Regulatory background

in the development of medicinal products

for human use

produced by transgenic animals

– current situation and perspective

in the EU and USA

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TABLE OF CONTENTS

List of Abbreviation

AAALAC	Assessment and Accreditation of Laboratory Animal Care
AMG	German drug law
APHIS	Animal and Plant Health Inspection Service
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte; Federal Institute of Drug and Devices
BfR	Bundesinstitut für Risikobewertung; German Institute of Environmental Risk Assessment
BIV	Bovine Immunodeficiency Virus
BSE	Bovine Spongioform Encephalopathy
BVDV	Bovine Viral Diarrhea Virus
BWP	Biotechnology Working Party
CA	Competent authorities
CBER	Center for Biologics Evaluation and Research
cf	Confer
CFR	Code of Federal Regulation
CFSAN	Center for Food Safety and Applied Nutrition
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Control
CPMP	Committee for Proprietary Medicinal Products (after review: CHMP)
CVM	Center for Veterinary Medicine
CVMP	Committee for Veterinary Medicine Products
D	Germany
EA	Environmental Assessment
EC	European Commission
EEC	European Economic Community
EIS	Environmental Impact Statement
EMEA	European Medicinal Product Evaluation Agency
ERV	Endogenous Retrovirus
EU	European Union
FD&C	Food Drug and Cosmetic Act
FDA	U.S. Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDCA	Food & Drug Control Administration

FISIS	Food Safety and Inspection Service
GAP	Good Agriculture Practice
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMO	Genetic modified organism
GMP	Good Manufacturing Practice
HEPA	High Efficiency Particulate Air Filter
ICH	International Committee of Harmonization
IND	Investigational New Drug Application
NADA	new animal drug application
NEPA	National Environmental Policy Act
NIH	National Institutes of Health
NtA	Notice to Applicants
PCR	Polymerase Chain Reaction
PEI	Paul Ehrlich Institut; Federal Institute for Sera and Vaccines
PERV	Porcine Endogenous Retroviruses
rDNA	Recombinant Deoxyribonucleic Acid
SAF	Source Animal Facilities
SOP	Standard Operation Procedure
SPF	Specific Pathogen Free
TMP	Transgene Medicinal Products
TSE	Transmission of agents causing Spongiform Encephalopathy
U.S.C.	United States Code of Federal Regulation
US	United States of America
USDA	United States Department of Agriculture

I. Introduction

For thousands of years, mankind has attempted to improve animal genetics by selective breeding. Animal biotechnology has therefore a long history, beginning as far back as 8,000 years ago with the domestication and systematic selection of animals. Rapid changes in animal production had been made in previous decades through procedures such as artificial selection, vaccination to enhance health, and artificial insemination to enhance reproduction. Targeted mating strategies are based on the presence or absence of specific traits that can be identified and transmitted to offspring. Improvements have been limited to naturally occurring events or mutations. However, modern, genetically based biotechnology only began in the 1960s, following the discovery of the genetic code. Starting in the early 1970's, the advent of recombinant DNA technology has introduced a variety of new techniques intended to accelerate and refine the process of genetic manipulation (cf. 6.6, 6.3 and 6.8).

Research on genetic engineering has led to the development of a substantial variety of food and agricultural products (e.g. soy, maize) as well as pharmaceutical and human health related products derived from several types of animal or human depending cell cultures (e.g. monoclonal antibodies). The new growing field of biotechnology started with the experiments in the simplest organism: cells, yeast and bacteria. Initial work involved a splicing technique to insert foreign genetic materials into mammalian cells maintained in culture. This in vitro work rapidly progressed into laboratory rodents, providing a more targeted and proactive approach for the establishment of new animal models for biomedical research. The results have been very successful and provide a unique and precise mechanism for the study of a variety of specific conditions or diseases with a genetic basis or influence. After establishing the methods for several cell cultures and the first experiences with cell-culture based pharmaceuticals (e.g. monoclonal antibodies or human insulin, human growth factors, human erythropoetin, etc; cf. 6.101) the new technology was focused on whole animals. The advantages of greater amounts of active substance and the more similar nature to human target protein, especially regarding posttranslational alterations, promises a good future for this new technology in the field of biotechnology production.

The technology and science of producing genetically engineered animals has advanced very rapidly in the past few years. Production of genetic modified animals for research purposes and commercial applications is ongoing for approximately 20 years and is increasing in frequency and scale. Much of the early work on mammalian biotechnology as mentioned above is based on studies with common laboratory animals like mice. Genetically engineered mice have become models of choice in many biomedical applications for the investigations of

diseases and to show the mechanism of action of pharmaceutical medicinal products (e.g. in toxicological investigations in the field of carcinogenicity studies transgene animals are currently used as alternative methods (transgenic mice models: p53+/-, Tg.AC/TgHras2, XPA, ICH guideline S1B, cf. 6.97). Even animals can be produced that are nearly identical copies of animals chosen for useful traits, such as milk or meat production and high fertility. A number of methods presently employed can modify the germline of various animal species for these purposes (cf. 6.102). Genetic engineering has also the potential to produce domestic animals that can be used for biomedical purposes. Such uses can be divided into three major categories: living cells, tissues, and organs for xenotransplantation, biopharmaceuticals for animal or human use, and raw materials for processing into other useful end products.

Transgenics is the science of intentionally introducing a foreign gene or genetic construct (series of genes and associated regulatory elements) into the genome of a target animal (for more details see 2.2.1.1). The molecular biological methods used for the creation of transgenic animals include (cf. 102):

Introduction of new genes by transfection, retrovirus vectors or transposons, removal or modification of genes by direct germline manipulation, and propagation by nuclear transfer of nearly identical copies of an animal (one method the microinjection is shown in Figure 1.1).

The development of transgenic applications in livestock is a logical next step for this technology. Insertion of modified human gene constructs into livestock is being utilized to create "designer production animals" capable of producing useful proteins, tissues, and organs for pharmaceutical and biomedical use. Additionally, the manipulation of indigenous gene sequences has the potential to convey enhanced disease resistance and/or improve production in target animals. The primary objective of using transgenic technology in animal agriculture (cf. 6.77, 6.29 and 6.84) is to improve the quality of livestock by altering the animal's biochemistry, hormonal balance, or harvested protein products. Scientists hope to produce animals that are larger and leaner, grow faster and are more efficient at using feed, more productive, or more resistant to disease. It is now possible to create animals with useful novel properties for dairy, meat, or fiber production, for environmental control of waste production, and for production of useful products for biomedical purposes or other human consumption (e.g. Laboratory use: cf. 6.85). Studies on laboratory animals such as the mouse are conducted but are not the focus of this report. The focus of this thesis is on concerns related to animal products used for the production of medicinal products for human use like transgenic produced mAB (e.g. see Figure 1.1).

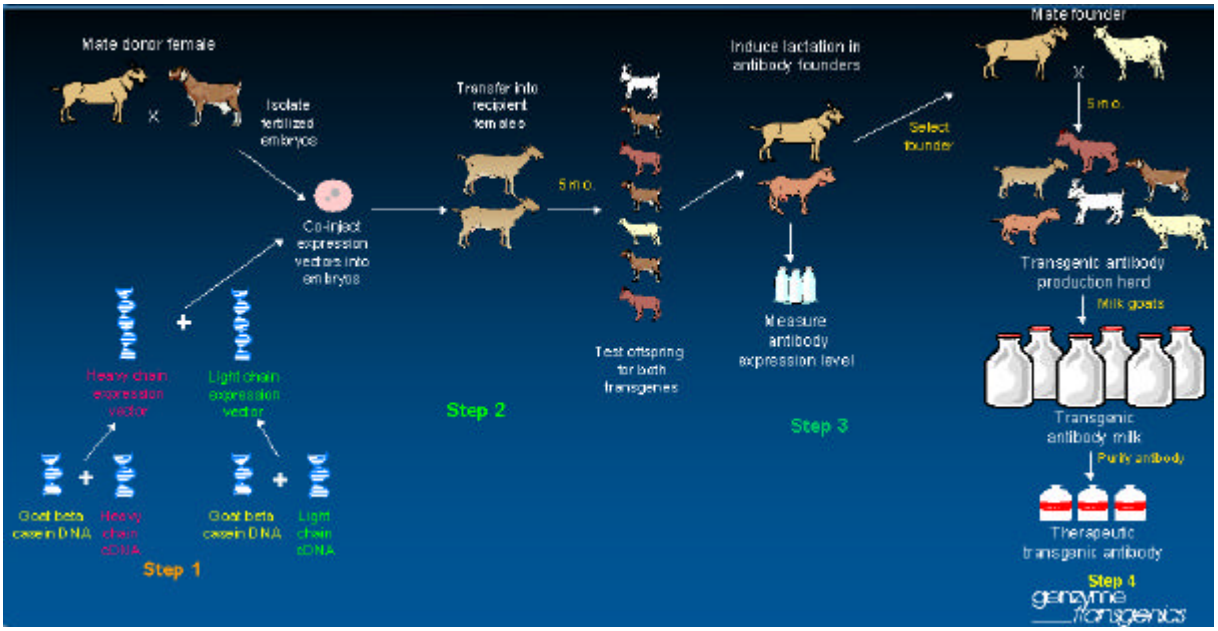

Fig 1.1: Example for the development of a transgenic animal and the production of transgenic medicinal products (TMP) (cf. 6.78: Genzyme transgenics 2001).
Step 1: Production of the expression constructs each containing the goat beta casein promoter and insulator sequences. One construct contains the antibody heavy chain coding region and the other contains the light chain coding region.
Step 2: Begins with mating of a superovulated donor female with a fertile male and the subsequent isolation of fertilized eggs from the female. The heavy and light chain expression constructs are mixed and co-injected into the pronuclei of the fertilized goat eggs. The microinjected eggs are then transferred to recipient females and 5 months later offspring are born. The pregnancy rate after embryo transfer is approximately 50%. On average 1.5 offspring result from each pregnancy. Once born, blood and ear tissue are collected from each animal and analyzed by PCR for the presence of the transgenes encoding heavy and light chains of the target antibody. Approximately 5-10% of the offspring are transgenic, although not all may carry both antibody transgenes. Animals confirmed by Southern blotting as transgenic are termed “founders”.
Step 3: Milk is obtained from female founders by induction of lactation either hormonally at 2-6 months of age or by massage during the later stages of pregnancy. Concentration of the antibody in the milk can thus be determined prior to natural lactation of the transgenic animal. Some transgenic males can also be hormonally induced allowing selection of the best founder for the production herd. Natural breeding is used to expand the herd of transgenic females whose milk contains the recombinant antibody.
Step 4: The antibody is purified from the milk, appropriately formulated and then filled and finished.

In some instances where very large amounts of material are required for therapy the use of transgenic animals may be one of the few viable production strategies. Transgenic animals may produce higher quantities of material in more concentrated form than existing culture methods, and therefore have considerable advantages in the cost of producing the starting material and in its downstream processing, improved risk management for capital investment, predictability for up-scaling the process and the technological enablement for the production.

An example for possible favorable economics was given by Genzyme Transgenics Corporation in an in-house presentation (Table 1.1, cf. 6.78) and in several other available publications the economical advantage was claimed (cf. 6.2, 6.3 and 6.112).

Table 1.1: Favorable economics of transgenic mAB production compared to cell culture production (cf. 6.78: Genzyme Transgenic Corporation 2001).

	CHO (1g/l)	**Transgenic (>5g/l)**
Capital Investment for production		
100 kg	$ 20M	$ 5M
500 kg	$ 75M	$ 10M
Cost of goods (partially purified)		
100 kg	$ 500	$100
500 kg	$ 200	$ 40

As mentioned above with the availability of the transgenic technology to produce medicinal products many collaborations and projects for the development of transgenic products were started in the mid of the 90ies. (cf. 6.609, 6.120 and 6.46). Some clinical programs in humans were initiated (e.g. Pharming, Netherland, started phase-III clinical trail for recombinat protein (rhC1INH), cf. 6.107) and one product from GTC Biotherapeutics (Atryn®) is currently under review for market authorization in Europe. Nevertheless, until now no product has been approved (companies: Genzyme Transgenic Corporation Framingham, Massachusetts: product: antithrombin III, cf. 6.79; PPL Therapeutics, Scotland, product: alpha1-proteinase, cf. 6.110; Cooperation Bayer with PPL, cf.6.33; Pharming Holland, product: lactoferrin; Agrobiogen, Germany/Austria). This indicates that the development, potential concerns and requirements in the regulatory field for getting marketing authorization is more complex than expected by the companies developing transgenically derived medicinal products. The focus of this thesis is on the regulatory aspects and scientifically based considerations in the development of transgenic produced medicinal products as compared to conventionally manufactured medicinal products.

There are more scientifically based aspects to be considered in the latter products. The additional concerns are the field of Good Agricultural Practice (GAP) (including housing of animal, animal protection, etc) and potential environmental risk during the biotechnological production (excretion of metabolites or gut bacterial which had contact with the genetic material; escape or release of genetic modified animals by sabotage or accidents) and in the

latter clinical development (not used material and excretions). Additional risk to public health should be discussed regarding the potential infection of the population by treated patients (including volunteers in clinical Phase I studies) with unknown contaminations.

Therefore, the regulations and agency guidance documents for animal housing, production of biotechnology products and the special guidance documents for the production of medicinal products for human use by transgenic animals were the basic discussion platform in this thesis to summarize the regulatory situation. There are two guidance documents presented by the FDA and the EMEA specific for transgenic animal produced drugs, but these guidelines are outdated, as the last versions were published in 1995 (cf. 6.63 and 6.73). In the last 9 years many things changed in the field of biotechnology. New safety investigations, e.g. TSE/BSE and other new human pathogen viruses detected by better analytical methods, additional new experiences in the productivity of transgenic animals and new requirements in the field of animal protection and environmental risk assessment has to be considered. In the fact of the new technology and methods described before a revision of the current guidance documents would be necessary and the EMEA had the guideline revision on the last two yearly working plans. But no revised version of the guideline has been published yet.

II. Scientifically and technologically based considerations and common regulatory framework

2.1 General overview

Transgenic organisms contain a foreign gene, which has been experimentally inserted into the normal genetic component, and currently include a number of animal species.

