ELSEVIER

Drug Discovery Today: Technologies

Vol. xxx, No. xx 2011

Editors-in-Chief
Kelvin Lam – Harvard University, USA
Henk Timmerman – Vrije Universiteit, The Netherlands

DRUG DISCOVERY TODAY TECHNOLOGIES

Innovative methods in drug regulatory sciences

On the edge of new technologies (advanced therapies, nanomedicines)☆

Spiros Vamvakas[1,*], Jorge Martinalbo[1], Ruben Pita[2], Maria Isaac[1]

[1]European Medicines Agency (EMA), Scientific Advice, Human Medicines Special Areas, 7 Westferry Circus – Canary Wharf, London E14 4HB, United Kingdom
[2]European Medicines Agency (EMA), Chemicals, Quality of Medicines, United Kingdom

Nanotechnology-based and advanced therapy medicinal products are at the cutting edge of innovation in translational drug development, potentially offering new treatment approaches for diseases with limited or no therapeutic alternatives. Their development from the laboratory to the clinic poses specific scientific and regulatory challenges, and some debate has recently arisen about the adequacy of the current EU regulatory framework for the assessment of quality, safety and efficacy of these medicinal products.

Section editors:
Bert Leufkens – Universiteit Utrecht, Utrecht, The Netherlands. Hans-Georg Eichler – European Medicines Agency, London, UK

Introduction

There is growing interest in translating the knowledge accumulated in the fields of nanotechnology, genetic engineering and stem cell research into the development of novel therapeutic approaches, with great expectations of significant advances in the diagnosis, prevention and treatment of diseases, potentially addressing currently unmet medical needs. So far, the potential of nanotechnology and Advanced Therapy Medicinal Products (ATMPs) in drug development has only been partially exploited, with a wide range of applications notably including novel therapeutic approaches, refinement of drug delivery with nanoscale systems, diagnostics, surgery/implants and regenerative medicine. Scientific challenges common to both technology platforms are derived from the gaps in current scientific knowledge about their biology, toxicology, pharmacology, as well as the complexity of their *in vivo* behaviour (e.g. biodistribution, persistence) and mechanisms of action, with properties transcending the classical pharmacological, metabolic and immunological functions.

Advanced therapies

In the European regulatory framework, ATMPs include medicinal products based on gene therapy, somatic cell therapy and tissue engineering (see Box 1 for legal definitions), prepared industrially or manufactured by a method involving an industrial process. ATMPs need to comply with the general quality, safety and efficacy requirements for marketing authorisation of medicinal products in the EU [1], but to facilitate their development and address specific issues (e.g. characterisation, traceability, and risks) dedicated legislation has been adopted [2], notably resulting in the recent creation of the multidisciplinary scientific Committee for Advanced Therapies (CAT) [3] of the EMA. The CAT delivers scientific recommendations for specific products in the frame of two optional procedures (see Table 1) and is responsible for the primary evaluation of marketing authorisation applications (MAAs) for ATMPs via the centralised procedure, together with the Committee for Medicinal Products for Human Use (CHMP), and for drafting relevant Guidance (see Links Box 2). The aim of the ATMP *Classification procedure* [4] is to confirm that the relevant scientific criteria for the ATMP definition are met, addressing questions of borderline overlaps with other

☆ The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

*Corresponding author.: S. Vamvakas (spiros.vamvakas@ema.europa.eu)

1740-6749/$ DOI: 10.1016/j.ddtec.2011.04.001

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001

Box 1. Definitions of Advanced Therapy Medicinal Products

Gene therapy medicinal products contain an active substance that contains or consist of a recombinant nucleic acid, obtained through a set of manufacturing processes aimed at the *in vivo* or *ex vivo* transfer of a gene via a delivery system known as a vector (viral or non-viral) and its subsequent expression *in vivo*, with a view to regulating, repairing, adding or deleting a genetic sequence. GTMPs are aimed to be administered to human beings, with diagnostic, prophylactic or therapeutic intention.

Somatic cell-therapy medicinal products consist of or contain cells or tissues (autologous, allogeneic or xenogeneic) whose biological characteristics have been substantially altered through manipulation or which are applied in a non-homologue manner. They are administered to humans with therapeutic, diagnostic or preventive intention, their effect is exerted through metabolic, pharmacological and immunological means, and they are not intended for the same essential function(s) in the recipient as in the donor.

