorization application
MDR	Multi drug resistance
MFD	Maximum feasible dose
MOA (moa)	Mechanism of action
MTD	Maximum tolerated dose
N/A	Not applicable
NDA	New Drug Application
NCI	National Cancer Institute (US)
NOAEL	No Observed Adverse Effect Level
NSCLC	Non small cell lung cancer
PET	Positron emission tomography
PK	Pharmacokinetics
PD	Pharmacodynamics
SAR	Structure-activity relationship
US	United States (of America)
WOCBP	Women of childbearing potential

1 Introduction

In general, every prescription drug needs a marketing authorization before it can be prescribed by physicians and dispensed to patients in pharmacies. In order to gain a marketing authorization, legislation and guidance has to be followed by the applicant. Basically, this legislation aims to provide a regulatory framework to ensure that only medicinal products are authorized for marketing that have been duly characterized, with respect to the product quality, its safety and efficacy for the intended patient population, indication and use. This characterization is performed by laboratory testing, and by testing of the product and its constituents in animals (nonclinical development) and in humans (clinical development). Because most diseases are spread globally and to ensure that patients worldwide can benefit of an innovative treatment, efforts have been undertaken to harmonize the underlying rules, and guidelines regulating the characterization of pharmaceuticals for human use in a process called ICH – this is the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Another reason was that unnecessary duplication of testing and use of resources including animals used for testing could be avoided if the requirements for registration were harmonized. ICH guidelines describe the basic scientific principles and minimum standards of how every medicinal product should be characterized before it can be marketed in the three ICH regions: the United States of America, the European Union and Japan. These ICH guidelines are addressed to developers of new drugs and applicants for marketing authorization (EU) or new drug application (US) and the equivalent in Japan of medicinal products and are generally not legally binding; however, deviations from the guidelines need to be justified because they represent the current scientific and technical standard at the time they become effective. The ICH guidelines are divided into four groups:

- E for efficacy or clinical development
- M for multidisciplinary
- Q for product quality or chemical and pharmaceutical development and
- S for safety or nonclinical development.

In brief, the E-guidelines summarize the requirements pertaining to clinical development; the M-guidelines comprise a somewhat artificial construct containing guidelines e.g. related to coding of adverse events, the format of a dossier for marketing authorization application, and interestingly, one nonclinical guideline. They have in common that they are overarching several groups of guidances, e.g. ICH M3, said nonclinical guideline, provides an outline of the nonclinical requirements during the clinical development life cycle including marketing authorization for pharmaceuticals, i.e. type and timing of nonclinical studies in relation to the clinical development phase of the product under study. The safety guidelines contain detailed information on the minimum requirements for nonclinical testing (test tube and animal testing) different categories of pharmaceuticals have to undergo in order to obtain the necessary and sufficient information to characterize their nonclinical

safety, depending on their intended use and indication. The Q-guidelines comprise advice pertaining to product quality and chemical and pharmaceutical development, i.e. they address the quality requirements that need to be adhered to during development of active drug substances and finished pharmaceutical products including the quality requirements while the product synthesis/manufacturing is undergoing early and late phases of development and for marketing.

This work aims to analyze the rationale why a recent initiative of the ICH was undertaken to establish a single, separate guideline, ICH S9, addressing the nonclinical testing requirements for an important subgroup of anticancer pharmaceuticals: anticancer pharmaceuticals for the treatment of advanced cancer. It is aimed to describe the basic characteristics of this guideline. Finally, this work attempts to predict the potential impact of the new guideline on the use of resources for development of anticancer pharmaceuticals for treatment of advanced cancer. Please note that the terms “pharmaceutical”, “medicinal product” and “drug” will be used as synonyms within this text if not expressly stated otherwise and may comprise small chemically synthesized molecules or biopharmaceuticals. This work does not specifically describe the nonclinical testing requirements for monoclonal antibodies intended for use in advanced cancer which had been described in the MDRA master thesis of Dr. Stefan Zwilling (27).

2 Results

Advanced cancer for the purpose of this work is defined as a heterogenic cluster of malignant tumor types that are life-threatening for the patients affected, associated with a high death rate, and at the same time leave patients suffering from these malignancies with very limited treatment options. It is necessary to distinguish advanced cancer according to this definition and pharmaceuticals intended to treat this subgroup of cancer from pharmaceuticals intended for treatment of other forms of cancer e.g. adjuvant therapies, prophylactic treatments, or for treatment of side effects of anticancer drugs. The main difference between these groups of anticancer pharmaceuticals is the patient population they are intended for, especially the life-expectancy of these patients and thus the potential difference in benefit these treatments may provide compared to drugs for treatment of advanced cancer: advanced cancer patients may only have a very limited life-expectancy from less than six months up to three years, thus the benefit of a drug intended for treatment of advanced cancer can be immediately life-prolonging. Consequently, many long-term effects of drugs which are part of the general nonclinical evaluation may be either dispensable or deferrable either due to the initial short life-expectancy of this target patient population, i.e. long-term toxicity testing or carcinogenicity studies may not provide relevant information because the use of the anticancer drug in many cases may be of rather limited duration. Even to the contrary, the unnecessarily long nonclinical evaluation of advanced cancer anticancer pharmaceuticals may have the opposite to the intended effect: instead of contributing to protect the safety and well-being of clinical study subjects and later on to a safe drug entering the market, it may lead to scientifically not justifiable prolonged drug development timelines and cause delayed marketing authorization of potentially effective and life-prolonging pharmaceuticals.

What did the regulatory environment look like for nonclinical evaluation of anticancer pharmaceuticals aimed for treatment of advanced cancer before ICH S9 was developed? Let’s have a closer look at the general scope of the various ICH safety guidelines and how specific properties of anticancer pharmaceuticals intended for use in advanced cancer are reflected in nonclinical testing requirements for their development and marketing.

2.1 Setting the scene – general nonclinical testing requirements for drugs

Generally applicable nonclinical testing requirements for medicinal products are laid down in the individual ICH safety guidelines ICH S1A to ICH S8 and in the overarching guideline ICH M3. Because it summarizes all nonclinical testing requirements and structures them along the clinical development life-cycle of pharmaceuticals, ICH M3 is a good start to review these. According to this “Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and marketing authorization for Pharmaceuticals” (ICH M3(R2)), the nonclinical safety of all pharmaceuticals must be sufficiently characterized before undergoing the various

phases of clinical development and prior to exposing certain populations of human beings, e.g. healthy volunteers, women of childbearing potential, elderly or children, to the medicinal product.

2.1.1 ICH M3

In its recent revision R2, dated June 2009, this document summarizes the general nonclinical testing requirements for pharmaceuticals intended for use in humans as follows:

- Pharmacology studies to assess nonclinical evidence for mechanism of action, efficacy in suitable animal models and to characterize important safety aspects
- General toxicity studies
- Toxicokinetic and nonclinical pharmacokinetic studies
- Reproduction toxicity studies
- Genotoxicity studies

Further testing requirements might apply but may be limited to some drugs either because of certain concerns or due to their origin (the way they are manufactured) or their intended use, e.g.:

- Assessment of carcinogenic potential (limited to few drugs, either due to concerns or because of intended chronic use); generally applicable to small molecules only
- Assessments of phototoxicity, immunotoxicity, juvenile animal toxicity, and abuse liability on a case-by-case basis, i.e. few drugs only, e.g. because of certain properties of the drug e.g. structure activity relationship (SAR), drug belonging to a class with specific concerns, intended use in certain patient populations, or triggered by results of preceding nonclinical or clinical studies
- Assessment of biotechnology-derived products which are generally exempt from ICH M3 apart from the timing of nonclinical studies

Additionally, ICH M3(R2) also addresses other topics as to provide a single reference document for several current “hot topics” in drug development and pertaining nonclinical testing requirements, e.g. acute toxicity studies and nonclinical testing requirements for so-called exploratory clinical trials.

Acute toxicity studies had been part of the nonclinical testing requirements for many years but recent practice based on scientific evidence led to almost complete replacement of these studies by dose-range finding studies in the general toxicity testing species preceding the general toxicity studies (19, 20). The most prominent clarifications for acute toxicity testing introduced by ICH M3(R2) can be summarized as follows: lethality should no longer be an endpoint of acute toxicity testing, tests can be limited to the intended clinical route, and if not used as primary support for clinical studies (i.e. if single-dose/acute toxicity studies are not providing the primary support for starting dose selection e.g. for a clinical trial intended to follow the microdosing or exploratory IND approaches) they can be performed as non-GLP trials.

Exploratory clinical trials are clinical studies that can be characterized by exposing humans to test items for the first time but at far lower exposure levels than in the traditional Phase I setting aimed to establish the maximum tolerated dose (MTD). According to ICH M3, these studies can be used to investigate a variety of parameters such as PK, PD and other biomarkers, which could include PET (positron emission tomography) receptor binding and displacement or other diagnostic measures. The subjects included in these studies can be patients from selected populations or healthy individuals. The amount and type of nonclinical supporting data that is needed for starting exploratory clinical trials will be dependent on the extent of proposed human exposure, both with respect to the maximum clinical dose used and the duration of dosing. Exploratory clinical trials were previously addressed to some extent in different separate guidance documents in the US and EU (22, 23, 24), but the corresponding section included in ICH M3 provides a more comprehensive overview of the various study designs that can be undertaken in this particular setting. In a recent publication, the use of this approach was described for testing anticancer drugs (25). Thus, it may happen that exploratory clinical trials will be much more frequently be seen in the development of anticancer pharmaceuticals, e.g. for the purpose of selecting the most promising candidate based on early human PK/PD data.