Many different species have been considered or developed for the production of biological medicinal products and by use of appropriate targeting sequences the transgene has been expressed in body fluids such as blood or in milk as well as in other source tissues (cf. 6.3 and 6.8).

The production facilities used will probably employ agricultural animals and techniques. It is important to bear in mind that the requirements for manufacture of pharmaceutical products will be more stringent than those for agricultural production, and the production process should be designed accordingly. The scope of this document emphasizes products derived from fluids of transgenic animals, particularly milk, as there is at present considerable interest in such sources, but many of the considerations will also apply to other source tissues. However in some respects the products resemble classical biologicals in that they derive from a whole animal rather than from definable culture systems. The considerations, which apply, are therefore a blend of those relevant to recombinant DNA (rDNA) derived materials and materials from less defined sources. In the following body text the different regulatory aspects with the relevant guidelines would be discussed. The veterinary and environmental issues relevant to animal welfare and the consequences of release for the environment and the public health have to been considered in special regulatory documents and the animals used in production must comply with existing regulations concerning the development of transgenic animals, especially for the mandatory manufacturing authorization for the facilities (Directives 90/219/EEC and Directive 98/81/EC on contained use; 90/220/EEC amended by the 2001/18/EEC on deliberate release of genetically modified organisms, cf. 6.39, 6.40, 6.41 and 6.33).

2.1.1 Competent authorities (CA)

2.1.1.1 US agencies relevant regarding the TMP production

In the development of TMP in the US many agencies were involved in the regulatory framework: The Animal and Plant Health Inspection Service (APHIS) and the Food Safety and Inspection Service (FSIS) of the USDA (cf. 6.4 and 6.118). The Office of Laboratory

Animal Welfare of the National Institutes of Health (NIH) has responsibility for the general administration and coordination of the Public Health Service Policy. From the FDA the Center for Veterinary Medicine (CVM), the Center for Food Safety and Applied Nutrition (CFSAN; jurisdiction over milk, eggs and other edible products) and in the latter phase the Center for drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) have to been contacted in the development of TMP (cf. 6.25; see Figure 2.1.1 - 1).

2.1.1.2 EU agencies relevant in TMP production

In the EU the EMEA with its Committees (CVMP, CPMP (now CHMP) with its biotechnology working group BWP) and through the implementation of the Commission Directive 86/609/EEC (recently amended by the Council Directive 2003/65/EC, cf. 6.28 and 6.37) the national competent authorities should be involved by the use of transgenic animals (Art. 6, 12, 19). In the Directive 86/609/EEC every Member State should on national basis announce which was competent authority for animal research and commercial activities. In Germany for example the competent authority was based on the local authorities (§§ 15 and 16 Animal welfare law). The German registration procedures for the animal activities including transgenic animals were described in the animal welfare law (§§ 10a, 11b; cf. 6.80). The timeframe for the registration of animal testing including the use of animals to produce medicinal products is laid down in the animal welfare law and the sponsor has to submit a complete dossier. The testing could be started after 3-month review time by the competent authority (§§ 8 and 10a German animal welfare law). See also the details in figure 2.1.1 – 1.

US: USDA; CVM, APHIS; FISIS, FDA (CBER)

US: CFR; Guidance for industry; Animal welfare act (CFR); NEPA and FDCA; ICH guidelines

EU: EU Commission; EMEA (CPMP, CVMP, BWP); national authorities

EU: CPMP/CVMP guidance documents, EU Guidelines, Directives or Regulations; ICH guidelines

D: BfR; national competent authorities (BfArM/PEI); local authorities (e.g. Regierungspräsidium)

D: Law of animal welfare; EU guidelines, Directives and Regulations; German drug law (AMG)

Figure 2.1.1 - 1: Scheme showing the process of TMP production and the relevant guidelines to be considered and agencies to be contacted during the development.

2.2 Transgenic animal creation

2.2.1 General considerations

In the development of TMP the creation of the stable transgenic animals is the start point. During this development phase the source of the animals, animal welfare and environmental risk assessment will be the focus. For the species used might be subject of other laws and regulations than for "normal" medicinal products. The rules of Good Agriculture Practice (GAP) should be considered to support a safe and appropriate product (FAO (Food and Agriculture Organization of the United Nations) cf. 6.66, 6.117, 6.113 and 6.62). In the later phase, the purification of the bulk material, the guidance documents for biotechnology produced medicinal products should be considered especially regarding the GMP production process (cf. 6.65).

2.2.1.1 Definition of transgenic animal

The term transgenic animal is best defined in the FDA Points to consider guidance document (Points to Consider "In the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals", FDA, CBER; 1995, cf. 6.73):

"A transgenic animal is defined as an animal which is altered by the introduction of recombinant DNA through human intervention. This includes two classes of animals: those with heritable germline DNA alterations, and those with somatic non-heritable alterations. Examples of the first class include animals with germline DNA altered through methods requiring ex vivo manipulation of gametes, early embryonic stages, or embryonic stem cell lines. Examples of the second class include animals with somatic cell DNA alterations achieved through gene therapy approaches such as direct plasmid DNA injection or virally-mediated gene transfer. Transgene refers to a segment of recombinant DNA which is either: 1) introduced into somatic cells, or 2) integrated stably into the germline of its animal host strain, and is transmissible to subsequent generations".

In the EU the term "transgenic animal" was not specific defined, but described in guidance or legislation documents (Directive 2001/18/EC, cf. 6.34 and 6.63).

2.2.1.2 General safety concerns

Due to potential infectious disease risks associated with the use of TMP, appropriate source animal qualifications should be developed. These qualifications should include herd management and programs for prevention and screening for infectious agents. Although testing of the final TMP for infectious agents is crucial, appropriate control of animal sources

and husbandry provides important additional assurance for the safety of such products by controlling infections by both known and potentially even unknown agents. Therefore, the specific information of the used species for TMP production supplied by the sponsor regarding animal husbandry including housing, feeding, veterinary care, drug and biologic treatment of source animals, will be crucial in the evaluation of the potential for safe use of TMP from transgenic animals.

2.2.1.3 Regulatory relevant agencies and legislation documents in the US and EU

In the US the source animal facilities (SAF), the production process, and the records were subjects of agencies inspections especially regarding GMP production (cf. 6.16, 6.23, 6.14 and 6.24). Furthermore it should be recommended that the SAF should be accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). Additional the USDA regarding the animal welfare act and especially the APHIS (cf. 6.21) should be taken into considerations. The NEPA as part of the US code 40 CFR 1502 (EISs and EPA filing according 1506.9, cf. 6.18) described precisely the requirements provided by the applicant regarding environmental risks.

In the EU 1986 a first guidance document the Directive 86/609/EEC “on the protection of animals used for experimental and other scientific purposes” was generated as the implementing tool for the Europe Convention ETS 123 (cf. 6.42) and had to be implemented in all Members states. The Directive seeks to improve the controls on the use of laboratory animals, and to set minimum standards for housing and care, and for the training of the personnel handling the animals and supervising the experiments (Annex II which takes up Annex A of the EU Convention 123). Transgenic animal creation was indirectly covered by the Article 3a (EU Convention). In recent years, it has become clear that Directive 86/609/EEC needs to be revised in order to promote improvements in the welfare provisions for laboratory animals and to further promote the development of alternative techniques and to cover new biotechnology production processes like the animal cloning and the creation of transgenic animals for medicinal product production. In 1998 the Council adoption of the EU Convention “For the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes” was implemented as first reaction on the developing environment (cf. 6.61). The outdated Directive 86/609/EEC was not implemented in all Member States in the same manner, therefore the scope of the amendment of the Directive should be a harmonized implementation and understanding of current scientific background. Additional it was discussed to provide amendments in a simplified procedure because the amending of the

Directive was normally only undergo by the long-term way and by the simplified procedure the guidance document could be up-to-date with the latest scientific knowledge and research on the welfare of animals. The Common position No 23/2003 (cf. 6.32) adopted by the Council on 17 March 2003 prepared the amendment of the Directive 86/609/EEC, which was published in the Official journal of the EU on July 22th, 2003 (Directive 2003/65/EC, cf. 6.37) and should be implemented by all Member States on 16.09.2004 (Art 2).

2.2.2 Animal welfare and origin concerns

In this early development phase is the first step to the founder generation of the transgenic animals in the production of the TMP. One important field, which should be considered are the welfare and the source of the potential founder animals.

2.2.2.1 US situation

The procedures for animal husbandry, tissue harvesting, and termination of animals should be approved by an appropriate Institutional Animal Care and Use Committee, in accordance with the Animal Welfare Act in US (cf. 6.119) and the guidelines of GAP were strongly recommended. In the US it is recommended that the Association for Assessment and Accreditation of Laboratory Animal Care accredits the SAF (AAALAC; cf. 6.1).

2.2.2.2 EU situation

As mentioned in the paragraph before in the EU the Annex II of Directive 86/609/EEC amended by Directive 2003/65/EC should be considered for the regulatory framework in this phase of production. The inspection of the animal environment is not covered by the Directive and should be carried out under the national authorities concerning the national guidance documents, which were not harmonized in the EU. In Germany for example local institutions inspects and approve the start activities of animal use for scientific investigations.

Basic regulations are given from the EU, but not all areas in TMP production were covered by the EU regulations and guidance documents, especially the special areas of inspection of the production facilities (cf. 6.28, 6.37 and 6.63). This is the same complex situation as in US where not all kinds are covered by the regulatory framework of one single agency, e.g. the FDA.

2.2.3 Creation of founder animal

2.2.3.1 Creation method

Currently many different methods were in use to create founder animals for TMP production. In section I scheme 1.1 the general method of pronucleous injection, which is the favorable used method was described. The pronucleous injection method of DNA has the highest probability of incorporating the transgene construct in to the germ line and therefore expressing it in the appropriate intended tissue. The main different of the used species to create transgenic animals was the different percentages of full-integrated gene construct into the animals DNA. In several published papers the different proportion of animals carrying the transgene construct in their germ line were discussed (cf. 6.121, 6.5 and 6.108). For the creation of a usable founder many animals must be used. These should be considered as an important issue in the risk benefit assessment and ethic concerns for the TMP production, especially in respect to animal welfare and public acceptance.

2.2.3.2 Transgene incorporation

The methods used to introduce recombinant DNA into animals should be described in detail. For example, all procedures used during generation of animals with germline alterations should be presented including techniques used in: isolation of the ova, in vitro fertilization, microinjection of blastula or of the embryonic stem cell line, embryo development and transfer and other established or novel techniques (see Figure 1.1).

The genealogy of the production animals must be as precise as possible documented. A transgenic herd will derive from a single genetic founder animal, and animals from different transgenic lines should not be mixed. Estimates of the copy number should be made and evidence as to the accuracy of the incorporated gene sequence should be presented. The level of expression of the incorporated gene should be assessed and the tissue distribution of expression should wherever possible be shown to be consistent with the chosen strategy of expression. It is believed that while multiple copies of the transgene are usually incorporated, there is usually only a single site of integration. Thus, even where multiple copies are introduced it will be possible to identify the expressed sequence or sequences with confidence at the level of the genomic DNA. It is of doubtful value to determine multiple sequences of the insert but evidence that the correct sequence is present should be obtained. Some sequence data for example of cDNA clones will be valuable as will restriction endonuclease maps, which will serve to demonstrate that the site of integration has not changed in offspring of the founder animal where these are used. It should be clearly stated whether the animals used for

production are haploid or diploid for the transgene. The animals used in production should be characterized to ensure an acceptable level of consistency.

2.2.3.3 Transgene expression vector

To avoid any safety concerns considering the origin target gene system and about the stability of the construct and possible pathologic gene products of the treated animal on target population the clearly investigation and isolation of the target gene construct for the transgene transfer should be detailed described (guideline ICH Q5 B; CPMP/ICH/139/95, cf. 6.92). This information were covered by GLP and GMP guidance documents and in the specific CPMP (now CHMP) guideline 3AB7a (paragraph 4.2).

2.2.3.4 Virological status

The virological status of host animals should be shown to be acceptable; for example calves born to mothers infected with BVDV are likely to be persistently infected, and vertical transmission of BSE has not been eliminated as a possibility. Similarly bovine immunodeficiency virus (BIV) may be transmissible through semen. These are only some examples and detailed information will be discussed later (cf. 2.5.1).

2.2.3.5 Stability of gene transfer

Another important issue is the stability of the transferred gene construct in the host animals. After successful gene transfer and isolating the founder animal the production herd for the TMP have to be created by normal breeding techniques. During the breeding the genetic status of the next generation has to be the same as the founder animal. Greater consistency of production will be achievable if a uniform production herd can be bred in a reproducible manner. The strategy used to generate a herd of animals of similar productivity should be clearly delineated. Evidence should be presented that the animals are similar, in the yield of product and genetically in terms of numbers of copies of the gene incorporated and the site of integration in the genome. The requirements in this paragraphs are described more precisely in the US Points to consider “In the manufacture and testing of therapeutic products for human use derived from transgenic animals” than in to the EU CPMP guideline 3AB7a (cf. 6.63).

2.3 Production of TMP in animals (upstream process)

In this part considerations regarding the production of the TMP are described including concerns regarding the production and harvesting of the crude bulk material. In the production of traditional Biotech products based on cell culture conditions this step is named as the upstream process.

2.3.1 Brief introduction

The use of transgenic animals for the production of medicinal products is associated with difficult obstacles, including management of the risks of transmitting known and unknown pathogens. Importantly, there is the potential risk of introducing new infectious diseases into the general population through adaptation in a patient. The potential source of the infectious pathogens could be the animal itself or the environment, including food, water, housing and containment conditions, waste and transportation. However the general conditions for the husbandry and practical housing conditions might be contribute under virological and microbiological safety. The conditions under which the animals are bred and maintained should be described and precautions taken to ensure that the site is free of disease likely to affect the production animal species prior to use. The rules of Good Agriculture Practice (GAP) were very strongly recommended to be in-line with the current standards in animal housing and the regulatory guidelines (cf. 6.57).

In the relevant guidelines for transgenic animals in the EU and US the recommendations were in the similar way described therefore in the following paragraphs no separate parts were created for both areas (cf. 6.63, 6.58, 6.73 and 6.70).

