

# Advances and challenges in the development of drug delivery systems – A European perspective

## Authors

**Sanjay Jain**, Principal Consultant – Biologics; **Michael Edwards**, Regulatory Consultant; **Louise Spencer**, Regulatory Affairs Executive; Envigo, Ely, Cambridgeshire, UK.

## Keywords

Drug delivery system (DDS); Delivery system (DS); Microparticles; Orphan medicinal product (OMP); Diagnostic; Nanotechnology; Nanomedicine; Nanosystem; Nanosimilar; Guideline; European Medicines Agency (EMA); EU; US FDA; International Council on Harmonisation (ICH); Marketing authorisation application (MAA); Dossier; Pharmacovigilance (PV); Risk management plan (RMP); Rare disease; Medicinal product; Solubilisation; Stabilisation; Passive and active targeting.

## Abstract

Research and development of drug delivery systems (DDS) has grown rapidly in recent years. DDS-based agents have shown vastly superior therapeutic applications compared with their free or native counterparts for treatment of a diverse range of diseases. A global overview of the rapidly expanding field of DDS is provided. In addition, delivery systems (DS) have also been successfully used for diagnostic and theranostic (merging therapeutic and diagnostic capabilities into a single system) applications. According to the nature of the system developed, there are likely to be regulatory challenges in demonstrating adequate quality, safety and efficacy of the final product. While product-specific guidance may be available in some instances, a case-by-case approach will be needed to determine the most suitable data package (dossier) for each product. The existing relevant EU guidance is discussed.

## Introduction

Drug delivery systems (DDS) are engineered technologies used for the targeted delivery and/or controlled and prolonged release of therapeutic agents.<sup>1</sup> The search for new drug delivery approaches and new modes of action is a rapidly developing field. Modes of drug delivery have changed in the past few decades and the future looks set to provide even more therapeutic advances. DDS can be developed to target common and rare diseases; both come with their challenges and opportunities, which are explored in this article. In the EU, new DDS may be eligible for expedited approval processes, depending on the therapeutic area and if they are shown to address an unmet medical need in the target disease population.

A large number of small molecule drugs (eg, aspirin) are associated with non-specific action, toxicity, efficacy only at high concentrations, a narrow therapeutic index, and a short half-life. On the other hand,

peptide (eg, glucagon-like peptide) and protein (eg, erythropoietin) drugs are potent, specific in action and less toxic. Unfortunately, the optimal use of peptides and proteins is often compromised by limits inherent to their molecular arrangement. Depending on their structures, injected peptides and proteins can be degraded by plasma enzymes, excreted through the kidneys, removed by the reticulo-endothelial system (RES), and complexed with pre-existing antibodies before optimal action is achieved.<sup>2</sup> Pharmaceutical DDS have demonstrated the ability to reduce or overcome shortcomings associated with small molecule, protein and peptide drugs used for various diseases and applications. In addition, delivery systems (DS) also hold promise for delivery of diagnostic and theranostic agents.<sup>3–6</sup>

## Construction, opportunities and applications

Medication can be administered in a variety of ways, and designing new DDS has the potential to enhance the use of existing medicines. Finding a suitable carrier for a drug is important to ensure it is released at the correct location within the body; moreover, the use of DDS may allow the use of drugs which were previously regarded as unsafe.

Humans have sophisticated structures and mechanisms that allow compartmentalisation to be controlled in a regulated fashion. Understanding of these biological barriers (eg, blood brain barrier (BBB)) strengthens the rational design of DDS. Administering drugs locally rather than systemically is a common way to reduce side-effects and drug toxicity. The advantages of novel DDS include improved performance in a variety of dosage forms – for example, improved therapeutic action due to alteration in pharmacokinetic (PK) and pharmacodynamic (PD) parameters across various barriers in the body by passive or active targeting, and reduced toxicity with increased patient compliance.<sup>4–6</sup>

A wide range of pharmaceutical DDS have been investigated, which can be categorised in several classes including surfactant/lipid/vesicle based (eg, liposomes, niosomes, emulsions), polymer based (eg, dendrimers, polyethylene glycol (PEG) conjugated drugs, microsponges, cyclodextrins), virus based (eg, virosomes), protein based (eg, antibody drug conjugates (ADCs)), nanocomplexes and other systems (eg, metal nanoparticles, quantum dots (QDs), carbon nanotubes).