The more specific nonclinical testing requirements are laid down in further details in the various ICH safety guidelines, divided by topic, and will be discussed further below.

According to ICH M3, prior to marketing of almost all medicinal products, the most resource intensive nonclinical study types must be performed in two different species of mammals: usually a rodent and a nonrodent species (e.g. general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies and reproduction toxicity studies). Even if not intended for chronic use, most medicinal products must be tested for at least 6 months in general, repeat dose administration toxicity studies, usually for 6 months in the rodent and 9 months in the non rodent species (Table 2-1, ICH S4). Many chronically administered drugs must undergo carcinogenicity testing in two rodent species, the most resource and time consuming nonclinical evaluation (ICH S1A to C).

Some exceptions apply depending on origin/manufacturing of the drug or intended use. For biotechnology-derived products a general origin/manufacturing exception applies and appropriate nonclinical safety studies should be determined in accordance with ICH S6. For these products, ICH M3(R2) only provides guidance with regard to timing of nonclinical studies relative to clinical development and marketing. Pharmaceuticals under development for indications in life-threatening or serious diseases (e.g., advanced cancer, resistant HIV infection, and congenital enzyme deficiency diseases) without current effective therapy also warrant a case-by-case approach to both the toxicological evaluation and clinical development in order to optimize and expedite drug development (intended use exception). In these specific cases particular studies can be abbreviated, deferred, omitted, or added.

Other questions addressed in ICH M3 are the testing requirements for combinations of two or more drugs. This work will not generally elaborate on testing requirements for combination treatments.

Table 2-1 Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing

Duration of Indicated Treatment	Rodent	Non-rodent
Up to 2 weeks	1 month	1 month
>2 weeks to 1 month	3 months	3 months
>1 month to 3 months	6 months	6 months
>3 months	6 months	9 months

Source: ICH M3(R2)

To summarize, some anticancer pharmaceuticals for advanced cancer may fall in the above described category of intended use exceptions warranting a case-by-case approach for the required nonclinical evaluation, with opportunities to abbreviate, defer, omit but also add certain studies. In addition, more and more anticancer pharmaceuticals are biotechnology-derived products which are covered by ICH S6 for the type of nonclinical studies that may apply in conjunction with ICH M3 (timing of nonclinical studies). Therefore, many aspects of guideline ICH M3(R2) may not directly apply to anticancer pharmaceuticals intended for use in advanced cancer.

2.1.2 ICH S1A: Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals

Carcinogenicity studies in rodents are usually needed for pharmaceuticals expected to be administered regularly over a substantial part of a patient's lifetime. In addition, they are recommended for some pharmaceuticals if there is concern about their carcinogenic potential. Such concern could arise from: (1) previous demonstration of carcinogenic potential in the product class that is considered relevant to humans; (2) structure-activity relationship (SAR) suggesting carcinogenic risk; (3) evidence of pre-neoplastic lesions in repeat dose toxicity studies; and (4) long-term tissue retention of parent compound or metabolite(s) resulting in local tissue reactions or other pathophysiological responses.

In instances where the life-expectancy in the indicated population is short (i.e., less than 2 - 3 years) no long-term carcinogenicity studies may be required. For example, oncolytic agents intended for treatment of advanced systemic disease do not generally need carcinogenicity studies. Thus, this guidance contains clear instructions that usually carcinogenicity testing may be obsolete for drugs intended for treatment of patients with advanced cancer due to short life-expectancy of these patients. Further, if the drug is a cytotoxic compound that is genotoxic, carcinogenicity studies are not needed because genotoxicity is believed to result in

general carcinogenic hazard for humans. If the drug is not a genotoxic and cytotoxic compound and if it is intended for further development in less serious cancer e.g. for adjuvant therapy in tumor-free patients or for prolonged use in non cancer indications, carcinogenicity studies are usually needed according to guideline ICH S1A. As a conclusion, drugs developed for treatment of advanced cancer should be generally exempt from long-term carcinogenicity studies due to the short life-expectancy of these patients.

2.1.3 ICH S1B: Testing for Carcinogenicity of Pharmaceuticals

This guideline embraces all pharmaceutical agents that need carcinogenicity testing as indicated in Guideline ICH S1A. For biotechnology-derived pharmaceuticals reference to Guideline ICH S6 is made. The strategy for testing the carcinogenic potential of a pharmaceutical is developed only after the acquisition of certain key units of information, including the results of genetic toxicology, intended patient population, clinical dosage regimen, pharmacodynamics in animals and in humans (selectivity, dose-response), and repeated-dose toxicology studies. Repeated-dose toxicology studies in any species may indicate that the test compound possesses immunosuppressant properties, hormonal activity, or other activity considered to be a risk factor for humans, and this information should be considered in the design of any further studies for the assessment of carcinogenic potential as it provides hints for potentially increased risk. This guidance thus does not address testing for carcinogenicity of biopharmaceuticals and apart from the reference to Guideline S1A it does not address particularities in terms of testing requirements of drugs intended for use in advanced cancer. Due to the immunosuppressant activity of cytotoxic drugs targeting rapidly dividing cells, and its statement that such drugs may need to be evaluated, it may contain even conflicting information in relation to guideline ICH S1A.

2.1.4 ICH S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals

The scope of guideline ICH S1C is not deemed relevant to this work. It is about dose-selection for carcinogenicity studies only, especially selection of the high dose which is only applicable if studies need to be performed; no guidance is provided on whether or not the studies may need to be performed or under which criteria they may be dispensable.

2.1.5 ICH S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

The primary focus of this guidance is testing of “small molecule” drug substances, and not biologics as defined in the ICH S6 guidance. This is because biopharmaceuticals such as proteins usually are not deemed to interact with DNA (ICH S6). Genotoxicity tests can be defined as *in vitro* and *in vivo* tests designed to detect compounds that induce genetic damage by various mechanisms. These tests aim to identify hazards with respect to damage to DNA and its fixation. Fixation of damage to DNA in the form of gene mutations, larger scale chromosomal damage or

recombination is generally considered to be essential for heritable effects. Compounds that are positive in tests that detect such kinds of damage are generally considered as having the potential to be human carcinogens and/or mutagens. In summary, this guidance focuses on the testing of small molecules. It does not contain a waiver for substances intended for use in advanced cancer. This would be expected e.g. for genotoxic drugs intended for use in advanced cancer per their mechanism of action tested positive *in vitro*. If this is the case, the confirmatory test *in vivo* should no longer be necessary.

2.1.6 ICH S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies

This Note for Guidance concerns toxicokinetics only with respect to the development of pharmaceutical products intended for use in human subjects. In this context, toxicokinetics is defined as the generation of pharmacokinetic data, either as an integral component in the conduct of non-clinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure. These data may be used in the interpretation of toxicology findings and their relevance to clinical safety issues, i.e. the exposures in animal test species corresponding to certain toxicity findings can be compared to the exposures reached in clinical studies and hence be used e.g. in the assessment of safety margins.

Toxicokinetic procedures may provide a means of obtaining multiple dose pharmacokinetic data in the test species, if appropriate parameters are monitored, thus avoiding duplication of such studies; optimum design in gathering the data will reduce the number of animals required. Due to its integration into toxicity testing and its bridging character between non-clinical and clinical studies, the focus is primarily on the interpretation of toxicity tests and not on characterising the basic pharmacokinetic parameters of the substance studied. This guidance thus applies to biopharmaceuticals and small molecules irrespective of their intended use in the clinic.

2.1.7 ICH S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

The absorption, distribution, metabolism and elimination of a compound is important for the interpretation of pharmacology and toxicology studies and such evaluation is usually part of the nonclinical evaluation of every pharmaceutical. Often, single dose tissue distribution studies provide sufficient information. This guidance addresses the exceptional need for repeated dose tissue distribution studies without specifically noting whether it also applies to biopharmaceuticals or drugs intended for use in advanced cancer patients. On the other hand, these drugs are also not out of scope of this guideline.

2.1.8 ICH S4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)

The objective of this guidance is to set out the considerations that apply to chronic toxicity testing in rodents and nonrodents as part of the safety evaluation of a

medicinal product. It proposes that the general repeated dose toxicity study in rodents should have six months duration whereas the non rodent study should have a duration of nine months. This guideline does not apply to biopharmaceuticals and does not provide specific guidance based on the intended clinical use of the medicinal product, e.g. in advanced cancer.

2.1.9 ICH S5 Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility

The aim of reproduction toxicity studies is to reveal any effect of one or more active substance(s) on mammalian reproduction. Principally, these studies can be separated in three different tests: test for effect on fertility, test for effect on embryo-fetal development (EFD) and test for effect on the offspring immediate before birth and afterwards, until reaching sexually maturity (peri/post natal development). This guideline applies to biopharmaceuticals and small molecules. It does not contain any waivers or further guidance based on the intended clinical use of the test drug e.g. in advanced cancer. At least for some of these drugs which could be cytotoxic and/or genotoxic due to their mechanism of action it would be expected that they are teratogenic, affect fertility etc. For such drugs one might have expected that not all reproduction toxicity studies be necessary if one is clearly positive.