2.3.2 Animal safety and housing conditions

2.3.2.1 Housing of the founder animal

As mentioned above one of the important fields to avoid infectious pathogens in the final TMP are the animal itself and the environment, including the production process. The first step is the selection of the species. The source animal species may be those typically reared for consumption or conventional laboratory animals (e.g. goats and rabbits). The origin and derivation of source animals should be fully described considering possible infectious agents and diseases of the particular animal species. Founder and source animals should be healthy and should, at minimum, be Specific Pathogen Free (SPF) and raised in SPF conditions, including health monitoring and barrier systems. In principle, the level of microbial control in animals can be set on three different levels (according the FDA Guidance for Industries:

"Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans", April 2003, cf. 6.70):

1) Germ-free gnotobiotic animals. The establishments of gnotobiotic animals requires delivery by hysterectomy and maintenance in isolators under positive pressure for their entire life span. These animals are devoid of all infectious agents except for those that are transmitted in the germline, e.g. endogenous retrovirus (ERV) or via intrauterine or transplacental pathways, e.g. herpes virus.
2) Specific pathogen free (SPF) animals. The establishment of SFP animals can be achieved by hysterectomy of the dams and maintaining SPF breeding units of the descendent animals under barrier conditions to produce source animals.
3) Animals free of designated pathogens/qualified pathogen free animals. Source animals are from closed herds or colonies with documented health screening programmes. All infectious agents known to infect the species have to be considered.

In the use of animals for TMP production the number 3) animals will be appropriate through economic as well as rational issues.

To avoid any environmental impact on the animal health a separate facility should exist for founder and source animals. Animal facilities should be isolated from each other to prevent cross-contamination and should be operated in such a way, including the use of biosecure barriers, as to minimize the animals' exposure to infectious agents (cf. 2.3.2.3, Figure 2.1). All material entering a facility should be sterilized or decontaminated. Feed and bedding of a predefined quality should be obtained from a controlled source or vendor and should be stored under appropriate and controlled conditions. Environmental conditions, such as air flow (HEPA-filters, positive pressure) and water, should be controlled and analyzed. Standard operation procedures (SOP) for cleaning, disinfecting and sterilization of the animal cages and pens after usage, and for disposal of waste including animals, feed, bedding, equipments, reagents, etc. should be established. An adequate number of staff should be available and should include veterinarians, either permanent or available on consultation. Animal caretakers should participate in a document training program and health monitoring of them, including vaccination history, of them should be recorded. SOPs on tasks and responsibilities of animal caretakers should be established. Air treatment, handling and gowning procedures for personnel should prevent the transfer of animal diseases into humans (cf. 6.82).

2.3.2.2 Husbandry

For the animal husbandry conditions, procedures should be developed to identify and prevent incidents that negatively affect the health of the herd or colony, or that could negatively impact on the barrier facility or the SPF status of the herd. These standard operation procedures (SOPs) should present information including detail housing of animals and containment conditions, water, bedding conditions, performance and monitoring of health screening, removal from production and disposal of the animals and their by-products, identifying individual animals and recording their movements to, through and out of the facility, entry, exit and transportation of animals, disposition of dead animals, handling of ill animals, source and handling of feed and the isolation and quarantine of new animals. The areas for the TMP production animals and new or breeding animals should be clearly separated and additional the areas for harvesting and pooling of the crude bulk material should be separated from each other to avoid any contamination (cf. Figure 2.1). When transgenic animals died, a full necropsy should be conducted including histopathological and microbiological evaluation. Samples should be archived for future examination. When feasible, a sentinel animal program (also known as satellite subjects in normal non-clinical studies) that will allow periodic health evaluations should be considered. Such sentinel animals should be infertile, of the same species of origin, and should be maintained with the transgenic production herd.

2.3.2.3 Transportation conditions

Transportation of source animals exposes them to risks not encountered in closed herds and should be avoided. In exceptional cases where transportation is necessary, barriers equivalent to, or better than, those in place at the facility, should be maintained during transit to avoid source animal contamination. Transportation should use dedicated vehicles in which the animals are not exposed to any other animals and the method has to be documented. Quarantine facilities should exist at the destination to allow for clinical evaluation upon arrival prior to acceptance for further processing.

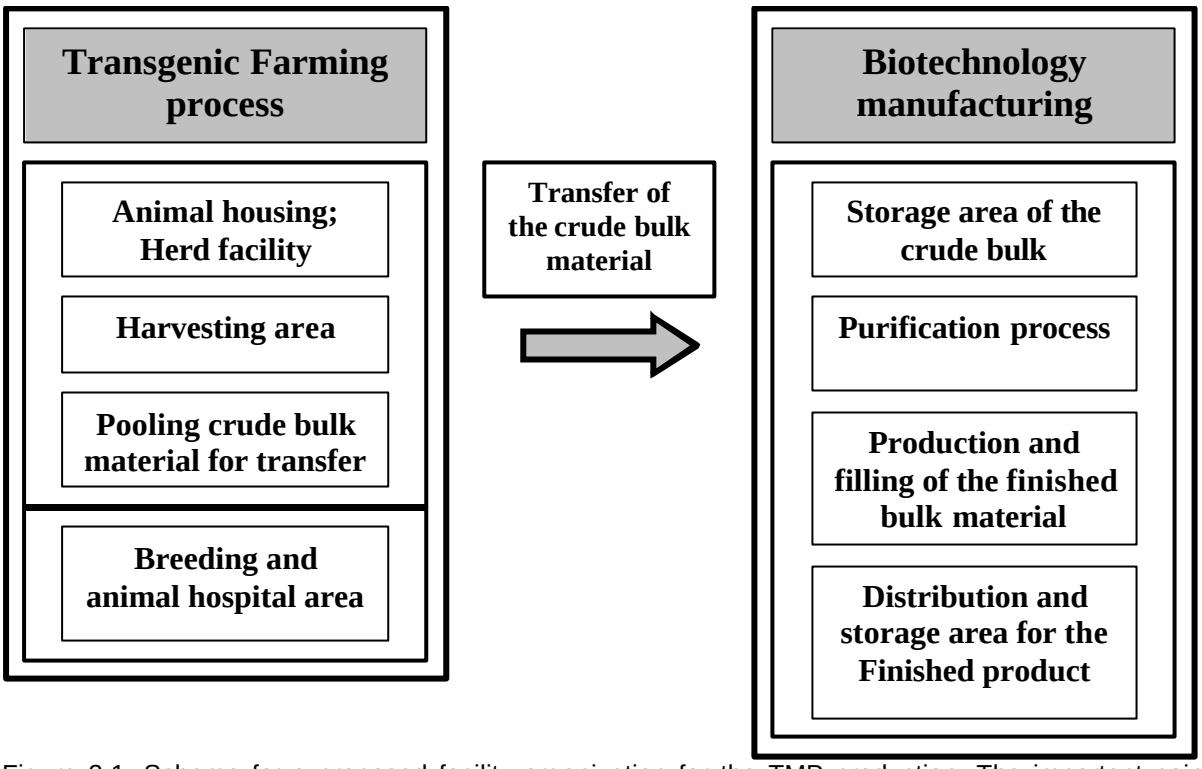

Figure 2.1: Scheme for a proposed facility organization for the TMP production. The important point that the facilities for the purification process of the crude bulk material and the animal production should be separated was clearly shown.

2.3.3 Testing of the crude bulk material after harvesting

The production of the bulk material by the transgenic animals was done by several individual animals compared to consistent producer like the cell cultures in fermenter for other Biotech production. For example the milk containing the crude product is defined as the crude bulk material. It should be confirmed that the expression of the genetic material is stable. During different period of the year especially lactation time, the expression could be vary. This should be important for the batch definition and limitations of the bulk material expression. There is a wide variation in the composition of milk or other expression fluids from different animals and there might be also variations between different days. The source material may therefore be variable, making purification procedures potentially less consistent. Acceptable limits for the level of active substance and the specifications in terms of productivity in the source material should be set. A single batch should be clearly defined by for examples material pooled of different harvests. Additional specifications regarding main impurities like host proteins and fat values should be defined for the crude bulk material. Also limits for the microbiological status of the crude bulk should be set. If milk is the carrier fluid the contamination with bacteria is normal, although such contamination may be minimized by good husbandry and housing conditions (cf. 2.2.2). If infectious pathogens could be detected

by specification tests of the crude bulk material this material is unacceptable. While bacteria could be removed by sterile filtration of the product, mycoplasma may not and efforts should be made to exclude them from the source material.

2.4 Manufacturing of the final TMP (downstream process)

2.4.1 Brief introduction

After the crude bulk material was pooled and harvested it was transferred in the separate facility for the purification (cf. Figure 2.1). The purity of the active substance should be in accordance with criteria accepted for products of rDNA technology (cf. 6.99, 6.92, 6,93, 6.94, 6.95 and 6.68). At that point there were only few differences between recombinant produced biologicals and the TMPs. A transgenic animal is unlikely a individual which means that in the production herd a variability of the expression of the active substance will be obvious. As other biotechnological products the TMP production is not independent from the production process and therefore the exactly description of the process will be a crucial point. The first step of TMP production the harvest of the crude bulk material as described in the paragraph 2.3.3. The purification of that material should be conducted according to the guidelines for rDNA produced material as mentioned above.

2.4.2 Purification process (downstream process)

The manufacturing step of purification of the crude material to receive the final bulk material is the core process for the TMP production. In the production of Biotech products by cell culture the Master cell bank should be detailed described (cf. 6.92). In the production of TMPs the role of the master and the working cell bank (MCB and MCB) should be replaced by the original founder animal and the production herd. As described before (cf. 2.3) the founder animal and the herd for production should be detailed tested and characterized by the sponsor. The consistent preparation of founder animals through breeding technology should be regular tested. The results of the analysis of the production herd (including genetic stability) for the phenotypic and the genotypic markers to confirm identity and purity should be included.

2.4.2.1 Validation plan and process controls of critical steps

A detailed plan of the production process with in process controls and limits (including the critical steps) in the purification and downstream process should be defined. Any reprocessing methods and conditions for batch eligibility should be described, but normally in the TMP

production not be recommended. Complete representative batch record of the process of production of the TMPs should be documented. A description and justification for the methods used for in-process controls, e.g. those involved in the harvesting and purification process (downstream process) should be provided. A description and documentation of the validation studies should be provided. If there were any changes in the downstream process or in scaling-up the revalidation of the purification process and the more uses of animals should be described. These seems to be easier in the TMP production than in normal cell cultures, but firstly the additional animals should be tested as described before for their use. To ensure the success of consistent production the critical parameters used for the harvesting process and the following pooling for crude bulk material batches should be identified and documented and appropriate referenced to the overall manufacturing process flow chart. The description and documentation of the validation of the purification process to demonstrate adequate removal of extraneous substances such as chemicals used for purification, column contaminants (protein A), endotoxin, antibiotics (eventually used by the animal housing), residual host proteins or DNA, and viruses, where appropriate, should be provided.

2.4.2.2 Reference standard and potency assay

Another important point should be the reference standard used for the potency assay to demonstrate the efficacy and for the characterization of the product. Normally the TMP were produced as an "biogeneric" product (definition as "similar biological product" Directive 2003/63/EC cf. 6.26 and 6.104). Therefore the reference standard to show the same efficiacy should be the marketed orginator product. The description of the preparation, characterization, specifications, testing and results of the used reference standard should be provided (cf. 6.69). By employing a detailed "product comparability program", an manufacturer for TMP can develop an understanding of a biologic's structure/function as it has been made over time by various process configurations. This could be used to show the similarity to the innovators product.

2.4.2.3 Specifications and analytical methods

The specifications and analytical methods used for the release testing, shelf life and stability of the TMP should be described. Specifications and tests for the crude bulk material and the final bulk sufficient to assure its identity, purity, strength and/ or potency, as well as batch-to-batch consistency should be set and conducted. The validation of the analytical systems and the produced results should be demonstrate the system suitability. Certificates of analysis and

the analytical results for at least three consecutive batches (cf. 6.93, 6.96 and 6.68) of the TMP should be prepared. The impurities profiles should be provided, including profiles of variants of the protein (e.g. cleaved, aggregated, deamidated, oxidized forms, etc.) as well as non-product related impurities (e.g., process reagents and cell culture components), should be described. Data referring to the stability of the crude bulk material as well as stability data of the final bulk product should be provided (including storage conditions, study protocols and results supporting the biological activity and degradation products such as aggregated, deamidated, oxidized, and cleaved forms). A minimum of 6 months stability data at the time of submission for marketing authorization application (MAA) should be conducted and prepared for submission as described in the ICH guideline Q5C (cf. 6.93).

2.4.3 Characterisation of the finished product

The defined characterization especially for biotechnology products is one of the crucial points in the description of the purity and consistency. The main guideline which should be considered in that point is the tripartite harmonized ICH guideline Q5C (cf. 6.93). Due to the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a biotechnological/biological product is extremely difficult to determine.

2.4.3.1 Methods

Thus, the purity of a biotechnological/biological product should be typically assessed by more than one method. For substances that can not be properly characterized or products for which an exact analysis of the purity cannot be meaningfully determined through routine analytical methods, the applicant should propose and justify alternative testing procedures. For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products. The use of relevant physico-chemical, biochemical and immunochemical analytical methodologies should permit a comprehensive characterization of the TMP (e.g. molecular size, charge) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulphoxidation, aggregation or fragmentation during storage, should be conducted. Methods that may contribute to this include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (HPLC; e.g. reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography), and peptide mapping.

2.4.3.2 Stability testing

Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated and/or stress stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products within the long-term stability program (cf. 2.4.2.3). Acceptable limits should be proposed and justified. The degree of purity, as well as individual and total amounts of degradation products of the transgenic produced product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the active substance and medicinal product used in the pre-clinical and clinical studies.

2.5 Biosafety and virus removal of the TMP

2.5.1 Safety concerns of the founder animal

Source animals may carry known or unknown infectious agents. The acceptability of the source animal as a donor for TMP production depends equally on prevention of infectious and on thorough testing of the source animals.

Programs for screening and detection of known infectious agents should be tailored to the source animal species and the manner in which the TMP will be used clinically. Program testing protocols should be updated periodically to reflect advances in the knowledge of infectious diseases.