Tissue-engineered products contain or consist of engineered cells or tissues of human and/or animal origin substantially manipulated (in order to achieve the biological characteristics, physiological functions or structural properties relevant for the intended function), administrated with the intention to regenerate, repair or replace a human tissue and not intended for the same essential function(s) in the recipient as in the donor. Adapted from [2]

Box 2. Links

EMA Advanced Therapies
http://www.ema.europa.eu/htms/human/advanced_therapies/intro.htm
EMA Regulatory and Scientific Guidelines related to ATMPs
http://www.ema.europa.eu/htms/human/raguidelines/advanced_therapies.htm
EMA Medicines and Emerging Science, including Nanotechnology
http://www.ema.europa.eu/htms/human/mes/introduction.htm
EMA Scientific Advice and Protocol Assistance
http://www.ema.europa.eu/htms/human/sciadvice/advice.htm
EMA Qualification of Novel Methodologies
http://www.ema.europa.eu/pdfs/human/biomarkers/7289408en.pdf
EMA Innovation Task Force
http://www.ema.europa.eu/htms/human/mes/itf.htm
EMA SME Office
http://www.ema.europa.eu/sME/sMEoverview.htm
EMA European Public Assessment Reports
http://www.ema.europa.eu/htms/human/epar/a.htm

areas such as medical devices or cell transplantation, which are regulated by different pieces of legislation. The *Certification procedure* [5] consists in the scientific evaluation of early-stage quality and non-clinical data, resulting in a certificate issued by the EMA which can prove helpful for small and medium-sized enterprises (SME) to gain financial support for the further development of a product.

Table 1. EMA activities related to ATMPs 2009–2010

	2009	2010	Total
SA and PA procedures (SAWP/CHMP/COMP)			
Scientific advice	10	9	19
Protocol assistance	8	6	14
Evaluation of MAA (CAT/CHMP)			
Submitted	3	1	4
Positive draft opinion	1	0	1
Negative draft opinion	1[a]	0	1
Withdrawals	1	1	2
Paediatric Investigation Plans (PDCO)			
CAT comments submitted	3	1	4
Classification procedure (CAT)			
Submitted	22	19	41
Adopted	12	27	39
Certification procedure (CAT)			
Submitted	1	0	1
Adopted	0	1	1

ATMP: Advanced Therapy Medicinal Product; CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; COMP: Committee for Orphan Medicinal Products; MAA: Marketing Authorisation Application; PA: Protocol Assistance; PDCO: Paediatric Committee; SA: Scientific Advice; SAWP: Scientific Advice Working Party.
[a] Application subsequently withdrawn.

Gene therapy medicinal products (*GTMPs*) aim at delivering a gene, inserted in a transfer vector, to the patient's target cells that, once modified by the GTMP, achieve a therapeutic effect through expression of a protein that is either lacking or not functional in the patient (e.g. enzyme replacement treatment for inherited monogenic diseases [6]) or modulates the pathogenetic mechanisms underlying the disease. Thus, depending on the type of vector, target cells and the mode of administration (systemic vs. local), GTMPs present an added degree of complexity, requiring successful vector delivery and gene transfer efficiency as well as achieving stable expression (with persistence of the transgene) of the gene of interest in the target cells [7]. These are crucial factors for the demonstration of clinical efficacy, which has proven to be one of the main challenges in the development of GTMPs so far. In terms of safety, insertional mutagenesis, linked with oncogenic risk particularly with the use of strong enhancers or promoters, and the environmental risk associated to shedding of genetically modified organisms (GMOs) are also of concern [8]. In addition, manufacturing hurdles encountered by GTMPs include the typically low vector titers achieved with gene transfer vectors of viral origin, currently the most frequently used, and the challenges around development of potency assays measuring expression and *in vivo* activity of the transgene.

Cell-based medicinal products (*CBMPs*) include several types of cell therapies, which show high heterogeneity due to the autologous, allogenic or xenogenic origin, the cell population type and stage of development and differentiation – for example blastocyst-derived embryonic stem cells (ESCs), mesenchymal/stromal stem cells (MSCs), tissue-specific progenitor cells or terminally differentiated cells – and the

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001

technicalities of the *in vitro* manipulation during the manufacturing process, which may include genetic modification. Human induced pluripotent stem cells (iPSCs), artificially generated by reprogramming somatic adult cells, have only emerged very recently, but their application is regarded as a potential breakthrough in regenerative medicine, because they provide the opportunity to select the genotypes of interest through genetic engineering and to be differentiated up to a specific phenotype, and the field is evolving rapidly [9,10], based on experience gained with reprogrammation and differentiation protocols in ESCs.

Tissue-engineered products have been developed for the repair of various tissue defects [11] (e.g. corneal, heart, liver, cartilage, bone and skin) with a structurally and functionally equivalent replacement tissue structure, which should ideally persist at the intended location.

Challenges in the quality development of CBMPs include the characterisation of the mixed cell populations in the starting material, viral safety, manufacturing process validation, controls and specifications of the final product (e.g. purity and potency testing). Despite the inherent difficulties, monitoring of quality consistency of CBMPs is of utmost importance because of its direct impact on clinical safety and efficacy [3,12] and guidelines for Good Manufacturing Practice (GMP) are currently under development.