2.1.10 ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

According to the ICH S6 guideline, the primary goals of preclinical safety evaluation of biopharmaceuticals are: 1) to identify an initial safe dose and subsequent dose escalation schemes in humans; 2) to identify potential target organs for toxicity and for the study of whether such toxicity is reversible; and 3) to identify safety parameters for clinical monitoring. It is intended primarily to recommend a basic framework for the preclinical safety evaluation of biotechnology-derived pharmaceuticals but frequently does not contain specific guidance in terms of what exactly to do but rather points towards the issues the drug developer needs to address with the planned nonclinical testing program. It focuses on the common particularities of these pharmaceuticals, e.g. immunogenicity, and provides specific guidance on some therapeutic classes e.g. monoclonal antibodies. Frequently, the specific properties of some biopharmaceuticals necessitate special study designs whereas for other drugs only data from the literature may need to be presented because of the long therapeutic experience with these e.g. human blood plasma derivatives. For “new” molecules, the specific study design and dosing schedule may be modified based on issues related to species specificity, immunogenicity, biological activity and/or a long elimination half-life. For example, concerns regarding potential developmental immunotoxicity, which may apply particularly to certain monoclonal antibodies with prolonged immunological effects, could be addressed in a study design modified to assess immune function of the neonate. This is to say that in many aspects, biopharmaceuticals may apply quite drug-specific study designs of the general toxicity study, evaluating many endpoints in the same study that “classically”, in the small molecule world, have been evaluated in dedicated studies. The routine

genotoxicity test-battery studies are not applicable to biotechnology-derived pharmaceuticals as are standard carcinogenicity bioassays. Again, this is owed to the fact that they comprise human proteins (plasma-derived proteins, monoclonal antibodies etc.) which are not believed to interact with DNA. Product-specific assessment of carcinogenic potential may still be needed depending upon duration of clinical dosing, patient population and/or biological activity of the product (e.g., growth factors, immunosuppressive agents, etc.). It should be noted that an addendum to this guideline is currently being developed (11); this addendum is currently in Step 3 of the ICH process. It addresses certain topics in ICH S6 and provides updated information on species selection, study design, reproductive and developmental toxicity, carcinogenicity and immunogenicity. However, both, the guideline and the addendum focus more on the common molecular properties of biopharmaceuticals and to a far lesser extent on the intended clinical use. In particular, they do not address the specific testing requirements of anticancer pharmaceuticals intended for use in patients with advanced cancer.

2.1.11 ICH S7A Safety Pharmacology Studies for Human Pharmaceuticals

This guideline generally applies to new chemical entities and biotechnology-derived products for human use. This guideline can be applied to marketed pharmaceuticals when appropriate (e.g., when adverse clinical events, a new patient population, or a new route of administration raises concerns not previously addressed). Safety pharmacology studies may not be needed where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low.

Safety pharmacology studies prior to the first administration in humans may not be needed for cytotoxic agents for treatment of end-stage cancer patients. However, for cytotoxic agents with novel mechanisms of action, there may be value in conducting safety pharmacology studies.

For biotechnology-derived products that achieve highly specific receptor targeting, it is often sufficient to evaluate safety pharmacology endpoints as a part of toxicology and/or pharmacodynamic studies, and therefore safety pharmacology studies can be reduced or eliminated for these products.

For biotechnology-derived products that represent a novel therapeutic class and/or those products that do not achieve highly specific receptor targeting, a more extensive evaluation by safety pharmacology studies should be considered.

In summary, safety pharmacology studies may not be needed for some biotechnology-derived drugs and for a class of drugs that could be intended for use in patients with advanced cancer, i.e. cytotoxic agents which is generally the case if their mechanism of action is well characterized and established. Novel mechanism of action cytotoxic drugs or non-cytotoxic anticancer pharmaceuticals for treatment of patients with advanced cancer are not generally exempt from safety pharmacology testing according to guideline ICH S7A.

2.1.12 ICH S7B The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) By Human Pharmaceuticals

This guideline applies to new chemical entities (NCEs) for human use and marketed pharmaceuticals when appropriate (e.g., when adverse clinical events, a new patient population, or a new route of administration raises concerns not previously addressed). Conditions under which studies are not called for are referred to be described in ICH S7A. Thus, due to this reference to ICH S7A, the same testing exemptions apply to drugs intended for use in advanced cancer with the further limitation to small molecules (NCEs), according to this guideline ICH S7B.

2.1.13 ICH S8 Immunotoxicity Studies for Human Pharmaceuticals

Immunotoxicity is, according to guideline ICH S8, defined as unintended immunosuppression or enhancement. The purpose of this guideline is to provide guidance for testing whether a compound is immunotoxic or not, excluding drug-induced hypersensitivity or autoimmunity; it's scope is limited to small molecules. Thus, it does not apply to biotechnology-derived pharmaceuticals covered by the ICH S6 Guideline. It specifically refers to cytotoxic oncolytic drugs targeting rapidly dividing cells and thus cause immunotoxicity e.g. to bone marrow cells both in nonclinical test species and humans. Thus, this guideline applies to small molecule, cytotoxic drugs intended for use in patients with advanced cancer; usually, the testing for endpoints of immunotoxicity can be integrated into standard toxicity studies.

2.2 Other perspectives: US and European thoughts about nonclinical development of anticancer medicinal products

In his master thesis (28), Dr. W. Meyer evaluated the papers of DeGeorge (FDA, CDER, 2) et al. and Tomaszewski (NCI, 21) as representatives of the US perspective, and the European Note for Guidance on the pre-clinical evaluation of anticancer pharmaceuticals (CPMP/SWP/997/96, 1), not discussing biotechnology-derived drugs. In this work, these three documents are briefly and independently analyzed once again. The paper of DeGeorge focuses on different therapeutic classes of anticancer pharmaceutical. The different nonclinical testing requirements are structured depending on the mechanism of action (moa) and corresponding anticipated duration of treatment of each therapeutic class (cytotoxic, hormonal therapy, adjuvant therapy, special categories like chemosensitizer, MDR modulator etc.) and phase in development (prior to entry-into-human (EIH), later phase development, NDA), based on the perceived risk associated with the moa and intended duration of use. For cytotoxic drugs, repeat dose toxicity testing in rodents and non rodents may be limited to 28-days according to the authors; only the embryo-fetal development studies may be necessary and the genetic toxicity test battery is deemed required by the authors, whereas in the other, rather chronically administered settings like adjuvant therapy to prevent cancer recurrence, the NDA-required testing program proposed by the authors resembles the usual, non-oncology indication program with in most cases full reproduction toxicity testing at least recommended and 6 months and 12 months durations of the general repeat dose

toxicity studies in rodents and non rodents, respectively (9 months for the latter, once ICH S4 would come into effect which had not been the case at the time the paper was published). Biotechnology-derived pharmaceuticals were not discussed by the authors.

Tomaszewski came to similar conclusions but added the class of molecular targeted compounds to the therapeutic classes evaluated and discussed the necessity of confirming the general toxicity results obtained in rodents in a non rodent species (the dog) as a better predictor of toxic effects in humans, even before EIH, again, based on the perceived risk of this class of compounds. In addition, he describes the example of Velcade for such a targeted therapy and promotes the use of cell-based assays *ex vivo* in addition to standard toxicity testing. He also touches briefly on biotechnology-derived pharmaceuticals, and introduces the science-based, case-by-case and step-by-step approach for these compounds.

Finally, the CPMP guideline cited above is restricted to cytotoxic drugs and single agent treatment. It proposes to conduct the general toxicity program in a rodent and non rodent species for “no longer than 6 months” for Marketing Authorization Application (MAA), and asks for primary *in vivo* pharmacology, safety pharmacology, acute toxicity studies including determination of MTD (including lethality as end point), but suggests to drop the reproduction toxicity and carcinogenicity studies because of the known class effects of cytoxic drugs.

In summary, the guidance available from these sources may be helpful in some cases but in my view may rather prompt the applicant to seek the advice from the regulators as it may raise more questions than it provides answers and does not necessarily add much clarity to the general ICH guidance. One problem certainly is the different scope of the three documents and the resulting heterogeneity in advice. Interestingly, all documents have in common that the authors determined the nonclinical testing requirements by addressing perceived risks associated with the pharmaceutical class they discussed; the authors did not take into consideration the potential benefit of the patient population with short life-expectancy, in my point of view. As a general conclusion, these three documents do not provide “user-friendly”, harmonized approaches for nonclinical evaluation of anticancer pharmaceuticals developed for use in advanced cancer patients.

