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Regulatory requirements for clinical trial and marketing authorisation application for gene therapy medicinal products

The legal framework and definition of gene therapy medicinal products

Gene therapy medicinal products (GTMPs) constitute a wide range of products of biological origin. The revised definitions for GTMPs and somatic cell therapy medicinal products (SCTMP) have recently been published within Directive 2009/120/EC amending Directive 2001/83/EC [1, 2]. In accordance with the revised definition, GTMPs include recombinant nucleic acid sequence(s) of biological origin, genetically modified virus(es), genetically modified microorganism(s) and cells genetically modified by one or more of these substances (**Fig. 1**). The revised definition excludes vaccines against infectious diseases, which are covered appropriately within the existing framework for vaccines. Similarly, chemically synthesized nucleic acids (e.g. RNA, DNA, oligonucleotides) are also not considered as GTMPs. GTMPs are developed to have a therapeutic or prophylactic effect, or are used as a diagnostic tool in the treatment of a variety of human diseases, both effects relating directly to the recombinant nucleic acid sequence included. The final medicinal product may contain as an integral part a medical device or an active implantable medical device.

The presentation of the marketing authorisation application (MAA) dossier for GTMPs must fulfil the same regulatory and scientific requirements as for any other medicinal products as laid down in the legislation [1, 2, 3, 4]. Specific requirements for GTMPs are given in the revised Part IV of Annex I and in product-specific guidelines. As GTMPs contain genetic and other materials of biological origin, many of the quality guidelines for biologicals manufactured by modern biotech-

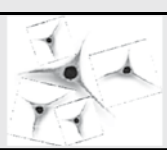
Type of drug substances in GTMPs (recombinant)		Examples
(a) recombinant nucleic acid sequence(s)		- oligonucleotides (of biological origin) - plasmid DNA → naked or formulated with synthetic delivery systems such as lipids, polymers and/or peptide ligands
(b) genetically modified virus(es)		- replication-deficient - replication-competent - conditionally replication-competent → e.g. retrovirus, adenovirus, adeno-associated virus, herpes simplex, vaccinia virus
(c) genetically modified microorganism(s)		- *Mycobacterium bovis (BCG), Shigella, Clostridia* → genetically modified e.g. by plasmids
(d) genetically modified cells		- autologous, allogeneic, xenogeneic - primary cells or stable cell lines → genetically modified by one of the products described above

Fig. 1 ▶ Types of GTMP

nological methods will also apply. These guidelines are not only valuable references for sponsors during product development but are also used by the competent authorities of the Member States responsible for clinical trial authorisation and the evaluation of MAAs. It is noteworthy that all technical requirements described in Part IV of Annex I are legally binding for approval of an MAA. An overview of applicable product specific guidance is given in **Tab. 1**.

Quality requirements for GTMPs

The principles of Good Manufacturing Practice (GMP) [5] are mandatory for the manufacture of all advanced therapy medicinal products (ATMPs), including GTMPs [6]. A manufacturing authorisation covering the manufacturing operations for the intended GTMP has to be requested by the manufacturer from the respective competent authority prior to applying for clinical trial authorisation. In Germany the provision of manufacturing licences is within the responsibility of the different federal state authorities ('Länderbehörden'). A manufacturing licence from another EU Member State is mutually recognised by all other States within the EU. The manufacturing process and facilities will be inspected to confirm GMP compliance with respect to product quality, consistency, process validation and raw material qualification, prior to issue of a manufacturing licence. Evaluation of meaningful definition of in-process controls and release criteria are essential to the process development. Where the product is not manufactured within the EU, the importer shall ensure that the product has been manufactured in accordance with standards at least equivalent to the European standards, and an import licence has to be obtained.

The complexity of the manufacturing process differs for all types of GTMPs and this will directly impact on process development. For example, establishment of a consistent manufacturing process for genetically modified, primary cells will be more difficult compared to the manufacture of a plasmid-DNA vector. The main

Abstract · Zusammenfassung

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Abstract

Over the last two decades, clinical trials using gene therapy medicinal products (GTMPs) have been carried out for a large number of rare, inherited monogeneic disorders as well as common multigeneic diseases such as cancer, cardiovascular and infectious diseases including AIDS. Despite some early difficulties and setbacks, the gene therapy field has slowly progressed and, nowadays, offers the promise of novel treatments for a growing number of diseases. On the other hand, gene therapy approaches are often associated with additional risks due to limited clinical experience with a given gene transfer system, long-lasting effects of the therapeutic gene, and/or a complex mode of action. As a result, specific regulations and guidelines have been introduced within the EU to help address these uncertainties. This article summarises the legislative framework and will provide an overview on the regulatory requirements for clinical trials and marketing authorisation applications.

