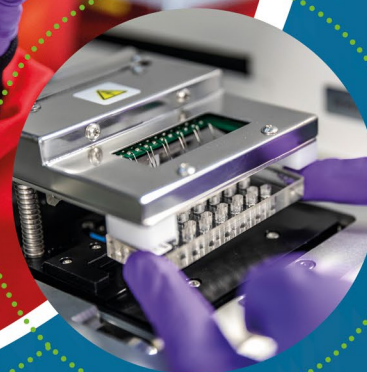


Proposed definition of 'complex medicine': identifying technologies requiring innovation and support

Medicines Discovery Catapult



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1 | Executive summary

In a quest to address novel and previously intractable targets, drug discovery is undergoing a rapid transition from traditional small molecule and antibody approaches to a more diverse range of therapeutic modalities, including RNA therapeutics and antibody-drug conjugates. These exciting new approaches raise challenges as well as opportunities, with a critical need for development of novel drug delivery systems and for advanced analytical methods.

Medicines Discovery Catapult has engaged and worked with a wave of new UK SMEs focused on the advancement of proprietary delivery technologies and small-and medium-sized enterprises (SMEs) has also witnessed the diversification in the portfolio of established therapeutic companies. There is enormous diversity in the field of 'complex medicines', yet there are areas of commonality in the requirement for: (i) advanced characterisation capability, and (ii) enabling drug delivery technologies. Medicines Discovery Catapult has worked with SEDA Pharmaceutical Development Services to bring clarity to the scope of the term 'complex medicines'. This is in the context of focusing the capability build required to support such developments based on a commonality of technical requirements. SEDA's expertise in formulation and pharmaceutical development, its client base of companies in the field and its extensive large pharma experience mean that it is well placed to deliver this report.

No formal, consensus definition for 'complex medicine' exists and the term is used to cover a broad field.

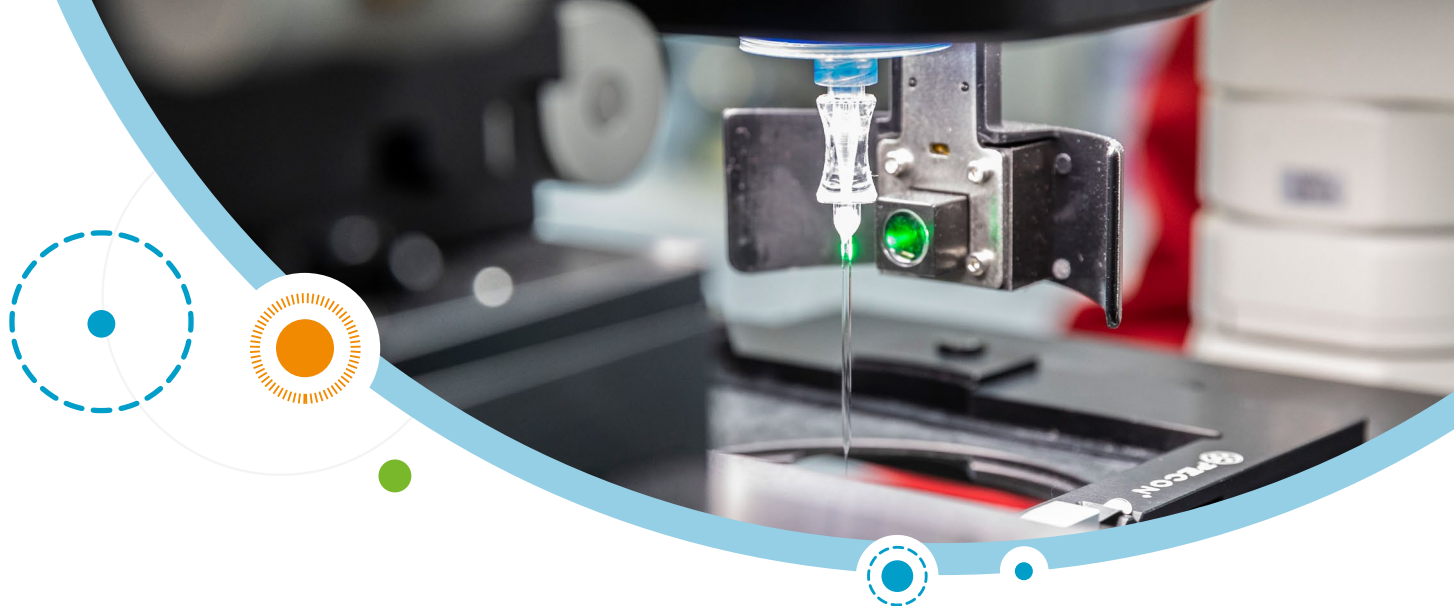
Regulatory authorities recognise an increased difficulty in demonstrating product 'sameness' or generic equivalence to the reference listed drug for certain types of medicine, due to complexities in their identification and characterisation.