Regarding the non-clinical assessment of mode of action, *in vivo* distribution and potential toxicological effects, the choice of a relevant animal model constitutes a key challenge, because the behaviour of ATMPs *in vivo*, particularly in the case of CBMPs, depends on the interaction with a specific micro-environment (receptors, ligands, cell-adhesion molecules, etc.) which may not be conserved across different species. In this respect, homologous models (i.e. using cells obtained from the model species) have been frequently investigated, despite the obvious limitation of assessing a surrogate product instead of the actual medicinal product. CBMPs pose safety challenges relating to ectopic engraftment in non-target tissues, cell de-differentiation, transformation and ultimately tumourigenicity [3], which, because of the methodological limitations of non-clinical safety assessment, has led to the adoption of a Guideline relating to the post-authorisation risk management [13]. For stem cell-based products, important safety aspects include the risk of tumour formation and the capability of pluripotent ESCs and iPSCs to form teratomas, especially if the latter occur in anatomically sensitive locations. The inherent tumourigenic potential depends on the origin, differentiation state, pluripotency or lineage commitment, extent of manipulation and specific culture conditions of the stem cells, as well as on the intended administration site/route, and could be of particular concern in the case of pluripotent or extensively *in vitro* manipulated stem cells, thus requiring careful investigation before the initial clinical use. At the level of manufacturing process development, *in vitro* assessment of genomic stability and tumourigenicity risk of the different cell subpopulations in the product should be conducted at critical stages, with particular attention to the potential impact of cell material origin (e.g. subject's age, gender, and treatment history), cell culture conditions (e.g. feeder cells, reagents) and manipulation steps. For non-clinical studies, genetically immunocompromised animal models or with humanised immune system are preferred.

With regard to the design of clinical trials, major methodological difficulties encountered by ATMPs are dose-finding (among other factors, due to significant inter-individual variability), optimisation of the mode of administration, impact of patient's gender and age in the case of stem cell-based products, limited feasibility of double-blind designs potentially biasing clinical evaluations (e.g. because of risks and ethical concerns associated with sham surgery), choice of a suitable comparator (e.g. pharmacological or surgical intervention) and of adequate efficacy variables to investigate the therapeutic effect in the intended indication, and definition of an adequate period of follow-up [3]. To maintain a stable effect, the therapeutic cell population needs to show persistent functional and/or structural integration in the patient. In some cases clinical efficacy or safety may only become apparent in the long term, thus requiring post-authorisation follow-up commitments to better characterise the benefit/risk [13].

Regulatory experience in the evaluation of ATMPs is growing, with four MAAs evaluated by the CAT and CHMP, one ATMP Certification procedure concluded successfully and more than 30 Scientific advice/Protocol assistance procedures completed, offering guidance on key scientific issues in the pharmaceutical, non-clinical and clinical development of ATMPs. The only centrally approved ATMP in the EU so far is ChondroCelect® (Tigenix NV), consisting of characterised viable autologous cartilage-forming cells expanded *ex vivo* expressing specific marker proteins. The centralised MAA for two GTMPs was withdrawn (see Links Box 2) before adoption of the CHMP opinion, namely contusugen ladenovec (Gendux Molecular Ltd.), an adenoviral vector delivering human p53 intended for treatment of head and neck cancer, and sitimagene ceradenovec (Cerepro®, Ark Therapeutics Ltd.), an adenovirus-mediated *Herpes simplex* virus-thymidine kinase gene used with subsequent administration of ganciclovir intended for treatment of high-grade glioma.

It is interesting to note that both technology platforms, ATMPs and nanotechnologies, have been recently combined with promising results, such as the use of therapeutic cells as vectors for actively targeted drug delivery by conjugation of adjuvant drug-loaded nanoparticles to the surface of CBMPs, providing sustained pseudo-autocrine stimulation to donor cells as a strategy to enhance efficacy [14].

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001

Nanotechnologies

A variety of definitions of nanotechnology and nanomedicines have been proposed in the past years, but so far there is no generally agreed upon consensus [15]. For EU regulatory purposes, nanotechnology has been defined as the production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale (ranging from the atomic level at around 0.2 nm up to around 100 nm), which often show improved and novel physical, chemical and biological properties [16]. In addition to the terminology controversy, for certain nanotech-based applications in medicine, the boundaries between medicinal product and medical device are not clear-cut. Although in most cases the nanotechnology component exerts an enabling or facilitating function, in some borderline products the nanomaterial itself plays a pivotal role in the therapeutic effect (e.g. iron oxide nanoparticles to induce hyperthermia after intratumoural injection, MagForce®). So far there is no specific regulatory framework in the EU concerning the use of nanoscale or nanostructured materials in medicine, and under the current pharmaceutical legislation (Article 1.2(b) of [1]) the primary mechanism of action determines the regulatory classification.