The passive or targeted (including sustained or controlled release) therapeutic and theranostic applications of DDS for various diseases and disorders include examples such as nanoparticles to deliver drugs directly into tumour cells; entrapment of anthracyclines into liposomes to significantly reduce cardiotoxicity; conjugation of PEG to erythropoietin to improve its stability, PK and PD properties, and reduce immunogenicity for treatment of various blood disorders; and brentuximab vedotin (ADC) for treatment of patients with classical Hodgkin lymphoma.<sup>3–6</sup> Further, DDS have been involved in facilitating the delivery of peptides by various routes (eg, oral and pulmonary), and offer key benefits through the ability of DDS to incorporate and protect vaccine antigens from rapid degradation, combined with their potential to effectively deliver antigens to appropriate cells within the immune system.<sup>5</sup>

Challenges with gene and small interfering ribonucleic acid (siRNA) therapy include low internalisation, targeting and stability of therapeutics. Polymer based nanoparticles (eg, chitosan nanoparticles) may improve transfection efficiency and decrease cytotoxicity.<sup>7</sup>

Some nanoparticles (eg, QDs), have been successfully utilised in various diagnostic/imaging techniques and may be used for fluorescence resonance energy transfer (FRET)-based analysis and magnetic resonance imaging (MRI). Conventional MRI contrast agents are being superseded by novel systems (eg, dendrimers).<sup>8</sup> Table 1 outlines several systems which have been investigated, and provides examples of marketed or advanced developmental products.

### Regulatory challenges and solutions in DDS development

Regulatory challenges and solutions associated with developing DDS include classification; chemistry, manufacturing and controls (CMC); nonclinical safety; clinical studies and post-marketing surveillance:

- **Classification:** DDS can pose challenges regarding their classification for authorisation by regulatory agencies, particularly with respect to nanosystems (including nanomedicines) and nanotechnology. A medicine usually acts through a pharmacological, immunological, or metabolic action,<sup>9</sup> whereas a medical device generally fulfils its principal mode of action by physical or chemical means.<sup>10,11</sup> Where the mechanism of action of a product incorporates elements of both, it may be difficult to discern the primary mechanism and thus whether the product should be viewed as a medicine or a medical device; although the claims presented for the product are also an important factor.<sup>9</sup> A case-by-case approach should therefore be adopted by regulators.<sup>12</sup> Where such determinations are made at a national level, a classification of a product as a device in one EU member state does not preclude another from determining it to be a medicine.<sup>11</sup>
- **CMC:** For a DDS where the product will be authorised as a medicine, the product would be expected to satisfy the same standards of quality, safety and efficacy as required of any other authorised medicine. From a manufacturing standpoint, the possible route of administration for a drug in a specific patient population will affect the presentation and formulation of the drug product. Equally, the nature of the delivery system developed presents challenges in terms of satisfying requirements for the control of drug product. Examples include scaling up of manufacture; identifying appropriate methodologies for characterisation (eg, of nanoparticles by laser diffraction, light scattering, X-ray diffraction, etc); predicting performance of the product *in vivo* (and providing validated predictive characterisation techniques for regulatory agencies); establishing acceptable stability data; and determination of quality aspects for finished product specifications which are critical for manufacture and clinical effect, to ensure choice of the most appropriate specification.<sup>12</sup> Some reflection papers have been published by the European Medicines Agency (EMA) specifically for nanomedicines, eg, surface coatings and issues regarding parenteral administration of coated nanomedicine products,<sup>13</sup> and on the development of block copolymer micelle medicinal products.<sup>14</sup> If production of a DDS involves “nanosize” manufacturing techniques, these processes are likely to be complex and involve considerable expertise.

Products to which PEG has been attached to introduce desired properties (PEGylation), such as PEGylated interferon- $\alpha$  2a or 2b (Pegasys®, Hoffman-La Roche; and PegIntron®, Schering-Plough, respectively) represent additional examples where thorough characterisation of the drug product is required, to determine the

number of PEG strands attached to the protein, specific sites of conjugation, descriptions of individual isomers and their relative activity (as certain positional isomers may display greater biological activity), and the stability and immunogenicity of the conjugates.