Keywords

Gene therapy medicinal products · Marketing authorisation · Clinical trial · Legislation

Regulatorische Anforderungen an die klinische Prüfung und Marktzulassung von Gentherapeutika

Zusammenfassung

In den vergangenen 20 Jahren wurde eine zunehmende Zahl gentherapeutischer Arzneimittel (GTMPs) in klinischen Studien getestet. Die Indikationen reichten dabei von seltenen, monogenischen Erbkrankheiten über multifaktorielle Krankheiten wie Krebs oder kardiovaskuläre Erkrankungen bis hin zu Infektionserkrankungen, wie zum Beispiel AIDS. Trotz anfänglicher Schwierigkeiten und Rückschläge eröffnet die Gentherapie mittlerweile eine vielversprechende Behandlungsoption für zahlreiche Krankheiten. Andererseits sind natürlich Behandlungen mit diesen Therapieformen aufgrund (i) geringer klinischer Erfahrung mit den entsprechenden Gentransfersystemen, (ii) der Langzeitwirkung der transferierten Gene und (iii) der oftmals komplexen Wirkungsweise der Arzneimittel mit zusätzlichen Risiken verbunden. Deshalb wurden in der EU zahlreiche Verordnungen und Leitfäden zu dieser Thematik veröffentlicht. Dieser Übersichtsartikel bietet einen Überblick über die regulatorischen Anforderungen an die Durchführung von klinischen Prüfungen mit und die Marktzulassung von Gentherapeutika und stellt die grundlegenden gesetzlichen Rahmenbedingungen dafür dar.

Schlüsselwörter

Gentherapie · Arzneimittel · Zulassung · Klinische Prüfung · Gentransfer · Gesetzgebung

Tab. 1 Collection of product specific guidance for the development of GTMPs

Designation	Subject	Scope
CPMP/BWP/3088/99	quality, non-clinical, clinical	guideline on quality, preclinical and clinical aspects of gene transfer medicinal products
CHMP/410869/06	quality, non-clinical, clinical	guideline on human cell-based medicinal products
CPMP/BWP/2458/03	quality	guideline on development and manufacture of lentiviral vectors
CPMP/ICH/294/95	quality	derivation and characterisation of cell substrates used for production of biotechnological products
CPMP/308136/07	quality, non-clinical, clinical	concept paper on guidance for DNA vaccines
EMEA/CHMP/VWP/141697/2009	quality, non-cinical, clinical	quality, non-clinical and clinical aspects of live recombinant viral vectored vaccines
CHMP/GTWP/607698/08	quality, non-clinical, clinical	draft ICH considerations on oncolytic viruses
CHMP/GTWP/125459/06	non-clinical	non-clinical studies required before first clinical use of gene therapy medicinal products
EMEA/273974/05	non-clinical	non-clinical testing for inadvertent germline transmission of gene transfer vectors
CHMP/GTWP/60436/07	clinical	draft guideline on follow-up of patients administered with gene therapy medicinal products
CHMP/SWP/28367/07	clinical	strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products
CHMP/GTWP/125491/06	environmental risk assessment	scientific requirements for the environmental risk assessment of gene therapy medicinal products
ICH considerations on virus and vector shedding	non-clinical, clinical	considerations on the general principles to address virus and vector shedding
Ph. Eur. 5.14	quality	gene transfer medicinal products for human use
Ph. Eur. 5.2.3	quality	cell substrates for the production of vaccines for human use
Ph. Eur. 2.6.16	quality	test for extraneous agents in viral vaccines for human use

challenges in the process development of GTMPs are the following:

- Demonstration of consistency of the final product while allowing variability in some process steps (i.e. starting material of biological origin, variability of primary cells)
- Establishment of meaningful in-process controls, which enable the monitoring of process controls in real-time, both rapidly and quantitatively
- Process optimization, since automation is sometimes not feasible
- Demonstration of product comparability following process changes (e.g. upscale)
- Development of final product specifications that adequately confirm product safety, quality, purity and biological activity at release

For an application for manufacturing authorisation of a GTMP, information on all starting materials used for manufacturing of the active substance should be provided. This will include the products necessary for the genetic modification of human or animal cells as well as materials used in the culture and preservation of the cells [7, 8]. As some of the substances employed for product development might be used for further down-stream manufacturing (**Fig. 2**), a definition of the starting materials is provided in the new Directive 2009/120/EC [2]. In line with this, the starting materials for a viral vector are the components from which it is manufactured, i.e. plasmid-DNA used for transfection, master/working cell banks and master/working virus seed lots. Producer cell lines and virus seeds used for the manufacturing of virus are considered to be critical starting materials, and to ensure consistent quality and safety of the product over its intended life time, the preparation of a two tiered cell bank and viral seed system is advisable. Beside tests for identity and the proof of absence of adventitious agents, the source and history of the cells or virus seeds used for generation of the respective banks should be described in accordance with available guidance. The absence of low-level contaminants is tested after expansion to the limit of in vitro cultivation used for production [9, 10].

In terms of genetically modified cells, which are defined as active substance, the starting materials are those used to generate the genetic modification, i.e. the transfer vector, including the starting materials to produce it and the cells to be modified. It should be noted that full quality dossiers on the manufacture of the transfer vector in this instance will be necessary at the time of an MAA. Specific requirements for SCTMPs and tissue engineered products, as laid down in the revised Annex I Part IV and the Directive 2004/23/EC [11], must also be considered. Implementing Directive 2004/23/EC, technical requirements for the donation, procurement and testing of human tissues and cells are laid down in Directive 2006/17/EC [12], whereas technical requirements for coding, processing, preservation, storage, distribution and traceability as well as notification of serious adverse reactions and events are implemented by Directive 2006/86/EC [13]. Particularly for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures shall be tested in accordance to the revised Annex I Part IV to Directive 2001/83/EC.

In cases where the active substance consists of plasmid-DNA or genetically modified microorganisms (other than viruses), the starting materials are the plasmid, host bacteria and the master microbial cell bank. For products consisting of

a microorganism or virus, information on the genetic modification and sequence analysis (i.e. regulatory sequences, packaging signals, resistance genes), attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence, pathogenicity and characteristics of the parental strain should be provided for both clinical trial application (CTA) and MAA submission.

Like all biologically and biotechnologically manufactured active substances, product- and process-related impurities and contaminating adventitious agents should be determined quantitatively. Possible process-related impurities might originate from cell substrate (e.g. host cell DNA and proteins), cell culture reagents and additives (e.g. benzonase, BSA, antibiotics), and from the purification process (e.g. column leachables, virus deactivation residue); while examples of product related impurities might be precursor and/or degradation products (e.g. aggregates) or replication-competent viruses (RCV). In particular, the presence of possible replication-competent virus contaminants has to be analysed carefully by quantitative assays with known limits of detection and quantification.

As many GTMPs consist of, or contain, genetically modified organisms (GMOs), the potential risk of the GMO to the environment also needs to be evaluated. Therefore, an MAA for GMO-containing GTMPs must be accompanied by an environmental risk assessment (ERA) specifically performed on the basis of the information specified in Annexes III and IV of Directive 2001/18/EC [14] and in accordance with the principles of Annex II of the Directive and its supplementing Commission Decision 2002/623/EC [15] on the deliberate release of GMOs.

Non-clinical requirements for GTMPs

Regulatory standards on the non-clinical development of a human medicinal product include analyses on pharmacology, pharmacokinetics and toxicology. In the following paragraphs the non-clinical requirements summarized in the revised Annex I, Part IV to Directive 2001/83/EC [1] are illustrated. As GTMPs differ in their complexity and heterogeneity, the most important aspects are discussed generally here; these will then have to be tailored to the actual product. In general, the extent of the non-clinical package will be determined based on the risk profile of the GTMP under development.