2.3 The need for ICH S9

In the above analysis of the general non-clinical testing requirements for pharmaceuticals, the objectives of all nonclinical ICH guidelines have been summarized. Also other selected information available in the literature was discussed. The following table 2-2 summarizes these requirements as they generally apply, as they apply to biotechnology-derived pharmaceuticals and finally as they may apply for anticancer pharmaceuticals intended for use in advanced cancer e.g. due to any language allowing for deviations from the general nonclinical evaluation program described in the safety ICH guidance documents presented above:

Table 2-2 General nonclinical testing requirements of different classes of pharmaceuticals

Nonclinical studies required per Guidance document reference	Pharmaceuticals in general, excluding biopharmaceuticals	Biotechnology-derived pharmaceuticals	Anticancer pharmaceuticals (advanced cancer)
S1A S1B S1C	Usually applies if chronic use indication or if concern e.g. due to molecular class, SAR etc.	Usually exempt from carcinogenicity testing unless hormonal treatment, immunomodulator etc.	Usually exempt from carcinogenicity testing if used to treat patients with short life-expectancy, cytotoxic and genotoxic drug; if not used as adjuvant therapy and not developed further for prolonged use in non cancer indications
S2(R1)	mandatory	Usually exempt	mandatory
S3A	mandatory	mandatory	mandatory
S3B	May apply (exceptional)	May apply (exceptional)	May apply (exceptional)
S4	mandatory	N/A	mandatory
S5	mandatory	mandatory	mandatory
S6	N/A	mandatory	Depends on origin (manufacturing) of drug
S7A	mandatory	mandatory	Mandatory for marketing, not needed for starting Phase I with cytotoxic drug in advanced cancer patients
S7B	mandatory	mandatory	See S7A
S8	Usually applies	N/A	Usually applies
Other studies referred to in M3(R2): 1° and 2° pharmacology, local tolerance, studies triggered by use of certain drug delivery systems	May apply depending on intended use, clinical route, mechanism of action, molecular properties	May apply depending on intended use, clinical route, mechanism of action, molecular properties	May apply depending on intended use, clinical route, mechanism of action, molecular properties

From the above tabulation it is clear that for many aspects developers of anticancer pharmaceuticals intended for use in advanced cancer require further guidance, usually in the form of scientific advice, because the existing guidance is not specific enough for the intended use in advanced cancer, especially for non cytotoxic drugs. This is even more the case for biotechnology-derived pharmaceuticals where the guideline ICH S6 generally suggests a flexible case-by-case and step-by-step approach which comprises scientific advice from regulatory authorities as the rule rather than the exception. Frequently, deviations from the general nonclinical

evaluation program are warranted due to the high medical need possibly served by these drugs but it is not clear what exactly these deviations would be:

- Waivers or deferrals to perform particular studies (e.g. carcinogenicity (ICH S1A-C), certain segments of reproduction toxicity testing (ICH S5), deferrals of studies to later phases of clinical development (ICH S7A/B)
- Shorter durations of required studies (e.g. general repeated dose toxicity studies (ICH M3))
- Other exceptions or deviations from general practice due to the intended use or due to known class effects e.g. of cytotoxic drugs targeting rapidly dividing cells e.g. bone marrow

In addition, specific information is dispersed at various places and consequently no comprehensive summary of all possible deviations exists. This is even more the case as more and more pharmaceuticals intended for use in advanced cancer are biotechnology-derived drugs which are usually exempt from specific preclinical guidance by referral to the guidance ICH S6. However, this is one of those guidance documents that provides little specific instructions (number and design of studies) but aims in showing the applicant all the pitfalls and issues she has to address in her attempts of developing a drug to market. Most recently, an addendum of ICH S6 has been discussed with some more specific language at various places within the document which has currently reached Step 3 (draft for comments to be solicited by each ICH regional regulatory authority), based on experience gained with the development of biopharmaceuticals in recent years. However, this guideline does not contain specific guidance on nonclinical testing requirements for biopharmaceuticals intended for use in advanced cancer.

Thus, it is also difficult for regulators to keep a common, consistent tone across all guidelines mostly because of the high dynamics of the science involved in developing pharmaceuticals for advanced cancer. Therefore, in 2006 at the St. Louis ICH conference the idea for ICH S9 was born following a proposal from PhRMA (the association of pharmaceutical companies in the US) because all parties agreed that such a guideline was needed.

2.4 Description of content of guideline ICH S9

This section follows the general structure of the ICH S9 guideline, stressing those aspects that make it such a special document.

Objectives and background

The new guideline ICH S9 aims to provide guidance on the design of the nonclinical testing program for the development of anticancer pharmaceuticals for use in patients with advanced disease and limited therapeutic options. It again stresses the ultimate purpose of nonclinical evaluations of drugs which are conducted to identify the basic pharmacologic properties of a pharmaceutical, to establish a safe starting dose for clinical Phase I and to understand the toxicological profile of the drug especially with

respect to target organs, exposure-response relationship and reversibility of toxicological findings.

Scope and general principles

The guideline applies to pharmaceuticals, small chemically synthesized drugs and biotechnology-derived drugs alike, intended to treat cancer in patients with serious, life-threatening disease ("patients with advanced cancer"). It describes the type and timing of nonclinical studies in relation to clinical development with appropriate references to other guidelines similar to ICH M3 which means that ICH M3 does no longer apply to drugs intended for use in advanced cancer unless ICH M3 is specifically referred to in ICH S9. This is the case e.g. when healthy volunteers are to be included in the clinical evaluation of a drug. It also describes the additional nonclinical data to be collected in case the development of the drug is broadened into populations with less severe disease as measured by long expected survival, or intended use, e.g. not treatment of disease but prophylaxis including vaccines or treatment of side effects. Further, certain groups of drugs are not within the scope of ICH S9, namely cellular or gene therapeutics.

Studies to support nonclinical evaluation

This section describes the type of studies to be conducted for nonclinical evaluation of anticancer pharmaceuticals for advanced cancer. Prior to Phase I studies, anti-tumor activity of the drug should be established by characterization of the mechanism of action (primary pharmacology), provision of nonclinical proof of principle using appropriate models, which in addition may aid in start dose selection and selection of investigational biomarkers, and help justifying pharmaceutical combinations. It recommends that information should be gathered on dosing schedules and dose-escalation schemes as well as the selection of appropriate test species. Obviously, the selection of appropriate test species is the main initial problem to solve for each developer of a biotechnology-derived pharmaceutical prior to the nonclinical evaluation in toxicology studies in animals. In this guideline, it is generally recommended for all drugs irrespective of how they were manufactured that dosing schedules and dose-escalation schemes used in nonclinical evaluation should reflect the intended practice in the clinic. Because the dosing schedule can significantly influence the toxicity observed with an anticancer drug this is even more relevant.

The safety pharmacology of the drug should be evaluated. Usually, if no specific concerns have been identified the evaluation of safety pharmacology endpoints can be performed as part of the general toxicology studies (the ECG must be performed in nonrodents). Limited pharmacokinetic parameters (AUC, half-life, C_{max}) should be evaluated in the animal species used for nonclinical evaluations. Further information on ADME (absorption, distribution, metabolism, excretion) should be generated as clinical development progresses. The general toxicology studies need not determine a NOAEL (No observed adverse effect level) or NOEL (No observed effect level) because an anticancer pharmaceutical is generally dosed to a MTD (maximum tolerated dose) in humans, identifying DLTs (dose limiting toxicities). The assessment

should include recovery groups to provide understanding as to the reversibility of toxicological effects. Complete recovery does not need to be shown. If a recovery group must be included due to severe toxicity at approximate estimated clinical exposure levels then the assessment of a general toxicology study including scientific assessment of the recovery group must be available before starting clinical development. If the anticancer pharmaceutical is a small molecule usually two species, a rodent and a nonrodent must be tested. However, if the drug is genotoxic and targets rapidly dividing cells, to start clinical development, a repeat dose toxicity study in one rodent species may be sufficient, provided that the rodent is a relevant species. If the anticancer pharmaceutical is biotechnology-derived ICH S9 refers to ICH S6 regarding the number of species to be tested. In brief, if only a single species is a relevant species for the test item (which must be scientifically justified) then evaluation in a single species can be sufficient. Further (according to the draft addendum of ICH S6), if the results of the 28-day general repeat-dose toxicity studies are comparable between the rodent and the nonrodent, the further long-term study can be conducted only in the rodent, provided that the rodent is a relevant species. Reproduction toxicology studies need only be performed to assess embryo-fetal toxicity, to be able to assess risk for the developing embryo and to communicate such potential risk to patients who are or may become pregnant. Results from these studies must be provided with the application for marketing authorization but are not needed to start clinical development in patients with advanced cancer. For pharmaceuticals that are genotoxic and target rapidly dividing cells in general toxicity studies or belong to a class of drugs known to cause developmental toxicity the embryofetal development toxicity studies (EFD) need not be performed, at all. For small molecules and if the study conducted in the first species is positive for embryo-fetal lethality or teratogenicity, the study in the second species is not needed. For biopharmaceuticals, the assessment of EFD in one pharmacologically relevant species is usually deemed sufficient. The assessment may be performed by evaluating toxicity during the period of organogenesis. Specific study designs as described in ICH S6 may be used, too. Other alternatives may be considered appropriate, too, and include literature assessment, assessment of placental transfer and other factors. A study of fertility and early embryonic development may not be performed. Relevant information can be obtained from general toxicity trials, e.g. the effect of the pharmaceutical on the reproductive organs, which may serve as the basis for the fertility assessment. A pre- and postnatal toxicology study is generally not needed for evaluation of pharmaceuticals intended for use in advanced cancer patients. Genotoxicity should be assessed prior to marketing. If the *in vitro* genotoxicity assay is positive *in vivo* testing may not be needed. For biopharmaceuticals the principles outlined in ICH S6 apply. Carcinogenicity assessment is not needed for drugs intended for treatment of patients with advanced cancer. For most pharmaceuticals, no dedicated immunotoxicity studies are needed but the design components of the general toxicity studies are considered sufficient to assess immunotoxicity. This may not be the case for immunomodulatory drugs and additional endpoints, e.g. immunophenotyping or flow cytometry should be included in the design of the general toxicity studies. Phototoxicity potential should be assessed prior to starting clinical studies based on photochemical properties of the

drug or other members of the chemical class. If data indicates a potential risk, appropriate protective measures should be taken in outpatient trials. Only if photosafety risk cannot be assessed based on nonclinical data or in clinical studies, a specific photosafety assessment consistent with the principles laid down in ICH M3(R2) should be provided prior to marketing.