Most nanomedicine developments so far have been oriented towards refined or 'smart' nanoscale drug delivery systems (NDDS) [17] (e.g. via preferential organ/tissue distribution, transport across biological barriers, targeted intracellular drug delivery) and improvement of biopharmaceutical properties of active substances (e.g. particle size reduction to increase bioavailability, multifunctional chemical structures) [18]. More recently, the application of nanotechnology has focused on novel *in vivo* diagnostics and imaging (e.g. integrated implantable sensory nanoelectronic multifunctional platforms) and *in vivo* 'theranostics' with both therapeutic and diagnostic functionalities [19]. In the field of diagnostics, relevant examples of commercialised nanotechnology-based products include lateral flow immunoassays based on colloidal gold nanoparticles used in rapid pregnancy tests, and contrast agents for magnetic resonance imaging (MRI) consisting of superparamagnetic iron oxide nanoparticles (SPIONs e.g. ferumoxsil, Gastromark®). Another notable application, in the field of regenerative medicine, has been the development of improved implants based on nanostructure scaffolds for tissue replacement. Oncology has so far been the therapeutic area capturing most attention [20,21]. The first generation of anticancer nanomedicines (mostly based on liposomal formulations and protein-polymer conjugates) is already in widespread use, and cutting-edge research is carried out [22] on innovative approaches such as nanocells that sequentially deliver different agents to the tumour [23] or targeted delivery of short interference RNA (siRNA) nanoparticles to human tumours [24].

Examples of 'established' NDDS include bi- or polyphasic systems for which the dispersed phase is in the nanometre size region (e.g. liposomes, polymerosomes and block copolymer micelles), polymer therapeutics, inorganic nanoparticles, nanospheres, nanocrystals and dendrimers, whereas other less established technologies include fullerenes, nanotubes, quantum dots and nanostructured biomaterials. Liposomes are lipid-based vesicles with a bilayered membrane structure, with great versatility as pharmaceutical carriers (e.g. targeted immunoliposomes with surface-attached ligands and pegylated long-circulating liposomes) [25]. Factors controlling their *in vivo* fate [26] include particle size, morphology, surface charge, rigidity of the bilayer and route of administration. Polymer therapeutics constitute another important group of nanomedicines [27,28], notably including polymeric drugs [29] and polymer–protein conjugates such as pegylated proteins [30] in which nanoscale polyethylene-glycol (PEG) strings are covalently linked to the active protein moiety (e.g. growth factor, antibody) to reduce its immunogenicity and prolong its plasma half-life.

Key differences between nanotechnology-based and 'conventional' approaches may have a direct impact on the assessment of quality, safety and efficacy of medicinal products. The nanoscale particle size range results in very large surface-area-to-volume ratios, allowing nanocarriers to be coated with a great number and/or variety of molecules, and thus enabling high surface loading with therapeutic agents or simultaneous inclusion of various types of cargo [31]. In general terms, encapsulation or integration of the active substance in nanoparticles enhances its stability and dissolution rate. Furthermore, other unique properties determined by the nanoscale size include the ability to cross biological barriers and the passive targeting of tissues enabling, for example accumulation at tumour sites due to the enhanced permeability and retention effect (tumours typically present poor lymphatic drainage and highly porous vasculature, which facilitates diffusion and accumulation of the nanomaterial in the tumour matrix). The ability to influence these biological properties by virtue of modifying critical attributes such as particle geometry (notably size and shape, which by themselves can influence cellular functions [32]) or surface coating may ultimately result in the improvement of solubility, potency, targeting selectivity, therapeutic index, or the reduction of immunogenicity, but at the same time novel risks may arise (e.g. related to blood–brain barrier passage). In biological environments, nanoparticles behave as functionalised particles, attracting proteins and lipids in slow exchange that constitute a dynamic nanobiointerface termed 'corona' [33], which defines its biological responses and significantly influences targeting selectivity. Recent research efforts have aimed at coating nanoparticle surfaces with biorecognition molecules capable of targeting nanoparticles to specific tissues or cell types [34]. As a consequence of their size, shape and surface characteristics, nanoparticles are recognised and taken up by cells through active processes

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001

(e.g. endocytosis, pinocytosis and phagocytosis) and selectively transported via intracellular trafficking (e.g. endosomal and lysosomal pathways) to specific subcellular locations. Therefore, if appropriate 'uptake signals' are associated with nanoparticles of purpose-built geometry, these biological phenomena can be exploited for designing subcellular targeting strategies (e.g. lysosomotropic NDDS) [35]. The possibility offered by NDDS of refining selective targeting may in the future prove as a fundamental advantage *versus* 'conventional' drugs, for which delivery is typically based on physicochemical parameters such as molecule size and partition into hydrophobic solvents.