From a regulatory perspective, complex medicines broadly include all biologics plus a subset of 'small molecules' termed 'complex products' or 'non-biological complex drugs'. Additionally, antibody drug conjugates (ADCs), being a combination of both biological and small molecule components, would also be considered complex medicines.

Chemically Synthesised nucleic acids - for example, short-interfering RNA (siRNA), messenger RNA (mRNA) and antisense oligonucleotides (ASOs) - are neither biological products nor traditional small molecules (which are typically under

900 g/mol). They are considered chemical drugs, and are regulated at the US Food and Drug Administration (FDA) by the Center for Drug Evaluation and Research (CDER), or as New Chemical Entities (NCEs) by the European Medicines Agency (EMA). If however they are promoter-driven or vector-based, they are considered biologics and are regulated by the CBER in the USA, or are viewed as Gene therapy medicinal products (GTMPs) in Europe.

'Complex products' can be subdivided into complex active pharmaceutical ingredients (APIs), complex routes of delivery and complex dosage forms/formulations, with certain medicines falling under one or more categories. Drug-device combinations and other products with complex approval pathways - for example, solid oral dosage forms for opiate abuse - are also identified by the FDA as complex but they are considered less relevant within the scope of this document.



From the regulators’ broad umbrella view of complex drug products (incorporating biologicals, non-biological complex drugs or NBCDs and hybrids of the two), the Medicines Discovery Catapult postulates that the specific technologies that would benefit from innovation and support include but are not limited to any biological or non-biological drug that falls under one or more of these categories:

Complex APIs	Drug-dendrimer conjugates, glatiramoids, polymeric compounds, antibody drug conjugates, oligonucleotide conjugates, N acetylgalactosamine (GalNAc)-siRNA conjugates.
Complex dosage forms/formulations	Nanomedicines such as liposomes, polymeric/solid-lipid/inorganic nanoparticles, polymersomes, micelles, nanocrystals, colloids, microbubbles, other carriers (chitosan-based carriers for example), albumin-bound agents, extracellular vesicles (exosomes, microvesicles), extended release injectables.
Complex routes of delivery	Products with a non-systemic site of delivery, including intratumoural, targeted therapies.

Unless included under one or more of the above categories, the following are examples of medicines not considered to be within scope (not an exhaustive list):

• Naked siRNA
• ASOs
• Monoclonal antibodies/nanobodies
• Proteins/peptides
• Vaccines
• Drug-device combinations
• Medical devices
• Advanced therapy medicinal products, including gene therapy medicines such as clustered regularly interspaced short-palindromic repeats (CRISPR) associated protein 9 (CRISPR Cas9) gene editing, somatic-cell therapy medicines and tissue-engineered medicines (except those formulated in complex drug delivery systems)

In conclusion, the proposed definition of a complex medicine is:

“A complex medicine is one that requires the application of novel technologies for the delivery and targeting of drugs, through the modification of the active pharmaceutical ingredient (drug-dendrimer complexes for example) or of the formulation (liposomes for example) and/or through novel routes of delivery (intratumoural delivery for example).”

2 | Introduction

This document outlines Medicines Discovery Catapult's proposed definition for 'complex medicine', and identifies specific technologies requiring innovation and support within this definition.