The used assays should be capable of detecting a broad range of infectious agents, as well as species-specific agents (e.g. pig, bovine, goat, etc) in the source animal. Appropriate in vivo and in vitro assays should be in place to characterize the potential of identified human pathogens. The putative pathogenicity of xenotropic endogenous retrovirus (ERV) and persistent viral infectious in source animal cells, tissues and organs is of particular importance (cf. Table 2.5.1 - 1). Assays used for the screening and detection of infectious agents should have well defined and documented specificity, sensitivity, reproducibility and validity in the setting in which they are to be used. Appropriate laboratory quality assurance standards must be exercised.

Special consideration needs to be given to screening the animals for the following infectious agents: their own recognised infectious agents and parasites; endogenous retroviruss (e.g. PERV); known infectious agents of humans; infectious agents known to have a high mutation or recombination potential such as influenza virus; antibiotic-resistant bacteria; geographically important infectious agents such as Trypanosoma cruzi (e.g. African Swine

fever); known zoonotic agents transmissiblt humans (e.g. rabies) and other zoonotic agents such as Toxoplasma gondii which are usally not considered zoonotic but which may infect through the therapy and infectious agents of humans relating to receptors/proteins expressed by transgenic animals (e.g. human complement-regulatory protein CD46). However, there is yet no uncontested example of acquisition of any gene, including drug resistance markers, by bacterial flora living in a transgenic animal (cf. 6.51). Of greater concern is the theoretical possibility of the generation of potentially pathogenic viruses by recombination between sequences of a viral vector containing a transgene and related, but nonpathogenic, viruses present in the same animal. Additional consideration also should be given to the commensal populations, the possibility of transmission of latent infectious agents via the intrauterine pathway (e.g. herpesviruses) and usage of sentinel animals to screen for subclinical infectious. Special concerns should be given to founder and source animals to be free of known TSE-diseases and the feeding history since establishment of the source animal herd should be documented and should not raise concerns regarding possible transmission of a TSE agent. In the use of cattle, goat and sheep, the requirements of the CPMP/CVMP Note for guidance on minimizing the risk of transmitting animal spongiform agents via human and veterinary medicinal products (EMEA/410/01-rev2, cf. 6.56) should be applied.

2.5.2 Virus removal of the TMP

A critical aspect in the production of TMP and other biotech products is the biosafety of the product. This includes different potential contamination in the different development stages of the product started with the crude bulk material after harvesting (here special concerns regarding species dependent potential risks should be considered), the purified bulk after the downstream process and the finished product. Unprocessed crude bulk material testing usually involves limited virus testing (a general in vitro virus screen and a specific virus assay), sterility (e.g. contamination with bacteria) and mycoplasma testing (cf. 2.5.1.2 table 2.5.1 - 1). Purified bulk material testing routinely consists of molecular and analytical characterization studies for product purity and potency, as well as sterility testing. Final product testing should include sterility and pyrogenicity testing. In the design of a biosaftey program in TMPs the focus is the evaluation of the ability of the purification process to remove or inactivate any adventitious agents (typically viruses, bacteria, or mycoplasma) that may be present in the crude bulk material (cf. 6.71 and 6.99).

Table 2.5.1 - 1: Specific species dependent pathogens (cf. 6.19, 6.22 and 6.20).

Virus type	
Swine	African swine fever
	Swine vesicular disease virus
	Classical swine fever virus
	Porcine endogenous retroviruses
Sheep	Sheep pox virus
Goat	Goat pox virus
Camel	Camel pox virus
Bovine	Rinderpest
	Lumpy skin disease virus
	Bovine viral diarrhea virus
Bacteria	
Bovine	Mycoplasma mycoides mycoides
	Mycoplasma capricolum
Prion	
Bovine	Bovine spongiform encephalopathy agent

2.5.2.1 Testing program for the purified bulk material

To determine potential contamination for the crude bulk material the testing program for the purified bulk material should be conducted according to the ICH guideline Q5A (cf. 6.99). This program should first focus on the detected viruses and bacterial contamination of the crude bulk material (if there were any infectious contamination, the material should be unacceptable) and the ability of the different removal procedures to increase the level to a safety level for the treatment of patients. The appropriate virus safety evaluation program is in detailed described in the above-mentioned guideline. Here only some key points should be mentioned. Whenever possible, samples from the crude bulk material (if the crude material is toxic appropriate not toxic formulations should be used) should be tested with co-cultivation assays that include a panel of appropriate indicator cells, in order to amplify and detect endogenous retroviruses and other type of viruses which may be capable of initiating infection in humans and other herd animals. The selection of the indicator cells should be determined by the used animal and the later clinical applications (e.g. for cancer diseases the results and

importance of virus testing will be different to other non life threatening diseases). Microscopic observations, reverse transcriptase assays, electron microscopy and PCR (polymerase chain reaction) methods may be appropriate. If cultures demonstrate the presence of viral agents, direct or indirect virus detection methods should be routinely employed. Universal nucleic acid amplification-based detection strategies whenever available would be preferred. Sensibility type of viruses without any clinical symptoms by the animals (e.g. herpesviruses, retroviruses, papillomaviruses) are of particular concern, as well as investigations concerning BSE or other prions or viroid pathogens.

2.5.3 Immunogenicity

The harvested crude bulk material will contain large numbers of host derived proteins other than the desired product, some of which may be present in large amounts which must be removed. For example if milk is the carrier fluid it is known to contain proteases, and the possible effect of these on the active substance should be addressed. The stability program detects potential degradation products from the active substance as well as for the impuriy profile (e.g. the host proteins). If degradation occurs, acceptable limits should be set for the crude bulk material and the impurities. Data on the carbohydrate components of the product should be presented. The non enzymic glycosylation or glycation of proteins in the presence of free carbohydrate such as lactose should be considered. The immunogenic potential of such glycated proteins is a known safety concern of biotechnologically produced proteins. Glycated proteins can cause the activation of end stage macrophages to produce cytokines an immungenic response which could be ended in anaphylactic reactions. Long term exposure to a glycated product is likely to be harmful. This findings increases the concerns associated with the immunogenicity of the proteins because of trace impurities or imperfect post translational modifications, and close attention should be given to the purity, quality and consistency of the product.

In conclusion the post translational glycosylation pattern should be in detail determined and understand by the applicant or manufacturer. The immunogenicity risk should be considered and therefore the amount of host cell proteins with the immunogenic potential should be minimized.

2.6 Environment and public health concerns

In the paragraph before the issues regarding the animal selection used for the TMP production were described. After the finding of the suitable animal and the issues regarding the housing

and the vector system are solved, the next important field to be considered was the risk for the environment and the public health regarding the genetic manipulation of the animals.

2.6.1 EU regulatory framework

The points regarding the risk of the created GMO (genetic modified organism) for the environment and the public health contain potential accidents and the release of animals into the environment, the infectious risk for the personal staff in housing activities, the risk regarding the new stable genetic system for the environment by housing the animals outside.
All these points were covered in relevant EU Directives (EU Directives 90/219/EEC, Directive 98/81/EC, 90/220/EEC repealed by 2001/18/EEC, cf. 6.34, 6.39, 6.40 and 6.41). These guidelines are dealing with the GMOs in closed facilities (e.g. fermentation processes of genetic altered microorganism; Directive 90/219/EEC and Directive 98/81/EC) and with the release of GMOs (e.g. plants released in the outside for food or medicinal product production; Directives 90/220/EEC and 2001/18/EEC).

2.6.2 Regulatory procedures in the EU

Transgenic animals are not clear caught in the above mentioned guidelines, but in the article 2 number 1 and 2 in Directive 2001/18/EEC (cf. 6.34) and number 4 paragraph 2 transgenic animals are covered. In the paragraph before it was mentioned that for transgenic animals used in closed facilities the criteria of Directive 98/81/EC (amended Directive 90/219/EEC) should be considered, because transgenic animals should not be normally released in the outside. In the Directive it was clear mentioned that all facilities for the contained used and production of genetically modified (micro)-organism (including transgenic animals) should be notified by competent authorities. Additional an environmental risk assessment including a risk plan for potential accidents and risk to public health should also be prepared and reviewed by the competent authority which results in a classification of the used GMOs (4 classes) and records should be kept by the user and should be made available for the notification procedure regarding the Art. 7, 9 and 10 depending on the class (Directives 98/81/EC Art. 5 and 14; 90/219/EEC Art. 9 number 2, Art. 14). The normal minimum requirements and measures necessary for each level of containment, which should be achieved through the use of good work practices, training, containment equipment and special installation design and additional for all activities the principles of good microbiological practice and the principles of good occupational safety and hygiene should be applied (Annex IV table 1A and 1C of Directive 98/81/EC). The timetables and the relevant documents for

the submission are described in the Directives (98/81/EC Annex III; 90/219/EEC Art 9 number 2, Art. 11 and attachment VB) and these timelines are to be implemented in national law of all Members States. The timelines for the approval for the use of the facilities for GMO production was fixed by a implicit procedure of maximum 90 days. That indicated that after submission of the relevant documents (Directive 98/81/EC Art. 8, 9 and 10 according Annex V Part A, B and C; Attachment VB Directive 90/219/EEC) the competent authority should respond to the application after a maximum of 90 days, if after this period the competent authority is not responding the production could be started. The competent authority should also inspect the regular process development. As mentioned before, in Art. 5 number 2 and Annex III of Directive 98/81/EG the principles and the relevant documentation for potential adverse effects on the environmental and the public health were described and additional in Art. 5 number 3 the four classifications for the different levels of containment were listed.

2.6.3 Specific regulatory procedures in Germany

For Germany the procedure and the requirements are fixed in the German law about Genotechnology (GenTech law come into force December 16, 1993; Last revision October 29, 2001; currently under revision; cf. 6.81). If a sponsor like to produce genetic modified organism like transgenic animals for TMP production a manufacturing authorization for the facility have to be granted by the competent authority (local authority; Art. 8 GenTech law). The granting procedure according to Art. 11 showed that the relevant documentation should be submitted to the local authority. The approval has to be given by the authority within 3 month. A standing expert committee at the Robert-Koch-Institute gives recommendations and scientific advises to the local competent authority (depending on the risk class). Additional for the specific genetic modification procedure, depending of the classification (1 – 4 class) of the modification procedure, a granting by the competent authority should also to be done before starting with the TMP production (Art. 12; German GenTech law). Compared to the manufacturing authorization an implicit procedure is the legal basic that means, if no respond is given by the competent authority within 3 month the process could be started.

2.6.4 US specific regulatory procedures

In the US the use of transgenic animals and environmental and public health concerns are regulated by special departments. The new drug provisions of FDCA (section 505) and biologics provisions of the Public Health Service Act (section 351) provide CDER and CBER authority to regulate (by requiring pre-market scientific review and licensing) the safety and

effectiveness of human drugs and biologics produced by genetically modified animals and to ensure that they are produced under conditions that ensure their purity and potency. The National Environmental Policy Act (NEPA, cf. 6.18 and 6.115) requires all agencies to conduct an environmental assessment (EA) and, when there may be significant impact on the quality of the human environment, an environmental impact statement (EIS) in connection with agency actions should be conducted. Under NEPA, CVM would conduct an EA in connection with its approval of genetically modified animals under its animal drug licensing authority and seek measures to ameliorate any anticipated adverse environmental effects. NEPA does not override the market entry standards of the FDCA, and CVM is not legally empowered to deny approval of an animal drug based on its NEPA assessment. CVM asserts that its animal drug authority permits it to regulate the environmental impacts of genetically modified animals to the extent they adversely affect, directly or indirectly, the health of humans or animals. This presumably would include requiring mitigation actions and monitoring of environmental impacts. While NEPA is intended to provide for public consideration of the environmental impact of government actions, the FDCA's animal drug authorities and regulations make the licensing process confidential between the applicant and the agency and preclude disclosure of information contained in the new animal drug application (NADA) confidential until the product is approved. FDA has issued regulations under NEPA, setting forth the procedures for EA's (cf. 6.15).

2.7 Social and ethical concerns

New technologies, such as biotechnology, often are characterized by a variety of uncertainties resulting in unexpected outcomes. Uncertainties can be placed in three categories: statistical, model and fundamental. These categories of uncertainty generally correspond to technical, methodological issues, which also can be described as inexactness, unreliability, and insufficient knowledge. The socioeconomic impacts of animal created through biotechnology methods might be manifest at level of the individual, family and community. Ethical considerations range broadly, generally are normative, and cannot be resolved scientifically. Some people, irrespective of the application of the technology, consider genetic engineering of animals fundamentally unethical. Others, however, hold that the ethical significance of animal biotechnologies must derive from the risks and benefits to people, the animals, and/or the environment. Yet another view focuses on the right of humans to know how their pharmaceuticals are being produced, and therefore labeling becomes an issue to be addressed.

2.7.1 Ethic concerns regarding animal welfare

The technique of transgenic production also raises serious ethical concerns, since it is possible to induce irreversible and often potentially far-reaching alterations in the genetic constitution of animals, for example, producing strains which express human genes, or which, in the case of disease models, are designed to suffer. This and the special housing conditions of transgenic animals consider concern regarding animal welfare. The three Rs mentioned in basic EU Directive 86/609/EEC in Art. 7 defined that animal use should be reduced if possible and in the case alternatives where in place regarding this regulatory advice the justification of the use of animals for TMP production must be specific explained. Only the better economic value should not be sufficient for the use of many animals for the production of medicinal products if alternative technologies like cell culture exists. This is clearly defined in the German Animal law that without any justification and alternatives animal experiments must be avoided (cf. 6.49, 6.50, 6.100 and 6.118).

2.7.2 Other ethic considerations

The moral acceptance of TMP is not as important like in the food production. The argument that it is acceptable to use animals as means to at least some human ends usually appeals to the benefits of that use – that, in at least some cases, the benefits of using animals can outweight the harms that are caused. Therefore, the main ethical concerns are about the consequences. In the case of genetic modification, there may be concern about consequences for the welfare of modified animals, and about the harms caused during production. There may also be concern about the hazards which modified organism might pose to human and animal health and the environment. Another kind of concern should be raised that although species change through natural events, it is extremely difficult to challenge species boundaries in selective breeding. Direct genetic modification is different from both these processes in that, potentially, it offers limitless possibilities for transferring specific genes between widely different species (cf. 6.47 and 6.2).