From a quality point of view, the control of materials in the nanoscale size range requires novel approaches to chemistry, manufacturing and controls (CMC), and often presents greater scientific and technical challenges compared to 'conventional' formulations. Critical factors related to the pharmaceutical development of nanotechnology-based medicinal products include the (often insufficient) knowledge about molecular mechanisms underlying the *in vivo* behaviour of nanoparticles in biological systems, the definition of the most relevant parameters predictive of product performance *in vivo* and stability, together with the adequate validation of characterisation methods to control the reproducibility of these critical attributes [36] (e.g. particle size specifications, shape, surface characteristics including area, chemistry, porosity, patterning and coating parameters).

Despite some speculation about potential nanomaterial-associated toxicity based on recent non-clinical data, so far evidence in humans is inconclusive. Because there is not a valid paradigm for the identification of potential hazards associated with the use of nanomaterials in humans, risk assessment is performed on a case-by-case basis. The potential for extrapolation of non-clinical safety results to humans is limited by the complexity [37] of the *in vivo* behaviour of nanoparticles (e.g. corona-mediated cell-adhesion, interaction with subcellular structures, and particle aggregation in biological media), their physicochemical/mechanical properties potentially resulting in toxic responses (e.g. size and shape of nanotubes) and pharmacokinetic (PK) parameters (active substance release rate, biodistribution, tissue accumulation, biodegradability and clearance). Recent reports of immunotoxicological effects of nanomaterials [38] suggest the need for a systematic non-clinical safety evaluation of potential immunological effects. In these respects, further investigations and adaptation of current methodology and concepts (e.g. surface area or particle number might potentially be more appropriate dose metrics for the purpose of toxicological evaluation than the traditional dose expression in terms of mass) may be warranted.

With regard to clinical safety and efficacy, no specific guidance is available for the development of nanotechnology-based medicinal products, which have so far been assessed on a case-by-case basis within the general regulatory framework. However, the need for specific requirements to account for the particular pharmacodynamic (PD) and PK properties of nanomedicines remains the subject of intense debate, in particular in relation to the assessment of quality and PK/PD comparability between nanoformulations.

So far EMA has reviewed under the existing regulatory framework around 20 MAAs for nanomedicines (Table 2) and more than 40 requests for scientific advice, the latter mainly focusing on areas such as CMC, demonstration of quality and PK/PD comparability and clinical therapeutic equivalence.

Table 2. Examples of centrally authorised nanotechnology-based medicinal products in the EU

Trade name/API – INN	Platform/technology	Indication	MAH	Approval[a]
Liposomes				
Caelyx® doxorubicin hydrochloride	API in sterically stabilised (Stealth®) pegylated liposomes, to increase blood circulation (long-acting) and reduce cardiotoxicity	Multiple myeloma, ovarian neoplasms, breast neoplasms, Kaposi sarcoma	Janssen-Cilag International N.V.	21/06/1996
Myocet® doxorubicin	Liposome-encapsulated doxorubicin–citrate complex to reduce cardiac toxicity and to increase tumour tissue distribution	Breast neoplasms	Cephalon Europe	13/07/2000
Mepact® mifamurtide	Fully synthetic analogue of a component of *Mycobacterium* sp. cell wall encapsulated in multilamellar liposomes to facilitate activation of macrophages	High-grade resectable non-metastatic osteosarcoma	IDM PHARMA SAS	06/03/2009
DepoCyte® cytarabine	Multivesicular liposomes with unique structure of multiple non-concentric aqueous chambers (DepoFoam®)	Meningeal neoplasms	Pacira Limited	11/07/2001
Visudyne® verteporfin	Liposomal formulation of semisynthetic mixture of porphyrins	Degenerative myopia, age-related macular degeneration	Novartis Europharm Ltd.	27/07/2000

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001

Table 2 (*Continued*)