With the ever-increasing diversity of modalities used to treat disease, and the reducing 'drugability' of targets, drug delivery technology is having to become more complex to maximise safety and efficacy, ensure adequate exposure in the target tissue and tailor product performance to patient need and to the properties of the molecule and target.

A review of the literature and of regulatory guidance documents revealed no consensus view or formal definition for 'complex medicine' and the term is used to cover a broad field of drug delivery technologies.

Regulatory authorities recognise an increased difficulty in demonstrating product 'sameness' or generic equivalence to the reference listed drug for certain types of medicine, due to the complexities in their identification and characterisation. From the broad, umbrella categorisation of complex medicines used by regulators, the Medicines Discovery Catapult has narrowed the definition, and explored the rationale for product types that would benefit from inclusion within this new scope.

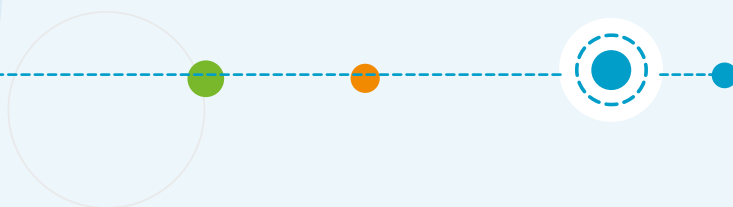
Regulatory perspective on complex medicines

Generics

A generic drug is a drug product that is comparable to a brand/reference listed drug product in dosage, form, strength, route of administration, quality and performance characteristics, and intended use. The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act) created an abbreviated mechanism for the approval of generic copies of all drugs that had been originally approved after 1962. It states that preclinical and clinical testing does not have to be repeated for generics if they can demonstrate bioequivalence. That is, they must demonstrate: (i) that the rate and extent of absorption do not show significant differences from the listed drug, or (ii) the extent of absorption does not show a significant difference, and any difference in the rate is intentional or not medically significant. Generic versions of small drug molecules receive marketing authorisation when they are considered to be both pharmaceutically equivalent and bioequivalent to the reference (innovator) product.

Biologicals

Biological products include a wide range of products, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapeutics, tissues, and recombinant therapeutic proteins. Based on the US Food and Drug Administration (FDA) position on products approved under Biologics License Application (BLA) (FDA, 2020a), the therapeutic biological products include monoclonal antibodies, cytokines, growth factors, enzymes, immunomodulators and thrombolytics, proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors), and other non-vaccine therapeutic immunotherapies. While most small molecules are chemically synthesised and their structure is known, most biologicals are complex mixtures that are not easily identified or characterised (FDA, 2018). To date, it has not been possible to develop generic versions of biologicals due to their complex manufacturing requirements and the difficulty in defining their exact composition. The FDA requires manufacturers to submit a proposed product for approval as a biosimilar drug or an interchangeable drug, rather than as a generic equivalent. As such, all biologicals would be considered 'complex medicines' from a regulatory standpoint.





Non-biological complex drugs

A subgroup of drugs termed non-biological complex drugs (NBCDs) was defined in 2010 (Schellekens, 2011). Like biologicals, NBCDs consist of different, though closely related structures that cannot be fully quantitated, characterised or described by physicochemical analytical tools. It is also often unknown which structural elements might impact the therapeutic performance. The composition, quality and in vivo performance of NBCDs are highly dependent on manufacturing processes and the controls on both the active ingredient and the formulation (Crommelin and others, 2014). The complex nature of NBCDs means that minute variations in the manufacturing process can substantially change the composition and performance of the final products, and this poses a challenge for the development of regulatory guidelines. Examples of NBCDs include nanomedicines, such as liposomes, polymeric micelles, glatiramoids, iron-carbohydrate complexes and nanocrystals, and dry powder inhalers (Generics and Biosimilars Initiative, 2017). The establishment of equivalence – pharmaceutical equivalence and/or bioequivalence – is recognised as a major challenge for NBCDs (de Vlieger and others, 2019a). Specific examples of NBCDs are described in further detail below (under ‘Specific technology examples’). Most suspensions in the nanoscale size range (for example, liposomes, emulsions and micelles, and polymeric, metallic and solid lipid nanoparticles) are NBCDs. These colloidal suspension types of NBCD clearly consist of two parts: a complex formulation and an easy-to-characterise, often small-molecule active pharmaceutical ingredient (API). NBCDs are not recognised as a distinct category of medicine, so no formal regulatory pathway has been defined for their approval (Klein and others, 2019). The NBCD Working Group has been convened by Lygature to support the development of NBCDs.