- **Nonclinical safety:** Where a novel DDS is being developed to target a rare or “orphan” condition, nonclinical investigations may be complicated by a lack of understanding of both disease aetiology and associated molecular mechanisms, in addition to the rarity of animal models.<sup>15</sup> More broadly, the nature of the delivery system will entail consideration of safety assessments such as biodistribution (and the effect of physico-chemical properties, eg, <100 nm nanoparticles can enter cells, <35 nm nanoparticles can pass the BBB), cell distribution, effects on immune system function (including potential for hypersensitivity, immunogenicity, and immunomodulation) and requirements/methodology for genotoxicity testing.<sup>12</sup> Nanotechnology-derived products can modulate immune function in biological systems – for example, carbon nanotubes have been reported to increase cytokine release and induce cyclooxygenase-2 production in macrophages in *in vitro* studies,<sup>16</sup> and a titanium dioxide fibre structure with a length exceeding 15  $\mu$ m constituted a particle capable of eliciting an inflammatory reaction in alveolar macrophages in murine *in vitro* and *in vivo* studies.<sup>17</sup> There is also potential for nanotechnology products to produce cytotoxicity or alter gene expression.<sup>18</sup> A case-by-case approach is likely to be necessary to determine what nonclinical testing is appropriate for a given product, as informed by relevant current guidance (eg, International Council on Harmonisation (ICH) guidance on immunotoxicity studies for human pharmaceuticals)<sup>19</sup> and any product-specific guidance (such as the reflection paper published by the EMA on data requirements for intravenous (IV) iron-based nano-colloidal products developed with reference to an innovator).<sup>20</sup> Developing suitable *in vitro* models to mimic the *in vivo* system also presents a difficult task, as factors such as route of administration, product formulation, and cell-surface interactions must be considered when evaluating safety.<sup>12</sup> Regarding selection of animal models for nonclinical safety studies, the minipig (eg, the Göttingen minipig) may represent a viable alternative for a non-rodent species.<sup>21</sup>
- **Clinical studies and post-marketing surveillance:** Regarding clinical development of DDS, technologies which are intended to target orphan conditions will be affected by limited medical knowledge of the disease pathology (particularly in terms of key opinion leaders (KOLs) and specialist treatment centres), and the necessarily limited numbers of patients available to participate in clinical studies,<sup>15</sup> which may need specialised treatment centres. Indeed, such centres may be the only setting in which a product can be used when authorised, and the agent is likely to be associated with a high treatment cost. Broader considerations for DDS development include availability and applicability of clinical guidance to novel technologies, although more product-specific guidance is likely to become available over time (eg, the EMA has published a reflection paper on data requirements for IV liposomal products developed with reference to an innovator;<sup>22</sup> challenges regarding demonstration of comparability of similar versions to an existing product (“biosimilars”, “nanosimilars”, “biosuperiors/biobetters”, or “follow-on products”), particularly concerning bioequivalence studies; the fate of non-biodegradable materials in the body and long-term consequences (eg, persistence of non-biodegradable silica/gold nanoparticles) and the importance

**Table 1: An overview of delivery systems with examples of EU-marketed or advanced developmental products.<sup>3-6</sup>**

Delivery system (type of application)	Description	Example	Regulatory guidance*
Crystalline systems (therapeutic)	Nanocrystals for substituting less optimal bulk materials; water-insoluble drug without any added excipient	Rapamune®, Sirolimus nanocrystals based tablet <i>Indication:</i> Graft rejection, kidney transplantation	EMA/CHMP/79769/2006, Reflection paper on nanotechnology-based medicinal products for human use
Polymer therapeutic conjugates, polymer-small molecule drug conjugates and polymer based systems (therapeutic)	PEGylation makes a hydrophilic cloud around molecules and increases their hydrodynamic radius, decreases proteolysis and renal excretion, improves stability, extends PK and PD <i>in vivo</i>	Cimzia®, PEGylated antibody – Fab fragment of a humanised anti-tumour necrosis factor (TNF)- $\alpha$ antibody for Crohn's disease and rheumatoid arthritis <i>Indications:</i> <ul style="list-style-type: none"> <li>Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy</li> <li>Treatment of adults with moderately to severely active rheumatoid arthritis</li> <li>Treatment of adult patients with active psoriatic arthritis</li> <li>Treatment of adults with active ankylosing spondylitis</li> </ul>	EMA/325027/2013, Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products
Emulsions (therapeutic)	Oil-in-water or water-in-oil emulsions tailor-made to encapsulate drugs	Neoral®, cyclosporine nanoemulsion in soft capsules <i>Indication:</i> Prophylaxis of organ rejection following organ transplant	EMA/CHMP/79769/2006, Reflection paper on nanotechnology-based medicinal products for human use
Lipid based systems (eg, liposomes; therapeutic)	Used for passive and active targeting of bioactives. Small unilamellar vesicles (SUVs) work by the enhanced permeation and retention (EPR) effect, targeting the RES, and multilamellar vesicles (MLVs) are the liposomes of choice for sustained release	AmBisome®, amphotericin B liposome suspension <i>Indications:</i> <ul style="list-style-type: none"> <li>Severe systemic and/or deep fungal infections</li> <li>Visceral leishmaniasis</li> </ul>	EMA/CHMP/806058/2009/Rev. 02, Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product
Antibody drug conjugates (theranostic)	A toxin is conjugated to a monoclonal antibody (mAb) using a linker	Adcetris®, ADC (brentuximab vedotin) <i>Indication:</i> Treatment of patients with classical Hodgkin lymphoma	ADCs are drugs as well as biologic molecules. This class is covered by multiple ICH guidelines
Virus based system (eg, virosomes; therapeutic)	Evolved over the years owing to their capability to insert genetic information into mammalian host cells	Epaxal®, inactivated hepatitis A virus <i>Indication:</i> Vaccine against hepatitis A virus	EMA/CHMP/79769/2006, Reflection paper on nanotechnology-based medicinal products for human use
Nanocomplex	Complexation	Ferrlecit®, sodium ferric gluconate solution <i>Indication:</i> Iron deficiency anaemia	EMA/CHMP/79769/2006, Reflection paper on nanotechnology-based medicinal products for human use
Non-ionic surfactant based system (eg, niosomes; therapeutic)	Uncharged single-chain surfactants with the incorporation of cholesterol/other amphiphilic molecules	These carriers have been investigated for delivery of hydrophilic as well as lipophilic drugs	EMA/325027/2013, Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products