Nonclinical data to support clinical trial design and marketing

This section describes the timing of nonclinical studies relative to clinical trials by outlining the knowledge that should be gained prior to exposing certain populations to the anticancer pharmaceutical. For EIH, a start dose should be identified that is expected to have pharmacologic effects and is reasonably safe to use, based on scientific justification using all available nonclinical data e.g. PK, PD, toxicity. Frequently for many small molecules, the start dose is set to 1/10 of the Severely Toxic Dose in 10% of the animals (STD 10) in rodents. If the non-rodent is more appropriate, then 1/6 of the Highest Non-Severely Toxic Dose (HNSTD) can be considered an appropriate starting dose. 26For most systemically administered small molecules, scaling of the dose in animals to a human equivalent dose is based on normalization to body surface area. For some small molecules and biopharmaceuticals, interspecies scaling based on body weight, AUC or other exposure parameters might be appropriate (26). For those biopharmaceuticals with immune agonistic properties, selection of the start dose should be based on the minimally anticipated biologic effect level (MABEL, 26). In general, the highest dose or exposure tested in nonclinical studies does not limit the highest dose investigated in a clinical study in advanced cancer patients because in this patient population dosing is usually performed up to the MTD, or to DLT. If a steep dose- or exposure-response curve for severe toxicity was observed in toxicology studies or no preceding marker for severe toxicity is available fractional increments for dose escalation rather than dose doubling should be considered. In Phase I clinical trials, treatment can continue as long as the patient is responding; the duration of nonclinical studies does not limit the duration of clinical trials. The schedule in the nonclinical studies should reflect the dosing schedules to be used in initial clinical studies. Table 2-3 summarizes dosing schedules of nonclinical studies corresponding to intended dosing schedules in the clinic.

The nonclinical data to support start of clinical Phase I would normally be sufficient for entry into Phase II for drugs intended for use as second or first line therapy in patients with advanced cancer. To support further development of such drugs, results from 3 months' duration repeat dose toxicity studies should be available prior to initiating Phase III clinical trials. For most pharmaceuticals intended for use in advanced patients nonclinical studies of 3 months duration are deemed sufficient for marketing. Changes in the clinical schedule may trigger additional nonclinical studies in a single species if evaluation of available clinical data is not sufficient to support the intended change in schedule.

Table 2-3 Examples of Treatment Schedules for Anticancer Pharmaceuticals to Support initial Clinical Trials

Clinical Schedule	Examples of Nonclinical Treatment Schedule[1,2,3,4]
Once every 3 weeks	Single dose
Daily for 3 days every 3 weeks	Daily for 3 days
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5-7 days, alternating weeks	Daily for 5-7 days, alternating weeks (2 dose cycles)
Once every 2 weeks	2 doses 14 days apart
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Twice or three times a week	Two or three times a week for 4 weeks
Continuous daily	Daily for 28 days
Continuous weekly	Once a week for 4-5 doses

Source: ICH S9

[1] The above table describes the dosing phase. The timing of the toxicity assessment(s) in the nonclinical studies should be scientifically justified based on the anticipated toxicity profile and the clinical schedule. E.g., both a sacrifice shortly after the dosing phase to examine early toxicity and a later sacrifice to examine late onset of toxicity should be considered.

[2] Further consideration regarding flexibility in the relationship of the clinical schedule and the nonclinical toxicity studies could be based on half-life in the test species and known or projected half-life in humans, exposure assessment, toxicity profile, saturation of receptors, among others.

[3] Schedules described in the table do not specify recovery periods, which should be incorporated into the study design. Timing of recovery sacrifices should be scientifically justified. For non-rodent studies, dose groups usually consist of at least 3 animals/sex/group, with an additional 2/sex/group for recovery. However, there can be instances where recovery groups are either not warranted or should be included at some or all dose levels, but this should be scientifically justified. Both sexes should generally be used or justification should be given for specific omissions.

[4] The schedules described in this table should be modified as appropriate with molecules with extended pharmacodynamic effects, long half-lives or potential for anaphylactic reactions. In addition, the potential effects of immunogenicity should be considered (see ICH S6).

If combination of pharmaceuticals is planned, the toxicology of each individual pharmaceutical should be well studied individually according to ICH S9. In addition, a scientific rationale and data supporting the combination must be provided by the drug developer. Generally, toxicology studies evaluating the safety of combinations of pharmaceuticals are not needed. In case one of the pharmaceuticals is in an early stage of development, i.e. its toxicity profile in humans has not yet been characterized, a pharmacology study supporting the combination should be performed. This study should show increased efficacy of the combination in the absence of a substantial increase of toxicity based on an evaluation of basic safety endpoints, e.g. mortality, clinical signs and body weight.

For development of an anticancer pharmaceutical intended for use in pediatric patients with advanced cancer, in general, at first a relatively safe dose in adult populations should be identified. Studies in juvenile animals should be considered only if available human and nonclinical data is insufficient to evaluate the safety in the intended pediatric age group.

Other considerations

Guideline ICH S9 also elaborates on other topics, e.g. conjugated products, liposomal products or other similar carriers, drug metabolites, and impurities. The general tone is that toxicokinetics of conjugated and liposomal products should be evaluated as appropriate, if possible separately for conjugated and non-conjugated material or free compound and liposomal product, respectively. In addition, the safety of the conjugated or liposomal product should be assessed. The unconjugated or unencapsulated material and the linker or carrier used need only be evaluated to a limited extent, e.g. single arm of a toxicology study.

Drug metabolites need not generally be qualified even if human-specific. Similarly, the evaluation of impurities is generally not needed with respect to negligible risk limits as discussed in ICH Q3A and ICH Q3B. Justification for exceeding limits should be provided and could include description of disease being treated, patient population, nature of the parent molecule including its pharmacologic properties, and potential for genotoxicity or carcinogenicity. Further, qualification of impurities assessment could be performed by describing dose or concentration of impurities tested in nonclinical studies relative to clinical levels, and impact of further purification steps on the manufacturing process. For genotoxic impurities, several approaches have been used setting limits based on increase in lifetime risk of cancer. Such limits are deemed inappropriate for pharmaceuticals intended for use in advanced cancer patients mostly due to the rather short life-expectancy of these patients and the limited treatment options these patients have.

Summary

The content of guideline ICH S9 is summarized below in Table 2-4 and compared with the nonclinical testing requirements for anticancer pharmaceuticals intended for use in advanced cancer patients before this guideline was crafted.

Table 2-4 Comparison of nonclinical testing requirements for advanced cancer drugs before and after launch of ICH S9, for marketing if not stated otherwise

Nonclinical studies required per Guidance document reference	Anticancer pharmaceuticals (advanced cancer) pre ICH S9	Anticancer pharmaceuticals (advanced cancer) post ICH S9
S1A S1B S1C	Usually exempt from carcinogenicity testing if cytotoxic and genotoxic drug, not used as adjuvant therapy or intended for further development in prolonged use non-cancer indications.	Exempt from carcinogenicity testing if not used as adjuvant therapy (long term use, less serious disease)
S2(R1)	Mandatory before starting clinical trials	Needed for marketing.
S3A	mandatory	As appropriate
S3B	May apply, exceptional	As appropriate, exceptional
S4	Mandatory, rodent and non-rodent; 6 months rodent, 9 months nonrodent for marketing	3 month duration deemed appropriate; rodent-only could be sufficient to start clinical trials if targeting rapidly dividing cells e.g. bone marrow
S5	Mandatory all three segments: EFD, fertility, peri/post natal. EFD in two species. Exceptions apply for biopharmaceuticals (see ICH S6)	EFD needed for marketing, one species sufficient if first study positive; fertility to be assessed in general toxicity studies; no peri/post natal studies needed
S6	If applicable (biopharmaceuticals) some testing waivers apply: genotoxicity, carcinogenicity, reproduction toxicity; case-by-case single (relevant) species sufficient	Some references to ICH S6 e.g. genotoxicity, number of species to be selected for general toxicity studies, if biotechnology-derived drug
S7A	Mandatory if novel moa; may not be needed before starting Phase I if cytoxic drug with know moa	Endpoints need to be assessed before starting clinical studies but could be done in context of general toxicity studies. Dedicated studies usually not needed if no concern.
S7B	Mandatory, same possible exceptions as ICH S7A	Endpoints need to be assessed before starting clinical studies but could be done in context of general toxicity studies. Dedicated studies usually not needed if no concern.
S8	Usually applies. Endpoints can be included in general toxicity studies.	Endpoints usually included in general toxicity studies.
M3(R2)	Mandatory for small molecules, and for timing of studies all molecules; biopharmaceuticals (type of study) see ICH S6	N/A – guideline addresses type and timing of nonclinical studies.