Trade name/API – INN	Platform/technology	Indication	MAH	Approval[a]
Nanoparticles				
Abraxane® paclitaxel	Solvent-free colloidal suspension of albumin-bound spherical nanoparticles to increase water solubility	Metastatic breast cancer	Abraxis BioSciences Ltd.	11/01/2008
Emend® aprepitant	Colloidal dispersion of nanocrystals to increase bioavailability (wet milling method)	Nausea and vomiting	Merck Sharp & Dohme Ltd.	11/11/2003
Rapamune® sirolimus	API particles in nanocrystal colloidal nanodispersion stabilised with poloxamer to reduce particle size for increased stability and bioavailability	Prophylaxis of organ rejection in renal transplant	Wyeth Europa Ltd.	13/03/2001
Micelles				
Taxotere® docetaxel	Micellar system using Tween 80	Non-small-cell lung cancer, prostate cancer, head and neck cancer, gastric cancer, breast cancer	Aventis Pharma S.A.	27/11/1995
Docetaxel Teva® docetaxel			Teva Pharma B.V.	26/01/2010
Docetaxel Winthrop® docetaxel			Sanofi-Aventis Pharma S.A.	20/04/2007
Docefrez® docetaxel			Sun Pharmaceutical Industries Europe B.V.	10/05/2010
Polymer-conjugates				
PegIntron® peginterferon alfa-2b	Pegylated derivative of interferon alfa-2b (IntronA®)	Chronic hepatitis C	SP Europe	25/05/2000
Somavert® pegvisomant	Pegylated recombinant analogue of the human growth hormone	Acromegaly	Pfizer Limited	13/11/2002
Cimzia® certolizumab pegol	Pegylated recombinant, humanised antibody Fab′ fragment against tumour necrosis factor alpha (TNFα)	Rheumatoid arthritis	UCB Pharma SA	01/10/2009
Pegasys® peginterferon alfa-2a	Pegylated derivative of interferon alfa-2a (Roferon-A®)	Chronic hepatitis B, chronic hepatitis C	Roche Registration Ltd.	20/06/2002
Neulasta® pegfilgrastim	Pegylated granulocyte-colony-stimulating factor (G-CSF), derivative of filgrastim (Neupogen®)	Neutropenia	Amgen Europe B.V.	22/08/2002
Mircera® methoxy polyethylene glycol-epoetin beta	Pegylated erythropoetin beta	Anemia, chronic kidney failure	Roche Registration Ltd.	20/07/2007
Macugen® pegaptanib	Pegylated modified oligonucleotide	Wet macular degeneration	Pfizer Limited	31/01/2006
Antibody–drug conjugates				
Zevalin® ibritumomab tiuxetan	Yttrium-90 radiolabelled anti-CD20 monoclonal antibody	Follicular lymphoma, follicular B-cell non-Hodgkin's lymphoma	Bayer Schering Pharma AG	16/01/2004
Gas dispersions				
SonoVue® sulphur hexafluoride	Sulphur hexafluoride gas as 'microbubbles' dispersion	Contrast agent for echocardiography and ultrasonography	Bracco International BV	26/03/2001

Further examples of nanomedicines authorised in Member States of the EU, but not through the centralised procedure,) include a pegylated derivative of L-asparaginase (Oncaspar®, Medac), glatiramer acetate (Copaxone®, Teva Pharmaceuticals), liposomal formulations of amphotericin B (Ambisome®, Gilead) and daunorubicin (DaunoXome®, Gilead), and sevelamer (Renagel®, Genzyme).

API: Active Pharmaceutical Ingredient; INN: International Non-Proprietary Name; MAH: Marketing Authorisation Holder.

[a] Date of issue of Market Authorisation valid throughout the EU.

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001

Conclusions

Several recent EMA initiatives in the field of emerging technologies have aimed at identifying the scientific and regulatory challenges and promoting dialogue and convergence of criteria. Worthy of note are the two recent international workshops on stem cell-based therapies [39] and nanotechnologies [40], creating a multidisciplinary platform to facilitate dialogue and transfer of up-to-date scientific knowledge between regulators, academia, industry, patients and other stakeholders. Furthermore, an *ad hoc* expert group including experts from academia and the EU regulatory network has been recently established to address challenging scientific questions in the development of nanomedicines.

In view of the scientific and regulatory challenges posed by the inherent complexity and idiosyncrasies of ATMPs and nanotechnology-based medicinal products, the applicability of well-established methodology to assess standards of quality, safety and efficacy has been questioned by some stakeholders. The CHMP Reflection paper on nanotechnology-based medicinal products [16] highlights the paradigm for the assessment of nanomedicines based on established principles of benefit/risk analysis, rather than solely on the basis of the technology *per se*. The need for a multidisciplinary science-based approach and for flexibility in accepting new development models and adapting testing methodology on a case-by-case basis is, however, acknowledged.