**Table 1 (cont'd): An overview of delivery systems with examples of EU-marketed or advanced developmental products.<sup>3-6</sup>**

Delivery system (type of application)	Description	Example (approval)	Regulatory guidance*
Metal-based nanoparticles (therapeutic; can also be used for diagnostic and theranostic applications)	Used for targeting of bioactives, drug discovery, bioassays, and imaging applications owing to surface functionalisation (eg, using sugars)	Feraheme®, carbohydrate-coated, superparamagnetic iron oxide nanoparticle. <i>Indications:</i> treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD)	EMA/CHMP/SWP/620008/2012, Reflection paper on the data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product
Transdermal drug delivery (TDD; therapeutic)	Non-invasive delivery of medications through the skin surface	Sancuso®, granisetron-releasing TDD (patch) <i>Indications:</i> Prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy	EMA/CHMP/QWP/608924/2014, Guideline on quality of transdermal patches
Quantum dot (diagnostic)	Semiconducting materials which consist of a semiconductor core (CdSe), coated by a shell (eg, ZnS) to improve optical properties, and a cap providing enhanced solubility in aqueous buffers	Product under development	EMA/325027/2013, Reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products
Dendrimer (diagnostic; can also be used for therapeutic and theranostic applications)	Compartmentalised chemical polymers, contain a central core, from which these molecules radiate in branching form; to create an internal cavity in addition to a sphere of end groups	Stratus® CS acute care diagnostic system (Siemens) Dendrimer-coupled antibody reagents have been utilised in the Stratus CS system, an automated clinical analyser	EMA/CHMP/79769/2006, Reflection paper on nanotechnology-based medicinal products for human use
Carbon nanotube (diagnostic).	Hexagonal networks of carbon atoms forming a layer of graphite rolled up into a cylinder.	Product under development.	–

\*EMA or ICH quality, safety, efficacy and multi-disciplinary (including product-specific) guidelines are also applicable for the development of DS.

of consulting with both regulators (through national/regional scientific advice procedures) and clinicians concerning design and conduct of clinical studies.<sup>12</sup> Post-marketing, pharmacovigilance (PV) and risk management plans (RMPs) for new products with novel DDS may need to focus on areas of potential concern such as biodegradability/bioaccumulation, immunogenicity, tumourigenicity, and pro-inflammatory effects. For example, Omontys® (peginesatide), a PEGylated erythropoiesis-stimulating agent, was subject to a voluntary recall in the US in 2013, and subsequently discontinued, following post-marketing reports of serious hypersensitivity reactions (anaphylaxis) which were fatal in some cases.<sup>23</sup>

The potential health risks associated with such systems (eg, unpredictable safety issues, environmental issues, final disposition of the product inside/outside the body) are elements that need to be further investigated and comprehensively regulated.<sup>24</sup>