2.8 Clinical and non-clinical development and preparation for Marketing Authorization Application

2.8.1 Non-clinical development

Before any clinical trial is carried out, results of non-clinical investigations or previous human studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in humans. Throughout drug development, emerging animal toxicological and

clinical data should be reviewed and evaluated by qualified experts to assess their implications for the safety of the trial subjects. The purpose and timing of animal pharmacology and toxicology studies intended to support studies of a given duration are discussed in ICH M3 guideline (cf. 6.91). The role of such studies for biotechnology products is cited in ICH S6 guideline (cf. 6.98).

For the first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite non-clinical pharmacokinetic, pharmacological and toxicological evaluations (see ICH M3 guideline, cf. 6.91). Early non-clinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide information about physiological and toxicological effects of a new drug. The very important field of biosafety for the TMP are prerequisites to use the drug in clinical trials. However, as in other biotechnology products the non-clinical investigations which were conducted should be evaluated case-by-case depending on the nature of the TMP. An important field in biotechnology products especially for TMPs should be potential immunogenicity observation by the first treatment in man, which could only determined in the clinical studies, but first sign from non-clinical studies should be considered in mind. As in other biotechnology-based products the use of appropriate animal models is an important, but also in some cases not possible, method to investigate the understanding of the mechanism of action.

2.8.2 Clinical development

The clinical development of the TMP depends on the indication and the patient population. If the product is indicated for life-threatening or serious diseases the clinical development will be different from those in not serious diseases. For example in cancer the persons treated in the first-in-man studies are the target patient population and not volunteers. This should be also logical from ethical point of view.

The principles and practices concerning protection of trial subjects are stated in the ICH Guideline on Good Clinical Practice (GCP; ICH guideline E6, cf. 6.89). These principles have their origins in The Declaration of Helsinki and should be observed in the conduct of all human drug investigations.

2.8.2.1 Quality of Investigational Medicinal Products

Formulations used in clinical trials should be well characterized. Information including bioavailability should be provided wherever feasible. The formulation should be appropriate

for the stage of drug development. During drug development some changes in the manufacturing process and different formulations of a drug may be tested. Appropriate exercises should be conducted to show the comparability between the different produced batches. Especially for the TMP batches it should be important to show the consistency in drug production. The comparability exercise on quality and nonclinical/clinical aspects should be conducted according to the two CPMP guideline documents (CPMP/BWP/3207/00/Rev.1 and CPMP/BWP/3097/02, cf. 6.52 and 6.53). After potential up-scaling or main changes in the production process in the case of TMPs (i.e. new herd animals or new harvesting methods) the consistency of the process is the main issue which should be considered. Also safety issues regarding new animals used for production or new feed stuff should be focused. In the TMP production new technology or material in the downstream process should be determined of potential impact on the product or impurity profile. A main issue will be potential alteration in the posttranslational pattern (e.g. Glycosylation), which might be ended in higher immunogenicity reactions.

2.8.2.2 Different steps in clinical studies

In the Drug development of TMP it should be similar as in other drug development program that a logical, step-wise procedure in which information from small early studies is used to support and plan later larger, more definitive studies. The case that the most TMP will enter the market as “biogenerics” the appropriate clinical program as described in the Directive 2003/63/EC in Europe should be conducted similar to other biotechnology produced products. It should be a case-by-case approach discussion between the sponsor and the agency which detailed program should be provided, but in all cases the traditional generics “well established use” term could not be used (Art 10(1)a(ii) 2001/83/EC; cf. 6.36 and 6.104).

Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials, except the TMP should be used in life-threatening diseases or through ethical concern through the special characteristic of the TMP. Most of TMP are proteins (e.g. monoclonal antibodies), which will used in many cases in life-threatening diseases like cancer. One of the main differences in using TMP as investigational medicinal products would be the potential occurrence of immunogenicity related adverse effects. This potential risk should be strictly described and documented by very precise monitoring of the treated persons. However, the special considerations by conducting clinical trails with TMPs will be the potential adverse effects

regarding potential biosafety concerns. Therefore clinical development of TMPs depends on the nature of the product and it would be always a case-by-case approach, which should be discussed with the relevant authorities. For the most TMPs a complete clinical program (described in several ICH efficacy guidelines E4 and E8, cf. 6.88 and 6.90) to generate safety and efficacy data would be required, as in the case of other biotechnology products produced as "similar biological medicinal products" according to the new Directives 2004/27/EC and 2003/63/EC (Part II, number 4) and the Council Regulation 724/2004/EC (cf. 6.38, 6.26 and 6.45).

The first transgenic produced product, recombinant human antithrombin III (Atryn®) produced in goats, is currently under the scientific evaluation process by the EMEA in the EU (cf. 6.87). In the clinical program a first-in-man study in 15 male volunteers for the evaluation of human pharmacodynamic (PD) and pharmakokinetc (PK) was conducted. This was similar to normal clinical development programs. In the next step the clinical safety and efficacy would be determined in a small patient population of only 14 patients plus 5 patients in the US in a compassionate use program (GTC Biotherapeutics, 2004; cf. 6.87). This is compared to the normal huge clinical program in other recombinant human proteins ("biogenerics"), e.g. human recombinant insulin or erythropoetin, very small. In the case of insulin (here insulin lispro, Eli Lilly, Netherlands; cf. 6.55) 8 clinical efficacy studies with 2951 patients were conducted. In the safety program 2247 and 2265 patients in the control group (comparator: Humulin R) were treated (EMEA: European Public Assessment Report Dynepo, Aventis Pharma S.A. and HUMALOG, Eli Lilly; cf. 6.54). Pharming (Netherlands) and Genzyme Transgenic Corporation develop together in a joint venture a transgenic produced alpha-glucosidase (excreted in the milk of rabbits) for the life-threatening disease Pompe's disease and the FDA granted an orphan drug designation in 1996 (cf. 6.111). The clinical program consisted of a Phase I in patients and successfully completed in 1998 and in the next step a phase II study with 12 patients was planned (8 infantile and 4 juvenile, Netherlands; cf. 6. 106). The pivotal trial was planned as a multi-center study in US and EU with 18-21 infantile patients and 30-40 juvenile patients. The MAA submission was expected in 1999, but the dossier was never submitted to any authority until today. The small clinical program of Atryn® in high risk patients was based on the results of a scientific advice by the EMEA. The assessment report will show if this small program will be sufficient for a favorable risk/benefit profile. Therefore these first transgenic program will show the potential requirements of future transgenic products.

In the Annex 1-3 at the end of this thesis the different work between EU and US agencies are shown during the development process. The closer contact of the FDA to the applicant than in the EU with the EMEA could be well described.

2.8.2.3 The clinical trials procedure in the US and EU

In general in the US before going in to first-in-man study an IND should be filed and after the review procedure of 30 days was done the study could be started by the sponsor (cf. 6.13). It is strongly recommended to have a pre-IND-meeting with the FDA (CBER in case of biologics like the TMPs) to solve and discuss main issues for the clinical development (see also Annex 3). During the clinical development in the US the FDA is regular informed about the product through the IND procedure process. Through formal scientific advises with the FDA problems and issues regarding the development could be early defined and discussed to support a successful development for the product. In the special manufacturing conditions of TMPs the same biosafety considerations should be included in the patient monitoring program, including parameters to stop the clinical trial because of patient safety concerns. This plan and program should be normally discussed with the FDA.

In the EU before the new Directive 2001/20/EC (cf. 6.35), also named as the clinical trials directive, every country has its own procedure for starting clinical trials. This complex and confusing situation should be harmonized by the implementation of this new Directive by every Member State until May 1st, 2004. But there are still some countries, including Germany and France, where the implementation was postponed. In the most other EU Member States before starting a clinical trial a clinical trial application (CTA) should be filed and approved by the competent authority and additional an independent positive ethic votum has to be needed. The EU procedure for the development of TMPs is described in Annex 1 (in the middle of the flowchart) including also the clinical development. The timeframe for both approval procedures is foreseen with 60 days (90 days for cell therapy, xenotransplantation) including time for answering authority requests by the applicant. After receiving both positive opinions the clinical trial could be started. To support the clinical development in the EU a formal scientific advise procedure could be filed with the EMEA and additional national advises in several Member States could be held to seek the input from authorities.

2.9 Regulatory environment for the granting of the Marketing Authorization Application (MAA)

As for other traditional biotechnology products the MAA for TMPs has to be submitted to the competent authority. In the EU the EMEA (centralized procedure, CP) and in the US the FDA (CBER; BLA biological license application) are the agencies where the Marketing Authorization Application are filed.

2.9.1 EU regulatory environment

In the EU the TMPs should fall under the scope of the centralized procedure because of two aspects described in the new EU Regulation 726/2004/EC (repealing Regulation 2309/93/EC; cf. 6.44 and 6.45). Firstly according to Art. 3 number 2 "…2.Any medicinal product not appearing in the Annex may be granted a marketing authorization by the Community in accordance with the provisions of this Regulation, if…(b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorization in accordance with this Regulation is in the interests of patients or animal health at Community level..." and secondly because of the requirements listed in the Annex of the EU Regulation 726/2004/EC. Therefore the centralized procedure have to be mandatory because of the new innovative technology on one hand and as a biotechnology produced medicinal product on the other hand. The required documentation should be submitted in the CTD format according to Annex I of the Directive 2003/63/EC amending Directive 2001/83/EC (cf. 6.26 and 6.36). If the TMP is a new active substance a whole clinical and non-clinical test program should be conducted and appropriate information should be provided in Module 4, 5 and the special Module 2 parts. Normally the TMP will be biological similar medicinal products (see section 2.8.2). In conclusion the TMP would be similar to the marketed product, but the manufacturing by transgenic animals will be a new process (biotechnology produced products are defined through their process) and that means that the product will be different from the marketed material. The term "essentially similar" could not be used in the field of generics based upon the Art. 10(1) (a) (iii) Directive 2001/83/EC and it was clear stated in the Directive 2004/27/EC (Art. 10 number 4) and Directive 2003/63/EC (Part II number 4) (both amending Directive 2001/83/EC) that for those "similar biological medicinal products" an appropriate clinical and non-clinical test program should be provided. The detail and the information to be supplied by the sponsor (applicant) should be determined on a case-by-case basis. In Directive 2003/63/EC Part IV "Advanced therapy medicinal products" specific requirements for Module 3 of the CTD format for gene

therapy were described, which should be helpful in providing appropriate information in the MAA or earlier as discussion point with the agencies for potential requirements for transgenic animals producing TMPs. During the clinical development the national authorities as well as the EMEA could be contacted to get advise on the development program to fulfill later requirements for the MAA. Before submitting the MAA in the centralized procedure to the EMEA (European medicinal agency) a pre-submission meeting could be used to clarify formal and content related issues depending on the submission. After the MAA was submitted to the EMEA, the agency dedicated a rapporteur and a co-rapporteur and an EMEA project manager to coordinate the submission until the recommended opinion by the CHMP (after 210 days plus additional clock stop time) and the final decision by the EU commission (after 90 days). After receiving the final decision process from the EU commission the drug, in this case the TMPs, could be marketed by the applicant. After going to marketed with the product the maintenance work started for the TMPs (including process optimizations, new formulations, changes in packaging companies, etc) should be implemented by the different EU variation procedures (acc. EU Regulation 1084/2003/EC; cf. 6.30).

2.9.2 US regulatory environment (FDA)

The granting of the marketing authorization in US would be done after positive review by the competent authority the FDA. The dossier should be submitted in the ICH harmonized CTD format. The way from the clinical development to the marketing approval is not similar in both ICH areas. In the US the FDA is during the clinical development in close contact with the sponsor. Before starting the first-in-man study the FDA should be consultated in the pre-IND meeting. Here the first direction in latter approval procedures could be made, by requesting for a fast track status (according FDAMA 1997). The benefit should be closer contact to the authority and early meetings with the FDA to seek their input on the development. Additional the option of a rolling BLA (biologicals) or NDA should be possible. Additional the request to have the option of evaluation clinical studies on surrogate endpoints could be made, this should be important in diseases were the time to reach the primary endpoint is very long. Criteria for the designation should be that the unmet medical need would be demonstrated and the drug had to be intended for the treatment of a serious or life-threatening condition. After the first two clinical development phases were done, there was the opportunity to have a end of phase II meeting with the FDA to discuss the pivotal clinical program to fulfill the requirements for MAA (cf. 6.11 and 6.12). When the results were available from the confirmatory studies the FDA should be contacted for pre-submission

meeting and the intended submission of a dossier could be discussed. After the dossier was submitted the possibility to request for priority review could be done during the review period (acc. FDAMA 1997) and the decision should be taken by the FDA within 60 days. The benefit was a decreased review time from 10 to 6 months (FDAMA 1997; cf. 6.60). The requirements for such drugs should be significant improvements increased effectiveness in treatment, prevention or diagnosis of diseases, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of patient compliance or evidence of safety and effectiveness of a new subpopulation. A second strategic tool, which could be used in the MAA and to be faster on the market, would be the accelerated approval (cf. 6.17).

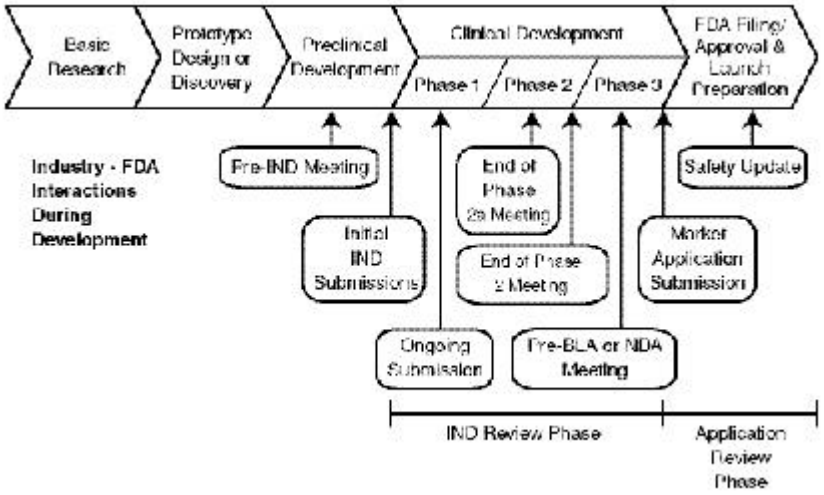

Figure 2.9.2 - 1: The close contact between the FDA and the applicant during the clinical development (FDA: "Stagnation and Innovation: Challenge and Opportunity on the Critical Path to New Medical products", March 2004; cf. 6.75).