From the above table 2-4 it is clear that testing requirements for pharmaceuticals intended for use in treatment of advanced cancer have been streamlined to quite

some extent in the new guideline ICH S9. This is mostly due to the fact that the rationale for the required testing packages is no longer based (almost) exclusively on the potential risks associated with the drug to be tested but the short life-expectancy of the intended patient population has gained substantial weight in providing the rationale for the testing requirements. The most prominent changes when comparing to a “standard nonclinical package” are:

- the applicability to small chemically synthesized molecules and biopharmaceuticals alike, within a single document
- the duration of the general repeated dose toxicity studies (3 months in both species instead of 6 months in rodents and 9 months in non-rodents) and
- general waivers for carcinogenicity testing and most segments of reproduction toxicity studies (peri-/post natal development, dedicated fertility studies).
- In addition, many testing obligations can be fulfilled by designing appropriate general repeat dose toxicity studies, e.g. immunotoxicity endpoints, safety pharmacology endpoints and some evaluations of reproduction toxicity (fertility assessment) can be included in these studies.

3 Discussion

According to the analysis of existing ICH guidance on nonclinical evaluation of anticancer pharmaceuticals and other literature sources presented in this work, there was a patchwork of guidance available with sometimes inconsistent, unclear and non-harmonized requirements for the nonclinical evaluation of anticancer drugs. The resulting uncertainty among drug developers may have led to the summarized nonclinical testing programs of drugs intended for use in patients with advanced cancer that were very similar or equivalent to the nonclinical testing programs usually conducted for pharmaceuticals intended for use in entirely different patient populations, namely, patients with long life-expectancy, not suffering from a serious immediately life-threatening disease, and corresponding longer nonclinical development timelines, potentially inadequate use of resources, especially of animals. This is summarized in Table 3-1. Anticancer pharmaceuticals are grouped in three different categories: cytotoxic drugs, biopharmaceuticals, and other, representing the group of more recently developed molecules which may not be grouped with the classical cytotoxic chemotherapies. From this summary table it is clear that drug developers have provided “complete” nonclinical evaluation packages at time of marketing authorization, rather reflecting typical ICH M3, small molecule, testing programs, e.g. involving carcinogenicity testing, six month and nine month general toxicity studies in at least two species and all segments of reproduction toxicology testing. One has to acknowledge, though, that some of these molecules had initially been developed for other diseases, e.g. thalidomide (pain killer, sleeping pill) or everolimus (transplantation). The exception are the biopharmaceuticals, which have been developed in a more tailored fashion taking into account the risks to be addressed, the patient population to be treated and biopharmaceutical particularities, namely that in some cases only among non-human primates a relevant species can be found and in these cases the studies are frequently conducted in a single (more) relevant species. Accordingly, the general long-term repeat dose toxicity studies were conducted in a single species only, no carcinogenicity testing was performed for any of these drugs cited in this work. This is highly likely due to the step-by-step and case-by-case approach, involving frequent interaction with regulatory authorities while the drug is undergoing its development, where learning from experience can be implemented in a more expedited fashion than in guidelines. From the programs undertaken for the different drugs there is also a tendency to “less testing” for a “more recently developed” drug (panitumumab), possibly because of the experience both drug developers and regulatory authorities have gained in bringing more and more such molecules to market or the random effect that the older drugs were developed by bigger pharmaceutical companies which tend to be more conservative and the newer one developed by a small biotech company using probably more risky approaches allowing to save on the resource input. It could of course simply be a random effect because of the limited sample size evaluated in this work.

Additionally, the more recent advances in cancer therapy, exploiting non-cytotoxic mechanisms of actions and employing biotechnology-derived drugs were not reflected in existing guidelines where guidance on nonclinical evaluation of

anticancer pharmaceuticals was provided. According to the concept paper S9, this gap has been acknowledged by both the pharmaceutical industry and regulators. Triggered by the fact that this regulatory “white area” was in the process of being addressed by regulators in the US and Japan, most likely leading to “independent proliferation of guidances focused on preclinical issues in oncology drug development” (concept paper S9) consequently not offering a harmonized approach for the nonclinical evaluation of these types of drugs, the idea for ICH S9 was born. Due to the high need expressed by all interested parties in the development of the guideline very aggressive timelines could be established and actually were kept.

Table 3-1 Summary of nonclinical evaluations performed by different applicants based on EPAR, section "scientific discussion" or other public information, compared to ICH S9 requirements

Category of nonclinical studies	Classic cytotoxic drugs (a)			Other anticancer drugs (b)			Biotech-derived drugs (d)			ICH S9		
	Done	Species	Duration	Done	Species	Duration	Done	Species	Duration	Done	Species	Duration
Primary pharmacology	Y	Mice		Y	Mice		Y	Mice		Y		
Secondary pharmacology	Y			Y	Mice, rats, cats		Y	Mice, cynomolgous*, rabbits*		Y		
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y			Y	Rats, mice		Y	Mice		N		
Safety pharmacology studies	Y			Y	Dog, cynomolgous		Y	Mice, dogs, rhesus		Y		
Pharmacokinetic/ toxicokinetic studies	Y	Rats, rabbits, mice		Y	Mice, rats, dogs, rabbits		Y	Rats, Mice, rabbits, monkey		Y		
ADME studies	Y	rats		Y	Mice, rats, dogs, rabbits, guinea pigs, cynomolgous			Mice[#], monkey		Y		
Single-dose toxicity studies	Y	Mice, rats, dogs, swine		Y	Mice, rats, dogs, monkey			Mice[#], rats[#], monkey		N		
Repeat-dose toxicity studies, species 1	Y	Mice or rats	6 months	Y	Mice, rats	Up to 26 w	Y	Rats, rabbits	Up to 26 weeks	Y		3 months
Repeat-dose toxicity studies, species 2	Y	Dogs	6 months	Y	Dogs	Up to 53 w	Y	monkey	Up to 39 weeks	(Y)		3 months
Repeat-dose toxicity studies, species 3	N			Y	Monkey	Up to 39 w	N			N		

Category of nonclinical studies	Classic cytotoxic drugs (a)			Other anticancer drugs (b)			Biotech-derived drugs (d)			ICH S9		
	Done	Species	Duration	Done	Species	Duration	Done	Species	Duration	Done	Species	Duration
Genotoxicity	Y	Mice		Y	Mice		Y	Rats**		Y		
Reprotoxicity, fertility	Y	Mice, rats		Y	Rats, rabbits		Y	Rabbit, monkey		N		
Reprotoxicity, embryo-fetal development	Y	Mice, rats, rabbits		Y	Rats, rabbits		Y	Rabbit, monkey		Y		
Reprotoxicity, peri-post natal	N			Y	Rats, rabbits		Y	Monkey		N		
Carcinogenicity studies	N			Y	Mice, rats*		N			N		
Immunogenicity studies	N			N			Y	monkey		(Y)		
Immunotoxicity studies	Y	Rats		Y	Mice		Y	In vitro		N		
Local tolerance studies	Y	Rabbits		Y	Rabbits guinea pigs		Y	Rabbit, monkey		N		
Additional, special tests	Y			Y	Rats, monkey	Metab., photot., impur., juvenile	Y	Monkey wound healg. Specif.		Y (phototoxicity)		

(a) Classic cytotoxic drugs were: docetaxel (Taxotere), paclitaxel (Abraxane), pemetrexed (Alimta)

(b) Other anticancer drugs were: erlotinib (Tarceva), bortezomib (Velcade), everolimus (Afinitor)*, thalidomide (Pharmion)*, nilotinib (Tasigna); carcinogenicity testing only in these* mostly due to prior development in non-cancer indication

(c) Biotech-derived drugs were: bevacizumab (Avastin), panitumumab (Vectibix), cetuximab (Erbitux),and trastuzumab (Herceptin); *secondary pharmacology in cynomolgous and rabbits only for Avastin, ** genotoxicity in vivo for Erbitux only, # non-relevant species tested, Erbitux only

See Appendix for detailed summaries by individual drug.

4 Conclusion and outlook

In this work, the regulatory landscape before the ICH S9 era is summarized. The need for this guideline is clearly pointed out, as follows:

- Incoherent and non-harmonized requirements for nonclinical evaluation of anticancer pharmaceuticals because
    - Biopharmaceuticals are usually treated separately
    - Basis for the requirements was mainly the potential risk of different therapeutic classes of drugs, considering their MOA, especially, cytotoxic or non-cytotoxic, known and established MOA versus novel MOA
- The short life-expectancy and resulting need for new treatments for patients lacking satisfactory therapy options was inadequately considered.
- More weight needed to be put on potential benefits of drugs under development and evaluation of the potential risks of a drug had to be set more into perspective of this high medical need of patients with advanced cancer.

The new guidance ICH S9 should allow certain streamlining of nonclinical evaluations of anticancer pharmaceuticals intended for use in advanced cancer. Compared to past practices (see Section 3., Table 3-1 and Annex) drug developers and applicants for marketing authorization could save a considerable amount of time, money, and last but not least animal resources to support their application dossiers when applying the principles and guidance that is provided in ICH S9 to the extent intended by the developers of this new guideline. This is due to the following features of this new guideline:

1. Providing an ICH guideline with harmonized requirements for nonclinical development of anticancer pharmaceuticals intended for use in patients with advanced cancer in the three ICH regions
2. Inclusion of both, small molecules and biotechnology-derived drugs into the scope of a single guideline
3. More specifically: by generally abandoning the need for 6 month and 9 month repeat dose general toxicity studies (3 months for rodents and nonrodents are deemed sufficient), carcinogenicity studies, and fertility and peri- and postnatal reproduction toxicity trials and by defining the need for only a single species embryo-fetal development study if the study is positive for teratogenicity or embryo-fetal lethality
4. Further, by allowing to include many endpoints for assessment, e.g. of fertility, immunotoxicity, safety pharmacology within the framework of well-designed general toxicology studies
5. Finally, by more precisely defining the evaluations needed prior to starting clinical development, e.g. for small-molecule, genotoxic drugs targeting rapidly dividing

cells a single repeat dose study in rodents only can be sufficient, and accordingly, showing recovery is also needed only for a single species prior to Phase I clinical trials.