### Marketing authorisation application and commercialisation for DDS

If the DDS is categorised as a medicine, marketing authorisation applications (MAAs) may be eligible for special review procedures, according to the region. In the EU, the centralised procedure is obligatory for some products, depending on the therapeutic area

or nature of the therapeutic, thus an application for a DDS MA may have to be submitted using this mechanism. Applications under the centralised procedure may be eligible for accelerated assessment (in a maximum of 150 days), conditional marketing authorisation (incomplete assessment with strict obligations to provide data within a specified timeframe), or authorisation under exceptional circumstances (authorisation where rarity of the condition or other considerations preclude presentation of a full dossier). The EMA's "adaptive pathways" approach (formerly known as adaptive licensing) seeks to provide timely access for patients to new medicines, and envisages either an initial approval in a well-defined patient subgroup with a high medical need, or a planned early regulatory approval.<sup>25</sup> The EMA has also introduced its priority medicines scheme (PRIME), the aim of which is to optimise development and accelerate the assessment of medicines that are of major public health interest, and where the EMA will offer early and enhanced scientific and regulatory support to eligible products. On a national level, the UK's early access to medicines scheme (EAMS) enables sponsors to provide medicines to patients with life-threatening or seriously debilitating conditions, where the product does not yet have an MA and there is an obvious unmet medical need.<sup>26</sup> Benefit–risk assessment of authorisations for DDS used for orphan conditions presents particular challenges for both sponsors



or applicants and regulators, as the patient populations may be comparatively small, there are often no comparator medications, and evidence is usually limited.<sup>27</sup> Ongoing benefit–risk assessment could be provided by integrating post-launch activities for an authorised DDS (eg, PV and risk management programmes).

Like biosimilars, nanosimilars or follow-on products will bring their own challenges, and as yet no formal guidance document has been issued by the EMA regarding the evidence needed to show comparability between the originator and a nanosimilar.<sup>28</sup>

If a DDS is classed as an orphan medicinal product (OMP), regional incentives are associated with this designation, including market exclusivity awarded to an authorised orphan therapy (in the EU, ten years' market exclusivity is awarded for the product, and prevents a similar product receiving an MA for the same indication unless certain derogations are satisfied) and scientific advice (for OMPs, this is referred to as protocol assistance in the EU and is available at reduced rates).

The International Organisation for Standardisation (ISO)'s Technical Specification (TS) 13830:2013: "Nanotechnologies – Guidance on voluntary labelling for consumer products containing manufactured nano-objects" intends to "provide a framework to facilitate a harmonised approach for the voluntary provision of labelling that may or may not exhibit or impart nanoscale phenomena".<sup>6</sup>

In the EU, many nanomedicines have been authorised (eg, nanoparticle albumin-bound paclitaxel, Abraxane®, an injectable formulation of paclitaxel used to treat breast cancer, lung cancer and pancreatic cancer; liposomes, microscopic fatty structures containing the active substance such as Caelyx® (doxorubicin), Mepact® (mifamurtide) and Myocet® (doxorubicin); nanoscale particles of active substance, such as Emend® (aprepitant) indicated for postoperative nausea and vomiting, and Rapamune® (sirolimus) for graft rejection).<sup>29</sup> Nanosystems are currently being investigated in clinical studies and attention must be given to potential nanosimilars, and the likely need for new regulatory frameworks for the evaluation of these,<sup>28</sup> which could involve adopting the regulatory approach established for biosimilars. Currently, nanosystems are regulated within a conventional regulatory framework. However, additional expert evaluations are necessary to confirm the benefit–risk assessment. In the EU, the Committee for Medicinal Products for Human Use (CHMP) has established a multidisciplinary expert group on nanomedicines and drafted a series of reflection papers to develop guidance within this area.

### Summary and future outlook

The rationale for the development of DDS includes factors such as superior versions of existing drugs, improved patient compliance, improved performance of healthcare systems, and improved quality of life for patients. DDS represent a prospect for achieving refined targeting, and have potential as carriers for spatial and temporal delivery of various agents in disease therapeutics as well as diagnostics.<sup>6</sup>

DDS development should focus on understanding the nature of the system and thus appropriate characterisation of quality, establishing a suitable nonclinical safety package for the system, and conducting appropriate clinical studies for the target condition in the relevant patient population following consultation with clinicians/KOLs. Equally, the relevant regulatory authorities should be consulted and involved, and kept updated throughout development (eg, through scientific advice/protocol assistance), as the final data set supporting an application for authorisation must be acceptable to the granting body.

There has been considerable demand for the rapid development of appropriate DS to address unmet medical needs, especially for rare diseases. Scientific societies, industries and government organisations are collaborating to realise the potential of these technologies, which are likely to transform the industry from a "blockbuster drug" model to "personalised medicine" across the globe.<sup>30</sup>

The EMA has created the Innovation Task Force (ITF) to ensure EMA-wide coordination of scientific and regulatory competence in the field of emerging technologies, and to provide an environment for early discussion with applicants on regulatory, scientific or other developmental issues that may arise.<sup>31</sup>

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