Complex drugs

As part of the FDA’s generic drug user fee amendments (GDUFA II), the regulator committed to develop a programme to assist abbreviated new drug applications (ANDAs) for complex products (primarily aimed at non-biological products) (FDA, 2020b). Under GDUFA II (Lionberger, 2019), complex drugs are defined as:

- 1

Products with complex active ingredients (for example, peptides, polymeric compounds, complex mixtures of active pharmaceutical ingredients, naturally sourced ingredients); complex formulations (for example, liposomes, colloids); complex routes of delivery (for example, locally acting drugs such as dermatological products, and complex ophthalmological and otic products that are formulated as suspensions, emulsions or gels); or complex dosage forms (for example, transdermals, metered dose inhalers, extended-release injectables).
- 2

Complex drug-device combination products (for example, auto-injectors, metered dose inhalers).
- 3

Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

Figure 1 has been produced based on the definition presented in FDA guidance (FDA, 2020b, in accordance with GDUFA II) and slides presented by the FDA (Zhang, 2020).

1	Complex active pharmaceutical Ingredient (API)	<ul style="list-style-type: none">Any drug product containing a complex API regardless of administration routes and dosage forms, such as peptides, polymeric compounds, complex mixtures of APIs.e.g. Conjugated estrogen tablet, glatiramer acetate injection.
2	Complex routes of delivery	<ul style="list-style-type: none">Any non-solution drug product with a non-systemic site of action, such as topical ophthalmic, local gastrointestinal (GI) action.e.g. cyclosporine emulsion, acyclovir cream.
3	Complex dosage forms/ formulations	<ul style="list-style-type: none">Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation such as liposomes, colloids.e.g. doxorubicin HCl liposomes, leuprolide acetate for depot suspension.
4	Complex drug-device combinations	<ul style="list-style-type: none">Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labelled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption, such as auto-injectors, metered dose inhalers.e.g. epinephrine injection (autoinjector).
5	Other products	<ul style="list-style-type: none">Other products where complexity or uncertainty concerning the approval pathway or possible approach would benefit from early scientific engagement, such as solid oral opioid drug products for deterrence of drug abuse.e.g. hydrocodone bitartrate ER tablet.

Figure 1: Classification of complex products
Adapted from Zhang (2020) and FDA (2020b)

Since the FDA produced Figure 1 in specific relation to generic drug products, it may be assumed that it is concerned primarily with ‘small’ drugs – that is, non-biologicals. There could feasibly be some overlap in categorisation, in that a complex API may also be delivered via a complex route of administration.

Nucleic acids

Nucleic acids – for example, short-interfering RNA (siRNA), messenger RNA (mRNA) and antisense oligonucleotides (ASOs) – are neither biologicals nor traditional small molecules (which are typically under 900 g/mol) but are approved under the new drug application (NDA) process rather than BLA. They are considered chemical drugs, and are regulated at the FDA by the CDER, or as NCEs by the EMA. If however they are promoter-driven or vector-based, they are considered biologics and are regulated by the CBER (FDA) or are viewed as GTMPs (EMA).