From a regulatory point of view, it is foreseen that several ATMPs and nanotechnology-based applications could span the boundaries between medicinal products and medical devices, thus generating some debate about the classification of converging technologies and the requirements for marketing authorisation. One of the tasks of the EMA is the provision of scientific advice on the conduct of the various tests necessary to demonstrate the quality, safety and efficacy of individual medicinal products. There are different pathways to engage in dialogue with regulators during drug development (see Fig. 1 and Links Box 2), including the Innovation Task Force (ITF) briefing meetings in particular regarding the classification of borderline products, the CAT Classification and Certification procedures for ATMPs, and the CHMP Scientific Advice/Protocol Assistance procedures coordinated by the Scientific Advice Working Party (SAWP) and related to the prospective pharmaceutical, non-clinical and clinical development of a particular product, with involvement of the CAT in the case of requests concerning ATMPs (see Table 1), of the Committee for Orphan Medicinal Products (COMP) for questions on the demonstration of significant benefit for medicinal products with Orphan Drug Designation intended for the treatment of rare diseases, and, as required, of CHMP Working Parties with specific expertise in the issues covered by the advice request. More recently, to address the scientific challenges associated with the validation of novel methods and technologies, a new SAWP/CHMP

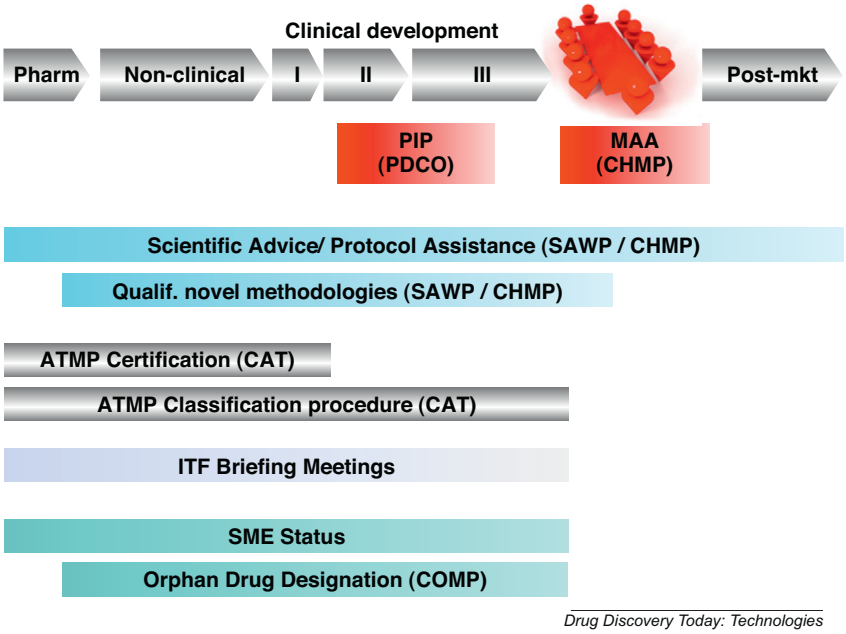

Figure 1. EMA involvement at different stages of drug development. ATMP: Advanced Therapy Medicinal Product; CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; COMP: Committee for Orphan Medicinal Products; ITF: Innovation Task Force; MAA: Marketing Authorisation Application; PIP: Paediatric Investigation Plan; SAWP: Scientific Advice Working Party; SME: Small and Medium-sized Enterprise.

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001

Qualification of novel methodologies for drug development procedure has been set up.

Conflict of interest

The authors declare no conflicts of interest.