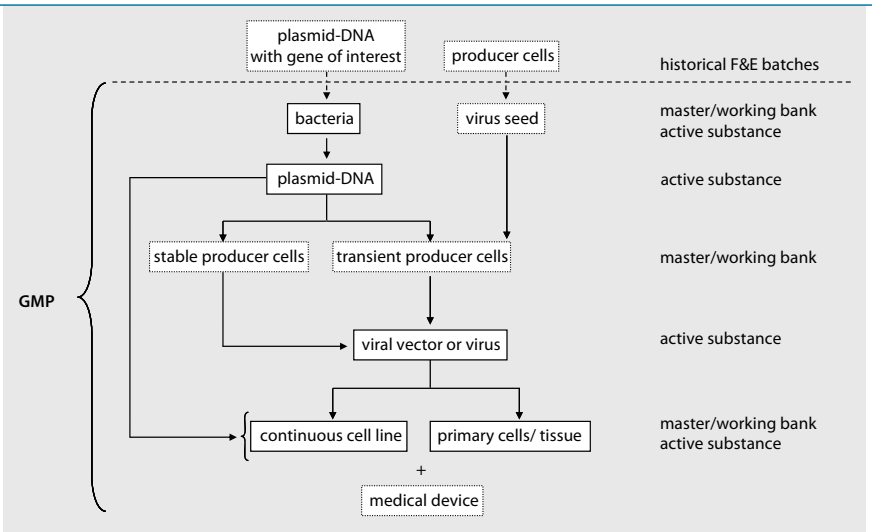

Fig. 2 ▲ Manufacturing of GTMP

Pharmacodynamic proof of concept of the therapeutic agent should be shown in vitro and, in particular, in relevant animal models. Dependent on the product, this includes analyses of the expression of the delivered gene or sequence, and on the proposed activity, and therapeutic effect of the respective product in an appropriate disease model. Where the GTMP consists of genetically modified cells, the therapeutic effects of both the recombinant sequence and the delivered cells should be determined and attributed to the respective component.

Secondary pharmacological studies might be required dependent upon the outcome of bio-distribution studies. For clinical studies, data on the duration of function of the therapeutic nucleic acid sequence should be demonstrated and the dosing regimen should be provided and justified by preclinical in vivo data. Pharmacokinetic analyses normally cover the study of the adsorption, distribution, metabolism and excretion of the active substance. Where the fate of GTMPs in the organism is under evaluation, conventional ADME studies are usually not applicable, rather a detailed analysis of the biodistribution of the GTMP including investigations on its persistence, clearance, mobilisation, and shedding should be addressed, particularly if viral vectors are used to deliver the therapeutic nucleic acid. Where the GTMP is considered 'targeted' to a specific cell or tissue type, this should be confirmed in vivo. For GTMPs consisting of a genetically modified organism, and in particular a viral vector, investigations of shedding and the risk of transmission to third parties should be provided within an environmental risk assessment [16, 17].

Bio-distribution should additionally address the risk of germ line transmission. Such studies are mandatory at the stage of an MAA for non-cellular GTMPs, unless otherwise justified [18]. Where genetically modified somatic cells are the drug product, the level and duration of expression of the therapeutic sequence and the distribution of the produced protein should be investigated in addition to the evaluation of parameters applying per se to the cells in use, such as their viability and their distribution and migration in the organism after application. Modified cells carrying the therapeutic genetic sequence should be also tested for their longevity and their capability to grow and differentiate into other cell types. If the introduced recombinant sequences are intended to induce cellular changes, i.e. for re-programming to induced pluripotent stem cells or differentiation of stem cells, the phenotype, morphology, and function of the modified cells should be examined in suitable in vivo model systems. The issue of immunogenicity of modified

Tab. 2 Possible release test of a viral vector batch

Category	Assay
Identity	- immunochemical (protein ID) or NATs (molecular ID)
Potency	- infectivity (number of infectious particles) - particles to infectious titre ratio - transgene expression - bioactivity/functionality
Purity	- RCV (e.g. replication competent Ad virus) - host cell protein - host cell DNA - residual reagents (antibiotics, benzonase, BSA) - sterility (bacterial, fungal) - adventiotious agents, mycoplasma, bacterial endotoxin
Physio-chemical characteristics	- appearance - osmolality (e.g. freezing point), pH - particle size distribution - volume - vector aggregates

human autologous cells for example, requires testing of "product-like" cells in a homologous animal model.