6. By including specific guidance on the nonclinical dosing schedules that would support corresponding clinical schedules, thus reducing the need to seek scientific advice.

In addition, due to the clarity and more specific language that is used in many places of the guideline (e.g. schedule table, clarification on recovery groups to be utilized in the general toxicity studies), the need for frequent discussions with regulators may no longer be as prominent, potentially leading to further savings in development time because less meetings for clarification of requirements for nonclinical evaluation of drugs intended for use in advanced cancer may be necessary to develop a drug for the initial NDA/MAA.

It may be envisioned that many drugs for treatment of advanced cancer benefit from the clarity provided in this new guideline boosting the number of drugs being developed and brought to market considerably, using fast track (US) or conditional marketing authorization (EU) regulatory pathways for expedited market entry. If the right treatments are combined they may eventually render the threat of cancer into a chronic disease much like HIV/AIDS.

5 Summary

Advanced cancer is defined as a heterogenic cluster of malignant tumor types that are life-threatening for the patients affected, associated with a high death rate, and at the same time leave patients suffering from these malignancies with very limited treatment options. It is necessary to distinguish advanced cancer according to this definition and pharmaceuticals intended to treat this subgroup of cancer from pharmaceuticals intended for treatment of other forms of cancer e.g. adjuvant therapies, prophylactic treatments, or for treatment of side effects of anticancer drugs. Because advanced cancer patients may only have a very limited life-expectancy from less than six months up to three years, the benefit of a drug intended for treatment of advanced cancer can be immediately life-prolonging. Consequently, many long-term effects of drugs which are part of the general nonclinical evaluation may be either dispensable or deferrable either due to the short life-expectancy of this target patient population, i.e. long-term toxicity testing or carcinogenicity studies may not provide relevant information because the use of the anticancer drug in many cases may be of rather limited duration.

In the past, the potential risks potentially associated with a new pharmaceutical have largely determined the requirements for its nonclinical evaluation, probably not putting adequate weight on the potential benefits for certain patient populations with advanced disease and limited treatment options like patients with advanced cancer.

The new guidance ICH S9 should allow certain streamlining of nonclinical evaluations of anticancer pharmaceuticals intended for use in advanced cancer. Compared to past nonclinical development programs, drug developers and applicants for marketing authorization could save a considerable amount of time, money, and last but not least animal resources to support their application dossiers when applying the principles and guidance that is provided in the new ICH S9 guideline. This is due to the following features of this new guideline:

1. Providing an ICH guideline with harmonized requirements for nonclinical development of anticancer pharmaceuticals intended for use in patients with advanced cancer in the three ICH regions
2. Inclusion of both, small molecules and biotechnology-derived drugs into the scope of a single guideline
3. More specifically: by generally abandoning the need for 6 month and 9 month repeat dose general toxicity studies (3 months for rodents and nonrodents are deemed sufficient), carcinogenicity studies, and fertility and peri- and postnatal reproduction toxicity trials and by defining the need for only a single species embryo-fetal development study if the study is positive for teratogenicity or embryo-fetal lethality

4. Further, by allowing to include many endpoints for assessment, e.g. of fertility, immunotoxicity, safety pharmacology within the framework of well-designed general toxicology studies
5. Finally, by more precisely defining the evaluations needed prior to starting clinical development, e.g. for small-molecule, genotoxic drugs targeting rapidly dividing cells a single repeat dose study in rodents only can be sufficient, and accordingly, showing recovery is also needed only for a single species prior to Phase I clinical trials.
6. By including specific guidance on the nonclinical dosing schedules that would support corresponding clinical schedules, thus reducing the need to seek scientific advice.

In addition, due to the clarity and more specific language that is used in many places of the guideline (e.g. schedule table for nonclinical schedules to be used for assessments of certain clinical schedules, clarification on recovery groups to be utilized in the general toxicity studies), the need for frequent discussions with regulators may no longer be as prominent, potentially leading to further savings in development time because less meetings for clarification of requirements for nonclinical evaluation of drugs intended for use in advanced cancer may be necessary to develop a drug for the initial NDA/MAA.

6 References

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7 Annex (Anlagen)

Where information was available in EPARs, this was included. Generally, a Y indicates testing was done (in vitro or in vivo). If both in vitro and in vivo tests were done, the species for in vivo test is provided. Duration is provided for general repeat dose toxicicity studies and carcinogenicity studies, where available. If the information in the EPAR was not clear the field was left blank. In many cases this could mean that no dedicated studies were performed but endpoints assessed in general toxicity study. Where this was mentioned it is included in the table.

Table 7-1 Summary of nonclinical studies performed, category (a) cytotoxic drugs

Category of nonclinical studies	**Taxotere (docetaxel)** **Autorisation date by EU Commission: 27 November 1995, and US label September 2007**		
Advanced metastatic breast cancer (in combination with doxorubicin) or locally advanced or metastatic NSCLC	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	Y		
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y		
Pharmacokinetic studies	Y		
Toxicokinetic studies	Y	Rats, dogs	
ADME studies	Y		
Single-dose toxicity studies	Y	Rats, mice	
Repeat-dose toxicity studies, species 1	Y	Rats	6 months
Repeat-dose toxicity studies, species 2	Y	Dogs	6 months
Genotoxicity	Y	Mice	
Reprotoxicity, fertility	Y	Rats	
Reprotoxicity, embryo-fetal development	Y	Rats, rabbits	
Reprotoxicity, peri-post natal			
Carcinogenicity studies	N		
Safety pharmacology studies	Y		
Immunotoxicity studies	Y		
Immunogenicity studies	N		
Local tolerance studies	Y		
Additional, special tests			

Category of nonclinical studies	**Abraxane (paclitaxel)** **Autorisation date by EU Commission: 11 January 2008**		
Advanced metastatic breast cancer	Done	Species	Duration
Primary pharmacology	Y	mice	
Secondary pharmacology	N		
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	N		
Safety pharmacology studies	N		
Pharmacokinetic studies	Y	Rats, rabbits, mice	
Toxicokinetic studies	N		
ADME studies	Y (DME)	rats	
Single-dose toxicity studies	Y	Mice, rats, dogs, swine	
Repeat-dose toxicity studies, species 1	Y	Mice	5d
Repeat-dose toxicity studies, species 2	Y	Rats	26 w
Genotoxicity	N		
Reprotoxicity, fertility	Y	Rats, males	
Reprotoxicity, embryo-fetal development	Y	Rats	
Reprotoxicity, peri-post natal	N		
Carcinogenicity studies	N		
Immunogenicity studies	N		
Immunotoxicity studies	Y	Rats	
Local tolerance studies	Y	Rabbits	
Additional, special tests	Y	Myelosuppression studies in	

Category of nonclinical studies	**Alimta (pemetrexed)** **Autorisation date by EU Commission: 20 September 2004**		
	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	N		
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	mice	
Safety pharmacology studies	Y	Mice, rats, dogs	
Pharmacokinetic studies	Y	Mice, dog	
Toxicokinetic studies	Y	Dogs	
ADME studies	Y	Mice, dogs	
Single-dose toxicity studies	Y	Mice, rats, dogs	
Repeat-dose toxicity studies, species 1	Y	mice	6w
Repeat-dose toxicity studies, species 2	Y	dogs	6m
Genotoxicity	Y		
Reprotoxicity, fertility	Y	Mice	
Reprotoxicity, embryo-fetal development	Y	Mice	
Reprotoxicity, peri-post natal			
Carcinogenicity studies	N		
Immunogenicity studies			
Immunotoxicity studies			
Local tolerance studies	Y	Rabbits	
Additional, special tests	Y	Rescue study in dogs	

Table 7-2 Summary of nonclinical studies performed, category (b) other drugs

Category of nonclinical studies	**Tarceva (erlotinib)** **Autorisation date by EU Commission: 19 September 2005**		
	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology			
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	Mice	
Safety pharmacology studies	Y	Mice, rats, dogs	
Pharmacokinetic studies	Y	Mice, rats, dogs, monkeys	Single and repeat dose
Toxicokinetic studies	Y	Mouse, rat, dog, monkey	
ADME studies	Y	Mice and rats; dogs metabolism only	
Single-dose toxicity studies	Y	Mouse, rat, dog	
Repeat-dose toxicity studies, species 1	Y	mouse	6m
Repeat-dose toxicity studies, species 2	Y	Rat	6m
Repeat-dose toxicity studies, species 3	Y	Dog	6m, 12m
Repeat-dose toxicity studies, species 4	Y	monkey	2w
Genotoxicity	Y	Mice	
Reprotoxicity, fertility	Y	Rat	
Reprotoxicity, embryo-fetal development	Y	Rat, rabbit	
Reprotoxicity, peri-post natal	Y	Rat	
Carcinogenicity studies	N		
Immunogenicity studies	N		
Immunotoxicity studies	N		
Local tolerance studies	Y	Rabbits, guinea pigs	
Additional, special tests	Y	Phototox rat	