The benefit should be approval on the endpoints of surrogate endpoint. The general requirements should be new product for treatment of serious or life-threatening illnesses, which provides meaningful therapeutic benefit to patients over existing treatments. The accelerated approval designation is independent from the priority review and it is granted as may be more provisional approval with commitments to complete clinical studies that formally demonstrate patient benefit.

After receiving the approvable letter from the FDA the MAA was reviewed according the granted priority and the approval for marketing authorization was given by the FDA. This was also reflected in the Annex 3 flowchart.

III. Discussion

The development of TMP as a part of clinical practice promises great benefits ensuring the potential increased demand on specific medicinal products. However, there are several areas of concern associated with the use of transgenic animals in drug production and development.

3.1 Transgenic farming

3.1.1 Facility and transgenic animal creation

Prior to the use of this new technology the facility and the production process have to be authorized by the competent authority (see Annex 2). During the TMP production the local authority in US as well as in EU could conduct inspections and audits to be sure that the production process is in line with the submitted documentation. In Germany the competent authority uses a special procedure for the notification of the production process before granting the approval (German GenTech law Art. 8, 10, 11, 12, 25 and 31; cf. 6.81) by considering the recommendation of a standing expert committee appointed by the Robert-Koch Institut (Berlin, Germany). In US the facility should be accredited by the AAALAC (cf. 6.1) and the inspection is under the authorisation of the USDA service FISI or APHIS. This is a first hurdle that has to be fulfilled in the field of TMP production in both areas. The strict use of the guidelines of GxP (including GMP, GLP and GAP) should be considered in this first step. It is already at the point of crude material collection (e.g. milk) that the quality and regulatory controls should ultimately ensure product safety, purity, potency and efficacy. Prior to the collection of the crude bulk material for purification processing, a number of practices, procedures, documentation and equipment-related functions need to be in place (e.g. relevant SOPs).

Regardless of the technique used for the creation of the transgenic founder animal, the predominant regulatory requirement is the stable integration of the genetic sequence without any alteration. In that phase of TMP production the GAP guidelines will be the scope to be focused. Testing the animal prior to collection is an additional control in transgenic production, especially pre-screening the animal's health (e.g. general health, body temperature, behavior, etc.). Compliance with quality assurance practices and regulatory guidelines starts at the level of construct development. Adequate documentation practices and the use of appropriate laboratory notebooks are essential. This same level of compliance also applies at the next stage when the construct is inserted into a host cell (e.g. a fertilized one-cell embryo) and subsequently transferred to a recipient animal. Proper documentation tracks the path from embryo microinjection to the birth of the transgenic founder animal. This level

of control is the same as that of a traditional cell culture-based recombinant protein production system.

3.1.2 Manufacturing (upstream process)

Once the requirement of GAP could be demonstrated the outbreeding to form the production herd could started. The requirement of genetic stability and a consistent expression of the active substance with appropriate limitations of specification settings is the first step which should be conducted to support the success in the steps of TMP production.

The use of transgenic animals for production does, however, add a new layer of quality and regulatory controls not needed in cell culture-based production. A understanding of the health and physiology of the species is essential. Unlike cell culture production, a transgenic animal, such as a goat, may live and produce for up to seven to 10 years. With cell culture production, each batch is made from an unique initiation or fermentation run. With transgenics, a production animal is bred and lactates annually. Additionally, each animal experiences its own physiological changes and various environments throughout its life (e.g. general housing, nursery, etc.) as it develops, gives birth, and ultimately lactates.

The production of TMP through the transgenic animals and the final harvest of the crude bulk material should be defined as the upstream process as compared to conventional Biotechnology products (e.g. products from cell cultures or yeast fermentation). The crude bulk material could be pooled from different animals or harvest times of a day for batch definition, and limits for the specification of the active substance and for the impurities including microbiological and protein contamination (including special species dependent potential pathogens) should be set. Appropriate tests for the detection should be developed. “In process” controls like in traditional Biotechnology production (including cell culture) could not be conducted and specified, but regular veterinary tests and especially blood investigations for animal health control during the production should be conducted. Production of small quantities of material early in the development is advantageous for starting the biochemical characterization of the molecule. Early crude bulk material collection can be accomplished through normal breeding and lactation. Typically this material is used for determining biological activity, measuring concentration of expression, amino acid sequencing, carbohydrate analysis and identifying contaminants. This information is necessary for any recombinant-produced product. Unique to transgenics however, this product characterization also should be done for each transgenic animal at different lactation to ensure consistency of the product throughout its production. Considerations about illness of animals

leads to the fact that these animals should be take out of the production herds. During the course of product development, many changes can occur in the manner in which a biologic product, including the TMP, is manufactured. These are changes that typically occur within a biologic production plant of one single company. Through the typical stages of drug development from “first dose in human” to product authorization, the product is made under one set of conditions early in development and the manufacturing conditions evolve over time as attempts are made to improve product quality, product yield and cost of goods. Experience from other products has shown that not all changes have the same potential to alter the product in a positive or a deleterious manner. However, in the absence of reference data, it is clear that it is usually not possible to predict what the impact of a new process change will be. Also the use of new animals for the production and the upscale process by using more animals for TMP production should be well determined. The comparability exercises to collect appropriate data should be conducted according to ICH guideline Q5E (reached step 2 in the ICH process; cf. 6.95) and in the EU according to the EMEA/CHMP guideline (CPMP/BWP/3207/00/Rev.1 and CPMP/BWP/3097/02; cf. 6.52 and 6.53). For the production process the GMP standards according to annex 2 Volume 4 of the EU legislation should be considered (EU legislation “Rules of governing medicinal products for medicinal use” Volume 4 (GMP) Annex 2; cf. 6.64) and in the US current Good Manufacturing Practice (cGMP) should be considered according 21 CFR Parts 210, 211 and for biologics see the special parts 600 subpart B and 610 (cf. 6.25).

3.1.3 Purification (downstream process)

Once the crude bulk material has been collected from the transgenic animals, purification of this source material again follows the traditional recombinant protein production requirements. At some point, pooling of crude bulk material is usually desired for processing. Pooling can happen immediately if crude bulk material, like milk, is kept fresh in a liquid state. Alternatively, if the crude bulk material is frozen for storage, it can be done when thawing individual collections. Additional testing, such as for endogenous and adventitious agents (e.g. bacteria, viruses, etc) can be performed on this pool. Here it should be recommended to have specific testing program, which should be developed with agency guidance depending upon the transgenic system being used. Because the crude bulk material is unique, a significant development phase is needed for the initial process steps and should be developed in parallel with the first lactations. During process development, variations in the processing scale need to be considered to address the increasing volume of the crude bulk

collected during herd scale-up. Whether the crude bulk is collected individually or as pooled bulk and whether the crude bulk material is processed fresh or frozen are a only few of the issues that need to be addressed.

Downstream purification needs to be able to ultimately produce a very safe, pure and reproducible finished product. Validation of the downstream process is required, as for traditional recombinant protein production. Unique to transgenics, however, is the high need to address specific removal or inactivation of species-specific endogenous and adventitious viruses and prions. Studies need to be geared toward addressing the viruses/prions of concern and incorporated into the viral validation studies.

3.1.4 Animal welfare and environmental concerns

The effects of genetic manipulation in transgenic animals on animal health and welfare are of significant public concern. Animal welfare has proven to be difficult to assess because it is so multifaceted and involves professional and ethical judgments. Considerations facets of animal welfare in discussing transgenic technologies are: their potential to cause pain, distress (both physical and psychological), behavioral abnormality, physiologic abnormality, and/or health problems.

An application to place a TMP on the EU market (e.g. the active substance of which is a purified transgene-expressed protein) is not expected to fall within the scope of Directive 2001/18/EC (repealing Directive 90/220/EC). On the other hand transgenic drugs should be fall under the Directive 90/219/EC (amended by Directive 98/81/EC). The transgenic drugs should be considered in relation to its potential for falling within the scope of the definition of a GMO which appears in Directive 90/219/EC (Art. 2(4) Directive 2001/18/EC). If the transgenic drug consist of or contain a GMO within the meaning of the Directive 2001/18/EC, a complete environmental risk assessment is required in the Module 1 section 1.4 of the CTD. In the most cases of transgenic drugs they would not fall under the scope of Directive 2001/18/EC therefore no environmental risk assessment should be prepared for the MAA Dossier. In all cases the facility and the genetic manufacturing process should be approved for transgenic production and housing of genetic modified animals as described in the Directives 90/219/EC and 2001/18/EC.

Possible environmental hazard pathways posed by escape or stocking of transgenic animals into natural ecosystems have not yet been thoroughly considered (e.g. escape of genetically modified salmons; cf. 6.48). Possible ecological risk posed by production of these transgenic animals is yet not full understand and determined. The transgenic technology can have

adverse effect on the welfare of animals. Transgenic animals produced by the current available technologies tend to have higher birth weights and longer gestation lengths than calves or lambs produced by artificial insemination. Large offspring syndrome (LOS) is much more frequent in cows produced by the transgenic methods (cf. 6.2). Through LOS intensive veterinary methods and special husbandry might be required. Some techniques in use are extremely inefficient in the production of transgenic animals. The percent of successful production range from 0 –4 percent in the different species (pigs, cattle, sheep, and goats) with about 80 to 90 percent of mortality occurring during early development (cf. 6.121, 6.5 and 6.108). A great amount of survived transgenic animals didn't express the inserted gene properly, often resulting in anatomical, physiologic, or behavioral abnormalities. It was published that in work with knockout mice (also produced by transgenic techniques) unexpected phenotypic effects, especially on behavioral traits of genetically altered animals could occur (cf. 6.50). These raises ethical as well as animal welfare concerns. An import animal welfare concern is the management and housing of transgenic animals intended for the TMP production. The animals are maintained in sterile, often isolated environment to minimize contaminations, which is a prerequisite for the appropriate production of biologics as medicinal products for human use (cf. 6.50).

Any analysis of transgenic animals and their potential impact on the environment needs to be focused in the area of TMP production of the potential release through accidents and the potential escape (possible by sabotage through theft/animal welfare organizations). The concerns that follow primarily focus on risks resulting from transgenic animals entering natural environment (cases of examples: cf. 6.74 and 6.114). The escape or release of the transgenic animals could result in a transgenic spreading through reproduction with wild type individuals of the same species. The risk of horizontal gene transfer (the transfer not by sexual contacts) is of considerably lower probability but of high risk depending of the ecosystem (cf. 6.48).

Although animals engineered to produce useful products will not be intended for consumption by humans or other animals, there are grounds for concern that adequate controls be in place to ensure restriction on the use of early removed, sick or older animals. Entry of removed animals into the food chain should be strictly forbidden and appropriate plans for withdrawal and retirement should be in place.

3.2 Biosafety

Treatment of patients with TMPs, however, will be exposed to considerable risk, including the risk of novel infectious disease. Such risk is not qualitatively different from the development of other new medical products and might be in some cases acceptable to the recipient because of the positive risk-benefit ratio of receiving a treatment. The principal concern is that the more uniquely close relationship, compared to the traditional used cell culture-based produced biologics, created between transgenic animals and the patient population will allow novel opportunities for transmission of infectious disease (e.g., TMP contains porcine endogenous retroviruses, or PERVs; cf. Table 2.5.1 - 1), and possibly creation of new disease agents in the process. PERVs are of special concern since the opportunity for the virus to evolve into a pathogen with the potential for transmission to others is unforeseeable.

In addition to species-specific pathogens, sponsors should consider the value of testing the pre-processed bulk for antibiotics or other medications such as bioburden, mycoplasma, fungi, and possibly prion proteins. There is a theoretical potential for microorganisms to acquire - by recombination or transduction - genes from the vector constructs used in gene transfer.

In the case of TMPs firstly the starting material, of the founder animal and the production herd must be fully characterized (cf. paragraph 2.5). Secondly, appropriate steps of the product purification process need to be validated for the ability to remove and/ or inactivate potential contaminants such as viruses, mycoplasma, endotoxins, and residual DNA and proteins (cf. 2.5.1 for the production animal safety). Thirdly, the final product, as well as the material from appropriate stages of the manufacturing process, must be tested to assure freedom from contamination. A core step to produce a safety product is a robust downstream process with the appropriate removal of potential contamination during the purification process. Only if this process demonstrated its robustness by reduction of contamination the use in clinical development could be started. The specific requirements for a testing program is the same as for traditional cell culture-based recombinant produced proteins and would be based on the ICH guidelines (ICH guidelines for recombinant produced proteins Q5A – E and Q6B; cf. 6.92, 6.93, 6.94, 6.94, 6.95, 6.96 and 6.99).

Regular veterinary control protocols for monitoring the herd for disease and infectious agents should exist. Specific screening procedures should include appropriate physical examination and laboratory tests. All infectious agents known to potentially infect the source species have to be considered including viruses, bacteria, mycoplasma, fungi, TSEs and parasites. Sourcing animals from Transmissible Spongioform Encephalopathy-free countries, such as New

Zealand or Australia, has significant benefits when dealing with FDA and EU regulatory agencies. The first case of potential BSE in the US (cf. 6.105 and 6.116) shows how important the control of the source country and the complete documentation should be to declare no safety risk regarding TSE problems in the product. The herd health surveillance system should include comprehensive documentation of all veterinary care received. The use of antibiotics and vaccination of source animals is not recommended. If the treatment of animals with any medicines is necessary for animal welfare reasons, an evaluation of the situation should be performed, and discussed with the competent authority. Any use of vaccines must be justified. All animals entering the facility have to be put under quarantine for a defined period to allow completion of screening procedures. Individual quarantine periods depend on the animal species and characterization and surveillance of the animal herd.