Normally, GTMPs do not only consist of the therapeutic nucleic acid, but also of gene delivery vehicles such as viral vectors and proteins or plasmids consisting of additional nucleic acid sequences which might be expressed in the target cell. Thus, toxicity shall be assessed on the final GTMP and testing of the active substance and excipients has to be taken into consideration. In addition, the effects of expression from nucleic acid sequences co-delivered but not intended for therapeutic function, such as virus proteins and marker or antibiotic resistance proteins should also be evaluated. In general, single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies. In cases where multiple dosing of the product is envisaged, repeated toxicity studies, reflecting the clinical dosing regimen shall be provided. The duration and depth of these studies has to be defined and justified based on the anticipated potential risk of the GTMP, i.e. in case of persistence of the vector.

An important aspect of toxicology associated with the use of GTMPs may be, dependent upon the type of product, the inadvertent immunological reaction to the recombinant gene product, or to the plasmid or viral vector delivering the respective nucleic acid sequence. Thus, immunogenicity and immunotoxicity studies with functional endpoints should be considered for GTMPs carrying genes which are known to have an effect on the immune system, such as growth factors and cytokines. In addition, evaluation of pre-existing immunity towards the vector and/or anti-viral immunity after multiple vector administration should be taken into consideration.

Evaluation of safety of the GTMP is required by extensive toxicological testing including analyses on genotoxicity, tumorigenicity, and reproductive and developmental toxicity. The need for such analyses strongly depends on the product type. Standard lifetime rodent carcinogenicity studies, for example, are not required. However, if applicable, the tumorigenic potential should be determined in relevant in in vitro/vivo models. Standard genotoxicity studies are only necessary for testing a specific impurity or a component of the delivery system. For many non-viral and viral vectors entry into the nucleus is required to permit expression of the delivered therapeutic gene(s). This introduces a risk of integration of foreign DNA into the host cell genome, in which case integration studies should be provided, unless the omission of such studies can be scientifically justified. Nevertheless, integration studies will need to be performed for GTMPs not expected to be capable of integration, if biodistribution data indicate a risk of germ line transmission. Reproductive and developmental toxicity studies might include evaluation of the effects of the GTMP on fertility and general reproduction as well as perinatal toxicity and germline transmission.

Clinical requirements for GTMPs

The challenges to the clinical development of GTMPs can arise not only due to their complexity, but also as a result of practical differences in application as compared to conventional medicinal products. Although the fundamental principles of demonstrating clinical benefits/risk still applies, as for any other medicinal product, in practice, the application of conventional approaches may need to be reconsidered, in the evaluation of pharmacokinetics, pharmacodynamics, efficacy and safety.

It should also be noted that the ATMP regulations allow post authorisation follow-up of efficacy and safety as specific requirements. The implications of this can be significant, although, with careful planning, the strategy for the long-term follow-up of safety and efficacy can be addressed adequately. The following sections highlight the challenges that are likely to be encountered during clinical development of a GTMP.

Pharmacokinetics

It is recognised that classical pharmacokinetic parameters covering absorption, distribution, metabolism and excretion may not be applicable. The following aspects should be addressed:

- Shedding studies to address the dissemination of the virus/vector through secretions and/or excreta of the patient: in general this requires an appropriate evaluation of excretion of the product. This might include, for example, testing various secreta and/or excreta, and should assist in identifying the potential for transmission to either immediate contacts or to the general environment [17].
- Bio-distribution studies: this should assist in evaluating how much of the product has reached the intended target and how widely it is distributed, and may also help in predicting any safety issues that might arise from a product reaching unintended targets. The extent of these stu-

dies will depend on the type of product used. For example, a viral vector capable of integration would require assessment of gonadal distribution to assess the possibility of vertical transmission.

- Pharmacokinetics of the product and/or the expressed proteins: if it is feasible to measure the classical parameters such as area under the curve of the product, maximal concentration and time to maximal concentration, these parameters should be studied. Alternatively, the expressed protein pharmacokinetics could be studied. The assays used should be standardised and, where possible, validated.