Category of nonclinical studies	**Tasigna (nilotinib)** **Autorisation date by EU Commission: 19 November 2007**		
Chronic myeloid leukemia	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	Y	In vitro	
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	N		
Safety pharmacology studies	Y	In vitro, dog	
Pharmacokinetic studies	Y	Mice, rats, rabbits, dogs, monkeys	
Toxicokinetic studies	Y	Mice, rats, dogs, monkeys	
ADME studies	Y	Rats	
Single-dose toxicity studies	Y	Rats	
Repeat-dose toxicity studies, species 1	Y	Mice, Rats	26w
Repeat-dose toxicity studies, species 2	Y	Dogs, monkeys	39w
Genotoxicity	Y	Mice	
Reprotoxicity, fertility	N*	Rats	
Reprotoxicity, embryo-fetal development	Y	Rats, rabbits	
Reprotoxicity, peri-post natal			
Carcinogenicity studies	N		
Immunogenicity studies			
Immunotoxicity studies			
Local tolerance studies	Y	Rabbits	
Additional, special tests	Y	Metabolites, phototox, impurities in rats	

*as part of the general repeat dose toxicity

Category of nonclinical studies	**Thalidomide Pharmion (thalidomide)** **Autorisation date by EU Commission: 16 April 2008**		
Multiple myeloma	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	Y	Mice, rats, cats	
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	N	Literature: sedative effects	
Safety pharmacology studies	Y	In vitro, dogs	
Pharmacokinetic studies	Y	Mice, rats, rabbit (semen, milk)	
Toxicokinetic studies	Y	Mouse, rat, dog	
ADME studies	Y	Rats, rabbits, dogs, mice, guinea pigs	
Single-dose toxicity studies	N	Literature: mice, rats, guinea pigs, dogs, monkeys	
Repeat-dose toxicity studies, species 1	Y	mice	13w
Repeat-dose toxicity studies, species 2	Y	Rats	13w
Repeat-dose toxicity studies, species 3	Y	Dogs	53w
Genotoxicity	Y	Mice	
Reprotoxicity, fertility	Y	Rabbits (fertility)	
Reprotoxicity, embryo-fetal development	N	Literature	
Reprotoxicity, peri-post natal	Y	Rabbits	
Carcinogenicity studies	Y	Mice, rats	
Immunogenicity studies			
Immunotoxicity studies	N		
Local tolerance studies	N		
Additional, special tests			

Initial indication of thalidomide was sleeping pill, pain killer

Category of nonclinical studies	**Velcade (bortezomib)** **Autorisation date by EU Commission: 26 April 2004**		
Multiple myeloma	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	N		
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	Rats, mice	
Safety pharmacology studies	Y	Cynomolgus	
Pharmacokinetic studies	Y	Rats, cynomolgus	
Toxicokinetic studies	Y	Rats, rabbits, cynomolgus	
ADME studies	Y	DME in rats, cynomolgus	
Single-dose toxicity studies	Y	Mice, rats, dogs, monkeys	
Repeat-dose toxicity studies, species 1	Y	Mice, rats	26w
Repeat-dose toxicity studies, species 2	Y	Rabbits, dogs, monkeys	38w
Genotoxicity	Y	Mice	
Reprotoxicity, fertility	N		
Reprotoxicity, embryo-fetal development	N		
Reprotoxicity, peri-post natal	N		
Carcinogenicity studies	N		
Immunogenicity studies	N		
Immunotoxicity studies	Y	Mice	
Local tolerance studies	N		
Additional, special tests			

Category of nonclinical studies	**Afinitor (everolimus)** **Autorisation date by EU Commission: 3 August 2009**		
Renal cell cancer	Done	Species	Duration
Primary pharmacology	Y	Mice, rats	
Secondary pharmacology	Y	Mice	
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	Mice	
Toxicokinetic studies	Y		
Pharmacokinetic studies	Y		
ADME studies	Y		
Single-dose toxicity studies	Y	Mice, rats	
Repeat-dose toxicity studies, species 1	Y	Mice	13w
Repeat-dose toxicity studies, species 2	Y	Rats	26w
Repeat-dose toxicity studies, species 3	Y	Mini pig	4w
Repeat-dose toxicity studies, species 4	Y	monkeys	52w
Genotoxicity	Y	Mice	
Reprotoxicity, fertility	Y	Rats, rabbits	
Reprotoxicity, embryo-fetal development			
Reprotoxicity, peri-post natal	Y	rats	
Carcinogenicity studies	Y	mice	
Immunogenicity studies			
Immunotoxicity studies			
Local tolerance studies			
Additional, special tests	Y	Juvenile in monkeys	

Table 7-3 Summary of nonclinical studies performed, category (c) biologics

Category of nonclinical studies	**Vectibix (panitumumab)** **Autorisation date by EU Commission: 3 December 2007**		
	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	Y	Mice	
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	Mice	
Safety pharmacology studies	Y	Cynomolgous	
Pharmacokinetic studies	Y	Cynomolgous	
Toxicokinetic studies	Y	Cynomolgous	
ADME studies	Y	Cynomolgous (DE)	
Single-dose toxicity studies	N		
Repeat-dose toxicity studies, species 1	Y	Cynomolgous	6m
Genotoxicity	N		
Reprotoxicity, fertility	Y	Cynomolgous	
Reprotoxicity, embryo-fetal development	Y	Cynomolgous	
Reprotoxicity, peri-post natal			
Carcinogenicity studies	N		
Immunogenicity studies	N	Cynomolgous, w/in repeat dose tox	
Immunotoxicity studies			
Local tolerance studies	N	Cynomolgous, w/in repeat dose tox	
Additional, special tests			

Category of nonclinical studies	**Erbitux (cetuximab)** **Autorisation date by EU Commission: 29 June 2004**		
	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	N		
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	Mice	
Safety pharmacology studies	Y	Cynomolgous, single dose plus as part of repeat dose tox	
Pharmacokinetic studies	Y	Cynomolgous, rats	
Toxicokinetic studies	Y	Cynomolgous, rats	
ADME studies	Y	Mice (not in relevant species)	
Single-dose toxicity studies	Y	Mice, rats (non-relevant species)	
Repeat-dose toxicity studies, species 1	Y	Rats	
Repeat-dose toxicity studies, species 2	Y	Cynomolgous	39w
Genotoxicity	Y	Rats	
Reprotoxicity, fertility	N	Cynomolgous, rats: fertility as part of repeat dose tox	
Reprotoxicity, embryo-fetal development	N		
Reprotoxicity, peri-post natal	N		
Carcinogenicity studies	N		
Immunogenicity studies	Y	Cynomolgous	
Immunotoxicity studies	N		
Local tolerance studies			
Additional, special tests	N		

Category of nonclinical studies	**Avastin (bevazizumab)** **Autorisation date by EU Commission: 12 January 2005**		
Metastatic colon or rectal cancer in combination w/5-Fluorouracil/Folinic acid	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	Y	Cynomolgous, rabbits	Up to 26w
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	In vitro	
Safety pharmacology studies	N	Cynomolgous, as part of repeat dose tox	
Pharmacokinetic studies	Y	Mouse, rat, rabbit, Cynomolgous	
Toxicokinetic studies	Y	Rabbit, Cynomolgous	
ADME studies	Y	D, clearance in Cynomolgous	
Single-dose toxicity studies	N		
Repeat-dose toxicity studies, species 1	Y	Rabbit	26w
Repeat-dose toxicity studies, species 2	Y	Cynomolgous	26w
Genotoxicity	N		
Reprotoxicity, fertility	N	Cynomolgous, rabbit as part of repeat dose tox	
Reprotoxicity, embryo-fetal development	Y	Rabbit	
Reprotoxicity, peri-post natal	N		
Carcinogenicity studies	N		
Immunogenicity studies	N	Cynomolgous, as part of repeat dose tox	
Immunotoxicity studies	Y	In vitro “hemolytic potential”	
Local tolerance studies	N		
Additional, special tests	Y	Cynomolgou	

		s, tissue specifity and effect on wound healing	

Category of nonclinical studies	**Herceptin (trastuzumab)** **Autorisation date by EU Commission: 28 August 2000**		
Her-2 positive breast cancer	Done	Species	Duration
Primary pharmacology	Y	Mice	
Secondary pharmacology	Y	In vitro	
Pharmacodynamics, drug interactions (usually anti-tumor activity of combinations)	Y	Mice	
Safety pharmacology studies	Y	In vitro, rhesus	
Pharmacokinetic studies	Y	Mice, rhesus, Cynomolgous	
Toxicokinetic studies	Y	Rhesus, c Cynomolgous	
ADME studies	Y	D, M	
Single-dose toxicity studies	Y	Mice, rhesus	
Repeat-dose toxicity studies, species 1	Y	rhesus	4w
Repeat-dose toxicity studies, species 2	Y	Cynomolgous	12w, 26w
Genotoxicity	Y	Mice	
Reprotoxicity, fertility	Y	Cynomolgous, fertility by hormonal status	
Reprotoxicity, embryo-fetal development	Y	Cynomolgous	
Reprotoxicity, peri-post natal	Y	Cynomolgous	
Carcinogenicity studies	N		
Immunogenicity studies	Y	monkeys, anti-drug antibodies	
Immunotoxicity studies	N		
Local tolerance studies	Y	Rabbit	
Additional, special tests			

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

(Dr. Thomas Hengelage)