3.3 Ethic concerns

The labeling of food, which contains genetic modified plants, is currently a most discussed issue and customers like to have the label which stated if genetic modified plants are used in the production (cf. 6.76 and 6.83). In the area of medicinal products the public pressure is less because of the medical need of a product and less existing drug alternatives. Another more public concern could be the amount of animals used to create the founder animal, if alternative methods without animal use exist. It should be remembered that many additional animals are required during the generation of new transgenic strains (cf. 6.2).

Other ethical concerns will become more important if other alternative technologies with the same production capacity exist, because only economic advantages will be insufficient for establishing this technology (cf. 6.47 and 6.8).

The general concerns in the public against new technology (cf. 6.72) are a normal behavior. But acceptance will be higher than in food products. In addition, it is important to encourage wider public discussion leading to greater understanding of the uses of genetically modified animals and of genetic engineering generally.

3.4 Clinical and non-clinical development

However, before proceeding into human clinical trials, manufacturers of biological therapeutics are required by regulatory agencies worldwide to show that their products are safe and free from adventitious agents. These regulatory authorities require a multi-tiered approach to thoroughly demonstrate the product biosafety. There are a number of regulatory and guidance documents, which provide guidance to assuring that appropriate biosafety

testing is performed for a variety of products (for details see 3.2 and 2.5). It is important to emphasize that the regulatory authorities consider each biotech-product on a “case by case” basis. This is especially the situation for TMPs with there special production of the active substance. With that special situation the biosafety of the product is one of the important fields, which would also be very critical proofed by authorities.

The clinical development should be undergo by closely contact with the relevant agencies. In the US before filing an IND (Investigational new drug application) at the FDA it should be strongly recommended to have a pre-IND meeting with the FDA (CA), where several specific issues could be directly discussed with the agencies. In the IND procedure after the Phase II studies a meeting with the FDA so called end-of-Phase II-meeting is foreseen before starting the pivotal trials. Additional to these procedures formal scientific advices with the FDA should be conducted to get more input and advise on several issues regarding the specific production of the TMPs (cf. Annex 3).

In the EU clinical trials should be conducted according to the new Clinical Trials Directive (Council Directive 2001/20/EC, cf. 6.35) and here it was obviously also recommended to have close contact with agencies whether as national scientific advises (e.g. in Germany BfArM or Paul-Ehrlich Institut (PEI)) or as scientific advises with the EMEA (guidance document). In the later phase if the proof-of-concept could be shown a scientific advice regarding the planning of the confirmatory study should be discussed with the EMEA. In the case of TMPs it should be recommended to include in this scientific advice special issues regarding the transgenic production and the specific safety concerns (a combined scientific advice with questions for non-clinical, clinical and CMC is recommended). It was crucial for the latter development to have at that point input from the agencies regarding these important and critical issues.

According to the new legislation review the clinical program for TMPs should be the same as for other biotechnology products and in case of “biogenerics” an appropriate clinical program has to be provided in the MAA according the EU Directives 2003/63/EC and 2004/27/EC and the Regulation 724/2004/EC. As mentioned in 2.8.2.2 the clinical program for the currently first TMP (Atryn®) under EMEA evaluation is very small (cf. 6.87). Only 14 and 5 compassionate-use patients were treated in the safety and efficacy clinical trial. This small program was based on a scientific advice with the EMEA during the development process. In another transgenic produced product (alpha-glucosidase in Pompe’s disease by the Dutch company Pharming) the clinical development consist of a complete clinical program detailed described in 2.8.2.2. Surprising is that the product was never submitted to any authority. In

other recombinant human proteins (insulin and erythropoetin, cf. 6.54 and 6.55) huge clinical trial programs (including blinded controlled randomized pivotal trials with several hundred patients) were conducted to show the safety and efficacy of the product. The outcome of the evaluation of GTC transgenic product Atryn® by the EMEA will point the way to future assessment of transgenic products.

3.5 How to enter the market

In the EU as well as in the US there are several strategies to come successfully to the market. There are different procedures to receive a marketing authorization. The first objection is in every drug development to enter prematurely as soon as possible the market and provide patients new therapies for better treatment, diagnosis or prevention of diseases.

In the EU the applicant can depending on the characteristic of the drug or indication early request for different ways to get the market authorization. For TMPs in the EU the centralized procedure is mandatory according to the outdated and current legislation (Regulation 726/2004 repealing 2309/93 and the Directive 2004/27/EC amending the Directive 2001/83/EC).

One special way for receiving a marketing authorization is the request for an orphan drug designation if the product fulfills the requirements for an orphan indication (not more than 5 in 10000 persons in the EU affected or expected return on sales does not justify the necessary investment; US not more than 200000 patients per US population; EU Council Regulation 141/2000/EC, cf. 6.43). This could be an alternative way for TMPs developed for rare diseases to reach the market. The FDA granted an orphan drug designation for the transgenic product alpha-glucosidase for Pompe's disease in the US (cf. 6.106). The incentive of close contact with the EMEA including protocol assistance for the pivotal clinical development could be the crucial point in the complex development of TMPs. An other incentive is the lower fees to paid for scientific advice and MAA.

The use of scientific advices in normal clinical development of TMPs before filing a MAA is the important step in both ICH areas in the successful way to market approval. The complex situation in TMPs and the less experience on both site (the applicant and the agency) generates many open questions which should be discussed and possibly solved before a submission of the MAA and obviously not during the review process which should than results with a high probability in a negative opinion by the CHMP or a refusal to file (RTF) or not approvable letter by the FDA. The tool of pre-submission meeting should give the

applicant the opportunity in a late phase but before submission to get the input from the authority.

Most of the TMPs were developed as alternative methods for protein or biological production. Therefore these products will be new biological entities (NBE) or claimed as “biogenerics”. As “biogenerics” they can not be filled as traditional “well established use” products according the Art 10(1)a(iii) of Directive 2003/63/EC amending Directive 2001/83/EC. The new term “similar biological medicinal products” should be used for TMPs and according to that an appropriate non-clinical and clinical program should be provided for the MAA ((Directive 2003/63/EC part 2 number 4). As in the case of an innovator product the applicant is forced to conduct a clinical trial development program. So far, not a single “biogeneric” has been submitted for approval in the EU but the industry expects it for the near future (cf. 6.60). In the US the FDA prepared currently a guidance document for “follow-on” (biogenerics) biologicals under the FD&C Act Section 505 (cf. 6.67). These indicated that both great ICH areas are preparing the field for “biogenerics” in the future. Indirectly TMPs are included, if there were produced as alternative to marketed products (cf. 6.59).

The fact that until today no drug on the basis of transgenic animal production was approved for marketing authorization worldwide, raises the question for the reasons which could not clearly be answered. Genzyme Transgenic withdraw their MAA, which was submitted to the FDA. The only available information, which was given by the FDA, mentioned that for the transgenic produced antithrombin Factor III additional information (the company agreed to conduct additional clinical studies) were required, which could not be provided by the applicant so far (cf. 6.7). Currently BTC Therapeutics submitted an MAA to the EMEA and the product, a recombinant form of human antithrombin ATryn® produced by transgenic rabbits, is under the evaluation for marketed authorization in Europe (cf. 6.86). The results of the assessment of this first product will influence the filling of further transgenic products and might serve as a business case. Such examples implicated that an early and close work between the agency and the sponsor could cover critical points and support the project possible to a successful MAA. Several terminations of cooperation’s in the field of transgenic animals production indicated that the complex development of TMPs (including complex regulatory aspects) with many uncertainties regarding necessary data for marketing authorization seems to be a huge risk for investing by companies.

Therefore any kind of scientific advice and close contact with the agencies will be in the field of TMPs the main important successful factor. A comparability or similarity program should be clearly defined and agreed to before further development. The first product produced by

transgenic animals, which would be approved for marketing authorization, will be standard for other products in terms of data to be submitted and the growing experience by the agencies will also help for further successful MAAs and future supportive financial investment in that growing new technology.

In both ICH areas US and EU two specific guidance documents (EU CPMP guideline 3AB7a "Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human Use", July 1995; US Points to Consider "In the Manufacture and Testing of Therapeutic Products for Human Use Derived from Transgenic Animals", FDA, CBER; 1995, cf. 6.63 and 6.73) exist. But both guidelines are from 1995 and outdated regarding state-of-art technologies and investigations. The revision of these outdated guidelines should be done as soon as possible. In the EU the EMEA has the revision included in their last two annually work plans, but no revised version as well as a draft has been published at time of this thesis. The similarity of the content of both the EU and US guideline could be a good basis to bring that as a potential topic for harmonization in the three ICH areas in one of the next ICH conferences. The missing revision of current guidance documents will be one of the major points for the agencies – but also for the industry - to help in progressing this new technology. It should be based on the experiences with TMPs under evaluation to revise or create new guidance documents to support better development of transgenic produced medicinal products. It will be a great challenge for the agencies and industry to create such guidance documents, because of the very complex field and the case-by-case approach of the TMPs.

IV. Conclusion and outlook

There are several regulatory aspects which have to be taken into account for the development and production of TMP. The technical areas of facility design and transgenic technology, including animal production and housing, are mostly covered by the Good Agriculture Practice (GAP). Environmental risk and biosafety considerations are of utmost importance for TMPs (on one hand the validation of virus removal and inactivation procedures in the downstream process and the minimizing the risk of transmission of agents causing spongiform encephalopathy (TSE)). The risk of potential microbiological contamination during the creation of the transgenic line including potential contamination from host and founder animals should be minimized. Maintenance of the production animals should minimize contamination of crude bulk materials such as milk or blood from which the active substance will be purified. The purity and microbiological safety of the finished product is also of major concern. Biosafety issues of TMPs represent a great disadvantage as compared to cell culture-based biotechnological products. There are a number of regulatory and guidance documents, which provide guidance to assuring that appropriate biosafety testing is performed for a variety of products (for details see 3.2 and 2.5).

The TMP production by transgenic animals and the purification process (including up- and downstream process) should be conducted according to current regulatory guidance documents for the production and quality control of medicinal products derived by cell culture-based rDNA technology. Up-scaling of a TMP process by adding new animals to the herd or changes in the purification process should be implemented with an appropriate comparability program, which demonstrates the consistency and comparability of pre- and post-change product.

In summary the selection of the host animal for the development of TMP production should not only focus on the potentially better economic situation compared to conventional biotechnology products (cf. 6.3). Animal welfare, the origin or source of the species and safety concerns regarding the animal should also be taken into account.

Cell-culture based production of recombinant proteins or other biologics has been significantly improved in recent years resulting in increased yields and the increased quality of the cell culture medium. The potential economical advantage of TMP is therefore not as pronounced as at the beginning of transgenic technology. The second advantage of TMP (especially complex proteins) regarding more human-like post-translational modifications will also be of less importance in the future. Improvements in cell culture technology showed in some cases the similar nature of cell culture-based proteins to human proteins. It has recently

been shown for instance, that genetically modified yeast can make a human glycosylation pattern (cf. 6.9). This new technology offers new opportunities to produce proteins very similar to those in humans. Additional gene pharming in plants is of increasing importance, because there are less ethical or environmental issues (cf. 6.103)

Before proceeding into human clinical trials, manufacturers of biological therapeutics are required by regulatory agencies worldwide to show that their products are free from adventitious agents. This requires a multi-tiered approach to thoroughly demonstrate product biosafety. The biosafety, in detail mentioned before, of a TMP will be assessed in detail by the authorities. It is important to emphasize that regulatory authorities assess each biotech-product on a "case by case" basis. Before a TMP enters the stage of clinical development consultation with the agencies will be a major success factor. A comparability strategy should be clearly defined and agreed to before further development.

Medicinal products containing biological active substances manufactured using transgenic animals are clearly covered under the term "biotechnological" as defined in the Annex to Council Regulation (EC) 726/2004. TMPs are therefore subject to the centralised procedure described in this Regulation. Most of the TMPs were developed as alternative methods for protein or biological production. Therefore these products will be new biological entities (NBE) or claimed as "biogenerics". As "biogenerics" they can not be filled as traditional "well established use" products according the Art 10(1)a(iii) of Directive 2003/63/EC amending Directive 2001/83/EC. The new term "similar biological medicinal products" should be used for TMPs and according to that an appropriate non-clinical and clinical program should be provided for the MAA ((Directive 2003/63/EC part 2 number 4). As in the case of an innovator product the applicant is forced to conduct a clinical trial development program. So far, not a single "biogeneric" has been submitted for approval in the EU but the industry expects it for the near future (cf. 6.60). In the US the FDA prepared currently a guidance document for "follow-on" (biogenerics) biologicals under the FD&C Act Section 505 (cf. 6.67). These indicated that both great ICH areas are preparing the field for "biogenerics" in the future. Indirectly TMPs are included, if there were produced as alternative to marketed products (cf. 6.59).

The first approved medicinal product produced by transgenic animals, will stimulate the development of other TMPs. Currently BTC Therapeutics submitted an MAA to the EMEA and the product, a recombinant form of human antithrombin ATryn® produced by transgenic rabbits, is under the evaluation for marketed authorization in Europe (cf. 6.86). There are currently two guidelines dealing with TMPs. These two guidelines from the FDA and the

EMEA were published in 1995 and are therefore not up-to-date. The revision of the guidelines including new technology and results from research should be done in the near future, hopefully before the next wave of these products reaches the critical point in development. This outstanding revision of current guidance documents will be one of the major points for the agencies to help in progressing this new technology. It will be a great challenge for the agencies to prepare such guidance documents, because of the very complex matter and the necessary case-by-case approach for TMPs. In addition the growing experience of the agencies will also help to clarify the regulatory framework and increasing confidence in the new technology will make future supportive financial investment more probably.

V. Summary

The purpose of this document is to provide guidance on the principles on the development of medicinal products produced by transgenic animals that can enable more effective development, both by regulators and industry. This thesis also provides and summarizes the existing quality practices, requirements, standards, and guidelines regarding the new technology, scientifically based considerations and the regulatory framework for the clinical development and the approval for marketing authorization in the two main ICH areas European Union and the United States of America.