Pharmacodynamics

This should address the assessment of the functional expression of the administered nucleic acid sequence. The pharmacodynamic parameters that are chosen should, preferably, have some clinical relevance. While a strict correlation with clinical efficacy is not mandatory, such correlation would be helpful in the interpretation of results of clinical studies. As for pharmacokinetics, the assays used for measuring the parameters should be standardised and, where feasible, validated. A reliable and reproducible result in pharmacodynamic parameters would assist in the clinical development. It would also help to establish the mechanism of action of the product clearly.

Efficacy

The "Proof of Concept" might be desirable and sometimes necessary. Where the mechanism of action is established and the condition to be treated is common, for example diabetes mellitus, it is sensible to establish efficacy in small studies before undertaking a large confirmatory trial, which could last several months. Such a study should preferably use a homogenous patient group. While a control group may be helpful, it is not mandatory. The duration of the study could be shorter and the endpoints chosen could be surrogate markers. Depending on the size and length of the study, this kind of study might provide some additional supporting evidence to confirmatory studies.

Dose finding is one of the most important aspects of the clinical development of any product, but often done poorly. A proper dose finding study is desirable to reduce the risk of choosing the wrong dose for confirmatory trials. The following should be considered:

- Basis of the chosen dose for the confirmatory trial
- Minimum active biological effect level (MABEL)
- Dose response
- A no effect dose or minimally effective dose

It is not always possible to establish a maximum tolerated dose. The number of doses to be chosen for a dose finding study will depend on the dose response relationship to efficacy and/or pharmacodynamic parameters. While a clinical endpoint provides authenticity to a dose response relationship, sometimes this might not be possible or sensitive enough. In such instances, a surrogate endpoint in the form of a biomarker or a pharmacodynamic parameter might be acceptable, as long as the dose response relationship is clearly known or can be established. If the study is of sufficient size and quality, it will also provide valuable supporting evidence for confirmatory trials. In the absence of sound dose finding experiments, there is a risk that the chosen dose might prove to be either ineffective or unsafe when studied in a larger population. Ideally, the lowest dose that is effective should be used. It is recognised that a clinical dose finding study may not be feasible, for example where the treatment effect can only be seen in the long term. Here, appropriate non-clinical studies may be undertaken. This could be in the form of, for example, tissue uptake followed by measurement of the expression products where feasible.

The measurement of efficacy itself will depend on the disease treated and use of accepted clinically relevant endpoints. This is not likely to be different for a GT-MP; however, there are certain aspects that need to be considered as part of pre-approval efficacy assessment. These include, but are not limited to:

- Number of administrations
- Frequency of administration
- Method of administration, i.e., route and delivery. For example, if it is intralesional administration, the details of how it is administered could be specific to the product and needs justification.
- Need for surgical approach. It should be noted that any such surgical procedure could be a confounding variable, influencing the overall assessment of the product. Any surgical procedure should be clearly defined and standardised.
- Effect of concomitant therapy. This could be important where combination therapy is used as in the case of cancers and HIV infection. A pharmacodynamic interaction or a direct effect on the product itself, for example on the viral vector, should be considered. An indirect effect could also be seen where, for example, an immunosuppressive agent would further enhance the expression of viral vectors.
- Availability of training for the administration and/or surgical procedure post-approval. If these are not part of the product approval, it is conceivable that the product may be inappropriately used, leading to loss of efficacy or worsening of any harmful effects.
- In the case of combined advanced therapy products, a formal clinical trial should be conducted with the combined product as a whole that is intended for the market.

A double-blind controlled clinical trial is ideal to provide evidence of efficacy. If this is not possible, for example due to extreme rarity of the target disease, then appropriate advice should be sought from regulatory agencies early in clinical development. Appropriate measures to minimise bias should be proposed a priori in the protocol and blinded evaluation of efficacy parameters would help as would a choice of objective efficacy endpoints. While a clinical endpoint that can be directly related to efficacy is always preferable, a well-validated surrogate is also acceptable for efficacy assessment. Subjective endpoints, such as quality of life, are

usually of supportive value but not considered objective enough in most situations. Typically, more than one confirmatory trial would be expected. However, if a single pivotal trial is contemplated, the relevant guideline should be followed [19].