References

1 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. *Off. J. Eur. Union* 28.11.2001 (*as amended*, Consolidated version: 05/10/2009)
2 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Off. J. Eur. Union* 10.12.2007, L324/121-L324/137 (2007)
3 Committee for Advanced Therapies, (2010) Challenges with advanced therapy medicinal products and how to meet them. *Nat. Rev. Drug Discov.* 9, 195–201
4 Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. *Off. J. Eur. Union* 15.9.2009, L242/3-L242/12 (2009)
5 Commission Regulation (EC) No. 668/2009 of 24 July 2009 implementing Regulation (EC) No. 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises. *Off. J. Eur. Union* 25.07.2009, L194/7-L194/10 (2009)
6 Aiuti, A. *et al.* (2009) Gene therapy for immunodeficiency due to adenosine deaminase deficiency. *N. Engl. J. Med.* 360, 447–458
7 Kohn, D.B. *et al.* (2009) Gene therapy fulfilling its promise. *N. Engl. J. Med.* 360, 518–521
8 Hacein-Bey-Abina, S. *et al.* (2003) LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. *Science* 302, 415–419
9 Yamanaka, S. *et al.* (2010) Nuclear reprogramming to a pluripotent state by three approaches. *Nature* 465, 704–712
10 Lengner, C.J. (2010) iPS cell technology in regenerative medicine. *Ann. N Y Acad. Sci.* 38–44
11 MacNeil, S. (2007) Progress and opportunities for tissue-engineered skin. *Nature* 445, 874–880
12 European Medicines Agency (2009). *Draft* Reflection paper on stem cell-based medicinal products. EMA/CAT/571134/2009. *EMA website*. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/07/WC500094124.pdf
13 European Medicines Agency (2008). Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products. EMEA/149995/2008. *EMA website*. http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf
14 Stephan, M.T. *et al.* (2010) Therapeutic cell engineering with surface-conjugated synthetic nanoparticles. *Nat. Med.* 16, 1035–1041
15 Wagner, V. *et al.* (2006) The emerging nanomedicine landscape. *Nat. Biotechnol.* 24, 1211–1217
16 European Medicines Agency (2006). CHMP Reflection paper on nanotechnology-based medicinal products for human use. EMEA/CHMP/79769/2006. *EMA website*. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069728.pdf
17 Farokhzad, O.C. *et al.* (2009) Impact of nanotechnology on drug delivery. *ACS Nano.* 3, 16–20
18 Petros, R.A. *et al.* (2010) Strategies in the design of nanoparticles for therapeutic applications. *Nat. Rev. Drug Discov.* 9, 615–627
19 Xie, J. *et al.* (2010) Nanoparticle-based theranostic agents. *Adv. Drug Deliv. Rev.* 62, 1064–1079
20 Davis, M.E. *et al.* (2008) Nanoparticle therapeutics: an emerging treatment modality for cancer. *Nat. Rev. Drug Discov.* 7, 771–782
21 Jain, R.K. *et al.* (2010) Delivering nanomedicine to solid tumors. *Nat. Rev. Clin. Oncol.* 7, 653–664
22 Scheinberg, D.A. *et al.* (2010) Conscripts of the infinite armada: systemic cancer therapy using nanomaterials. *Nat. Rev. Clin. Oncol.* 7, 266–276
23 Sengupta, S. *et al.* (2005) Temporal targeting of tumour cells and neovasculature with a nanoscale delivery system. *Nature* 436, 568–572
24 Davis, M.E. *et al.* (2010) Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. *Nature* 464, 1067–1070
25 Torchilin, V.P. (2005) Recent advances with liposomes as pharmaceutical carriers. *Nat. Rev. Drug Discov.* 4, 145–160
26 Samad, A. *et al.* (2007) Liposomal drug delivery systems: an update review. *Curr. Drug Deliv.* 4, 297–305
27 Duncan, R. (2006) Polymer conjugates as anticancer nanomedicines. *Nat. Rev. Cancer* 6, 688–701
28 Duncan, R. (2003) The dawning era of polymer therapeutics. *Nat. Rev. Drug Discov.* 2, 347–360
29 Dhal, P.K. *et al.* (2009) Functional polymers as therapeutic agents: concept to market place. *Adv. Drug Del. Rev.* 61, 1121–1130
30 Veronese, F.M. and Bossard, M., eds) (2009) *Series-Milestones in Drug Therapy: PEGylated Protein Drugs: Basic Science and Clinical Applications*, Birkhauser Verlag
31 Kim, B.Y. *et al.* (2010) Nanomedicine. *N. Engl. J. Med.* 363, 2434–2443
32 Jiang, W. *et al.* (2008) Nanoparticle-mediated cellular response is size-dependent. *Nat. Nanotechnol.* 3, 145–150
33 Cedervall, T. *et al.* (2007) Understanding the nanoparticle protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proc. Natl. Acad. Sci. U. S. A.* 104, 2050–2055
34 Lynch, I. *et al.* (2009) Protein–nanoparticle interactions: what does the cell see? *Nat. Nanotechnol.* 4, 546–547
35 Rajendran, L. *et al.* (2010) Subcellular targeting strategies for drug design and delivery. *Nat. Rev. Drug Discov.* 9, 29–42
36 European Medicines Agency (2010). Draft Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems (non-polymeric surfactants). EMA/CHMP/QWP/574767/2010. *EMA website*. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/10/WC500097751.pdf
37 Gaspar, R. *et al.* (2009) Polymeric carriers: preclinical safety and the regulatory implications for design and development of polymer therapeutics. *Adv. Drug Del. Rev.* 61, 1220–1231
38 Dobrovolskaia, M.A. *et al.* (2007) Immunological properties of engineered nanomaterials. *Nat. Nanotech.* 2, 469–478
39 European Medicines Agency (2010). Summary report on the EMA workshop on stem cell-based therapies. EMA/319294/2010. *EMA website*. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/07/WC500094124.pdf
40 European Medicines Agency (2010). Summary report – 1st international workshop on nanomedicines. EMA/538503/2010. *EMA website*. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500098380.pdf

Please cite this article in press as: Vamvakas, S. et al. On the edge of new technologies (advanced therapies, nanomedicines), Drug Discov Today: Technol (2011), doi:10.1016/j.ddtec.2011.04.001