Human proteins for therapeutic use have so far been produced by extraction from tissues and plasma and by recombinant technology from mammalian and microbial cells. Cost effectiveness large scale production of pure, native and stable proteins represents a challenge. Transgenic is the production of animals whose genetic make-up has been changed in some way. As transgenic technology makes considerable progress, so called “animal factories” have drawn much attention to this technology for the production of human proteins in a large and economically feasible scale. A gene from humans or another species is inserted into the animal’s DNA. Before starting the transgenic engineering the facility and the genetic transfection process and the use of these animals for TMP production have to be approved by the competent authorities in both the EU and the US.

Typically the expression vector is microinjected into fertilized eggs that are transferred into a recipient female. Offsprings are tested for the transgene. Transgenic animals mate and then the crude bulk material has to be harvested and to be tested on the expression of the active substance. In the farms for transgenic animal creation and TMP production GAP (Good Agriculture Practice) and GMP (Good Manufacturing Practice) is the prerequisite for a safe and high quality product.

There are several concerns in transgenic technology. One of the main concerns about genetic engineering is inefficiency in the production of transgenic animals. Gene transfer studies have revealed that fewer animals were born with the specific gene. Animal welfare problems should be considered because of the unpredictable nature in producing transgenic animals. Any “mistake” that happens usually has disastrous consequences for the animals involved. It is not known what the long-term effects of inserting a foreign gene will be on an animal’s health. The welfare of transgenic animals may be further undermined if any defects occur undiscovered. Unrecognized, such defects may cause severe pain and distress to that animal. Other concerns occur regarding the environment and ecosystem. There is a chance that genetically engineered animals can be released into the environment, either deliberately or by

accident. As transgenic animals can pass their new genes on to their offspring, it would be difficult to predict what their effect will be on the natural ecology of that area.

Before proceeding into human clinical trials, manufacturers of biological therapeutics are required by regulatory agencies worldwide to show that their products are free from adventitious agents. Regulatory authorities require a multi-tiered approach to thoroughly demonstrate product biosafety. There are a number of regulatory and guidance documents, which provide guidance to assuring that appropriate biosafety testing is performed for a variety of products, which could be reflected to TMPs (for details see 3.2 and 2.5). Regulatory authorities are assessing each biotech-product on a "case by case" basis. Potential biosafety issues of the product would be one of the critical points, which would be assessed in detail by the authorities. Biosafety issues of TMPs represent a great disadvantage as compared to cell culture-based produced biotechnological products. Once appropriate quality and controls are in place, the purification process developed and the biochemical characterization well under way, then, as for any product, non-clinical studies are necessary. The non-clinical plan is based on the product and its intended use, not the transgenic origin of the product. Route of administration, dose, frequency and duration are traditional parameters that need to be defined. To assess product safety and efficacy, both in vitro and in vivo animal models should be considered. At this stage of development the understanding of the mechanism of action, the pharmacodynamic and pharmacokinetic in animals and the toxicology of the recombinant product is the main focus. If the initial non-clincal studies are conducted and favorable, then development proceeds along the traditional path with clinical trials initiated at the different stages.

During that period in both US and EU a close contact to the agencies would be strongly recommended. This will be one of the main success factors in the development of transgenic drugs. In the US the IND process realizes this contact and in EU similar formal community scientific advices and national advices could be initiated.

Additionally, due to the wide range of applications for this new technology, there is a lack of uniformity of standards within the industry and uncertainty as to exactly what the regulatory agencies will require. Approval of the first product from this new technology is greatly awaited as a proof of principle for transgenic recombinant product production. Currently BTC Therapeutics submitted an MAA to the EMEA and the product, a recombinant form of human antithrombin ATryn® produced by transgenic rabbits, is under the evaluation for marketed authorization in Europe (cf. 6.86). The next step will be the revision of the specific guidance documents in the US and EU to support the clinical development and the market launch of

TMPs. In the EU the specific guideline revision is pending for two years on the workplan of the EMEA.

However, what is clear, as evidenced by the number of companies with regulatory and clinical milestone achievements, is that moving a transgenic product through both the FDA and European approval process is possible. Medicinal products containing biological active substances manufactured using transgenic animals are clearly covered under the term "biotechnological" as defined in the Annex to Council Regulation (EC) 726/2004. TMPs are therefore subject to the centralised procedure described in this Regulation. Most of the TMPs were developed as alternative methods for protein or biological production. Therefore these products will be new biological entities (NBE) or claimed as "biogenerics". As "biogenerics" they can not be filled as traditional "well established use" products according the Art 10(1)a(iii) of Directive 2003/63/EC amending Directive 2001/83/EC. The new term "similar biological medicinal products" should be used for TMPs and according to that an appropriate non-clinical and clinical program should be provided for the MAA ((Directive 2003/63/EC part 2 number 4). As in the case of an innovator product the applicant is forced to conduct a clinical trial development program. So far, not a single "biogeneric" has been submitted for approval in the EU but the industry expects it for the near future (cf. 6.60). In the US the FDA prepared currently a guidance document for "follow-on" (biogenerics) biologicals under the FD&C Act Section 505 (cf. 6.67). These indicated that both great ICH areas are preparing the field for "biogenerics" in the future. Indirectly TMPs are included, if there were produced as alternative to marketed products (cf. 6.59).The number of transgenic drugs in the pipelines is increasing and thereafter, one can potentially expect to see a number of TMPs approved through the centralized procedure in the EU and/or approved by the FDA for the market launch in the upcoming years. In addition the growing experience of the agencies will also help to clarify the regulatory framework and increasing confidence in the new technology will make future supportive financial investment more probably.

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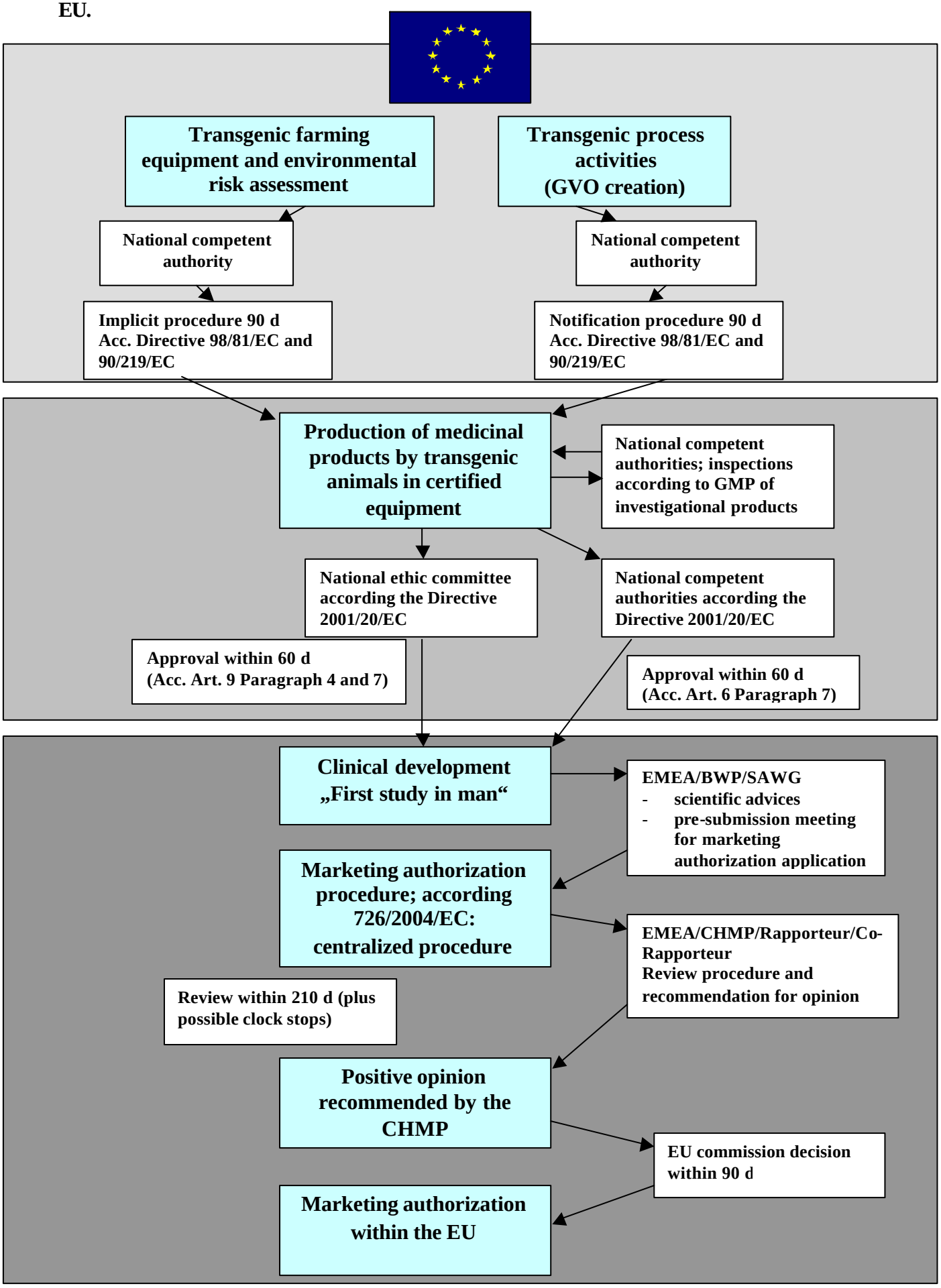
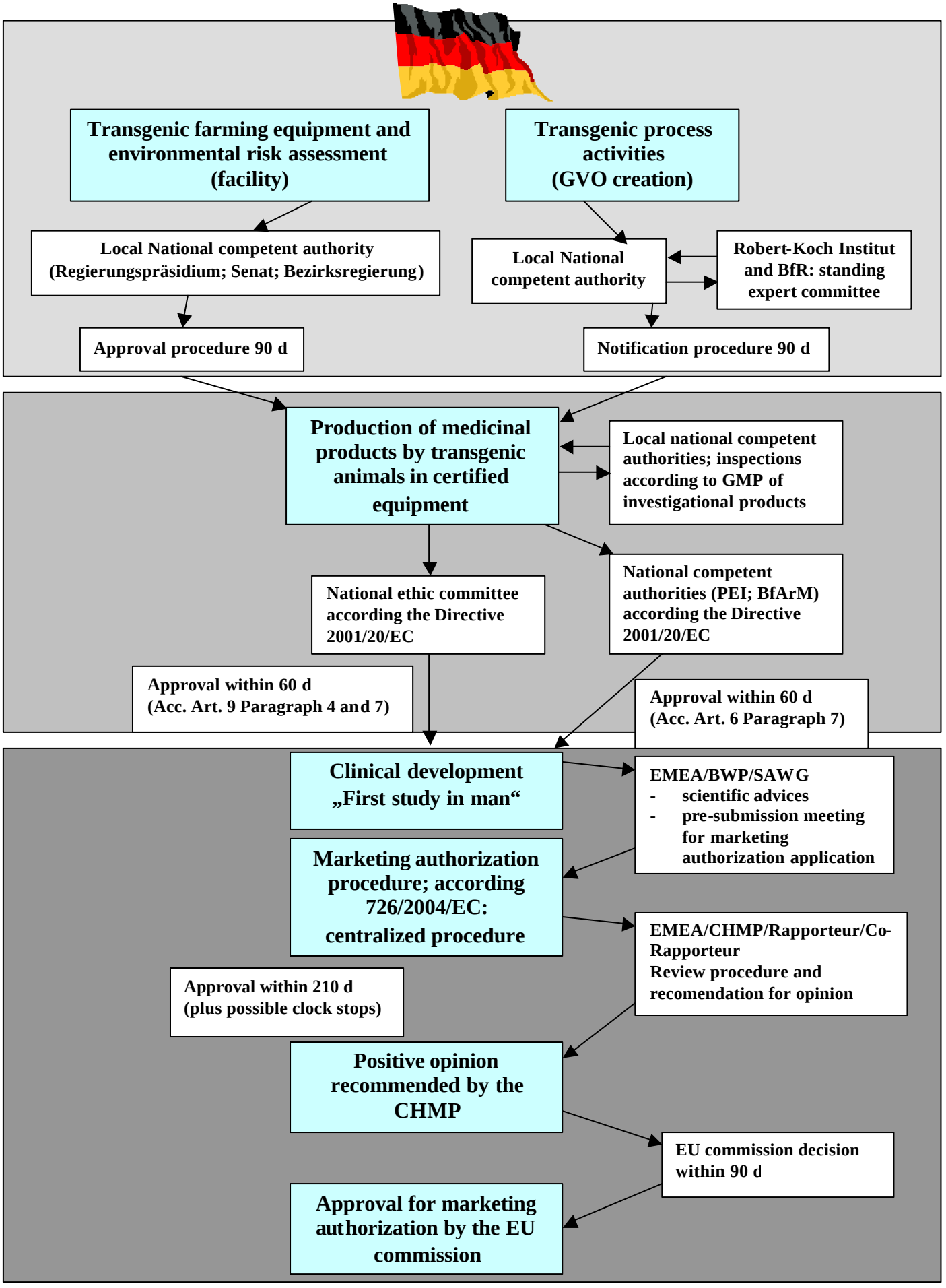
Annex 1: Flowchart of the regulatory environment in the field of TMP production in the EU.



Annex 2: Flowchart of the regulatory environment for TMP development in Germany.



Annex 3: Flowchart in the regulatory environment for TMP development in United States of America (USA).

Transgenic farming equipment (facility)

Transgenic process activities and environmental risk assessment (GVO creation)

National competent agencies: USDA/AAALAC FISI/ APHIS

National competent authority: FDA PHSA/ FDCA/ NEPA

Production of medicinal products by transgenic animals in certified equipment

National competent authorities FISI/APHIS: inspections according to GMP of investigational products

National competent authority FDA: IND submission

National competent authority FDA (CBER; CVM): Pre-IND meeting

Approval within 30 d Acc. 21 CFR 312

Clinical development „First study in man“

FDA:
- IND review process (acc. 21 CFR 312)
- scientific advices
- Orphan drug status
- end of phase II meeting
- pre-submission meeting for MAA
- Fast track status

Marketing authorization procedure; according 21CFR 314 and 600

FDA:
- priority review
- accellerated approval
- Review procedure and approval process

Approval within 6-10 month depending on the review procedure/ status (Acc. FDAMA 1997)

Approval letter granted by the FDA

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

Ort, Datum:

_____

(Dr. E. Schmitt)