Safety

In addition to the usual safety evaluation that is applicable to any medicinal product, there are some unique safety concerns that should be considered and addressed as appropriate:

- Emergence of replication-competent vectors
- Emergence of new strains
- Re-assortment of existing genomic sequence
- Neoplastic proliferation due to insertional mutagenicity

The assessment of causality should be based on scientific approach and free of bias. This is particularly important when treating a serious disease where the disease could be a confounding factor. Any death or serious adverse event should be evaluated methodically. If there is a pattern of adverse events, even if causal relationship is not obvious, this should be analysed thoroughly.

Follow-up of efficacy and safety

As treatment with gene therapy could be curative, maintenance of efficacy is important. Hence follow-up of efficacy has been enshrined in the regulations. Frequency and duration of follow-up for efficacy will depend on the disease being treated, its prognosis, and the nature of the therapy, e.g. curative, preventative, palliative. [20].

Because of the unique nature of the mechanism of action, which involves genetic manipulation, a potential exists for serious long-term consequences, which may not be apparent at the time of initial marketing authorisation. The long-term safety of GTMPs is currently unknown. Therefore, follow-up of safety post-marketing is important. As for efficacy, the duration and nature of the follow-up will depend on the disease and its prognosis.

Risk factors that should be considered as part of the follow-up include, but are not limited to the:

- Potential for the development of tumours following genetic manipulation
- Effects of long lasting genetic manipulation
- Potential for vertical transmission as a consequence of distribution to the gonads if gonadal distribution has occurred during pre-clinical or clinical investigations

It is not possible to give an exhaustive list of the conditions to be evaluated for safety follow-up as unknown safety signals might become obvious when gene therapy is in widespread use.

Immunogenicity

All biological products are potentially antigenic. Immunogenicity in the host is variable and dependent on the immunogenic potential. Further, the clinical effect will be dependent on the nature of immunogenicity such as the neutralising potential. It is not uncommon for antibodies to develop following administration of biotechnology products. In many cases, the antibodies are binding rather than neutralising and tend not to have serious clinical consequences. However, in the case of gene therapy with viral vectors, pre-existing immunogenicity to common viruses might interfere with the uptake of genes of interest and also cause immunologically mediated reactions. Where a product needs to be administered repeatedly, immunogenicity might develop more specifically against the product and could affect the efficacy of repeated treatments.

Demonstration of clinical benefit of gene therapy follows the same principles as for any other medicinal product. Because of the unique characteristics of a gene therapy product and its clinical use, additional factors would need to be considered, both pre-approval and post-marketing. Follow-up of efficacy and safety should be planned for as early as possible, taking into account the vector used and the diagnosis of the target population.

International harmonisation of technical requirements for registration of pharmaceuticals for human use

Scientific guidance on the technical requirements of a dossier to support the MAA of a GTMP is available from numerous sources, as described previously, such as the European Commission and EMEA web sites, as well as web sites for National Competent Authorities. Another source of guidance is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH is a joint initiative involving both regulators and industry as equal partners in scientific and technical discussions of the testing procedures that are required to ensure and assess the safety, quality and efficacy of medicines. It is comprised of six parties (representing the EU, the USA and Japan) and three observers (World Health Organisation (WHO), Canada (represented by Health Canada) and the European Free Trade Association (EFTA), represented by Swissmedic.

The parties and observers set up expert working groups in relation to a particular topic for which guidance has been considered necessary. Guidance documents are categorised as either Quality, Safety, Efficacy or Multidisciplinary guidelines. However, for GTMP harmonisation, a discussion group (gene therapy discussion group, GTDG) has been devised, whose role is to monitor emerging scientific issues relating specifically to these medicines and pro-actively set out principles that may have a beneficial impact on the harmonisation of regulations for GTMP. To achieve this goal the GTDG group has held workshops and published (or are working on) consideration papers relating to the following topics:

- General Principles to Address the Risk of Inadvertent Germ-line Integration of Gene Therapy Vectors
- Oncolytic Viruses (http://www.ich.org/cache/html/2699-272-1.html)
- General Principles to Address Virus and Vector Shedding

These papers and further information on ICH can be found at http://www.ich.org/cache/compo/276-254-1.html.

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