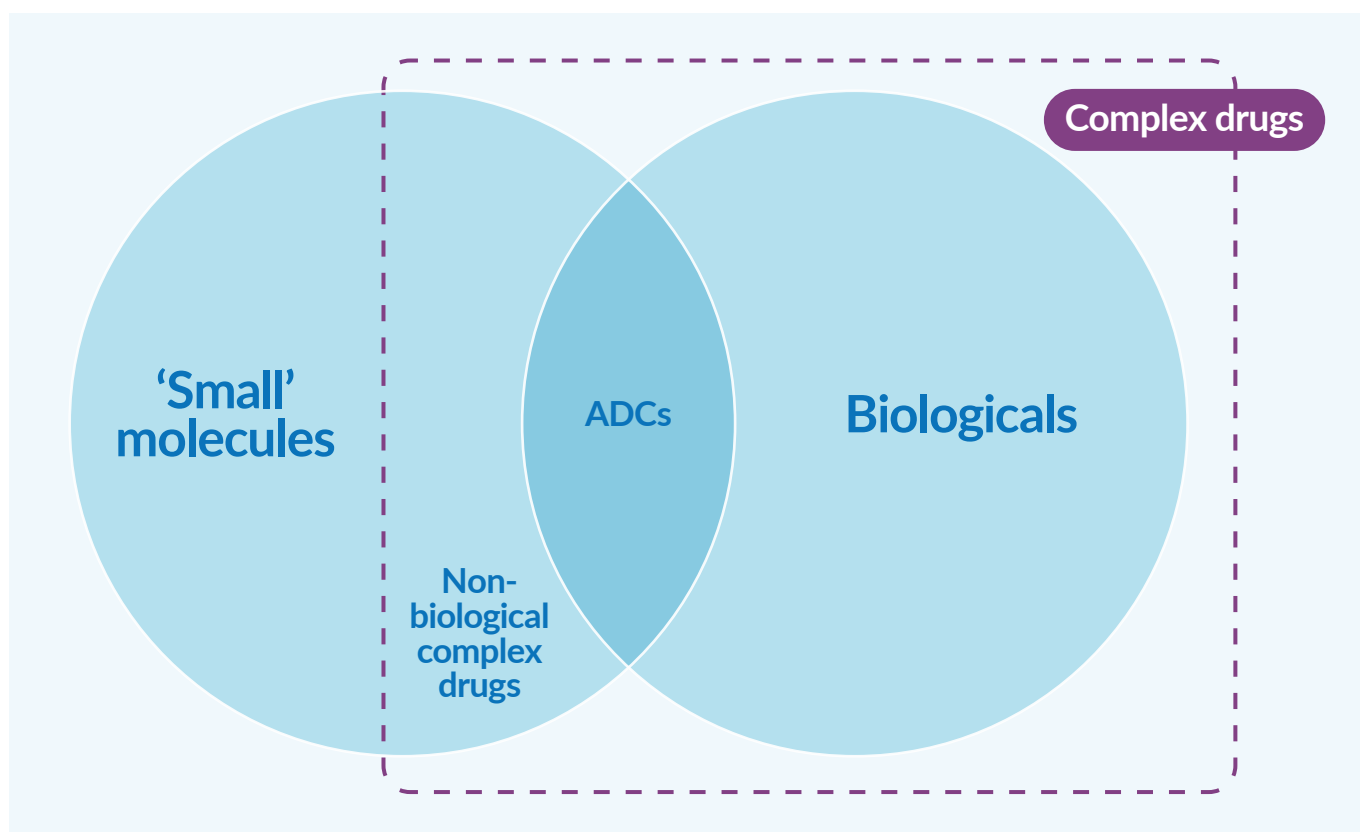
Nanomedicines

The FDA has not established regulatory definitions of 'nanotechnology', 'nanomaterial', 'nanoscale' or related terms. These terms are commonly used in relation to the engineering (deliberate manipulation, manufacture or selection) of materials that have at least one dimension in the size range from about 1 nanometre (nm) to 100 nm. The National Nanotechnology Initiative Program, for example, defines nanotechnology with sizes "between approximately 1 and 100 nanometres, where unique phenomena enable novel applications" (National Science and Technology Council, 2014). Various published definitions

mention other factors such as function, shape, charge, the ratio of surface area to volume and other physical or chemical properties (FDA, 2014). Draft nanomedicines guidance was issued by the FDA (2017) but it does not apply to biological products composed of proteins, cells, viruses, nucleic acids or other biological materials that naturally occur at particle sizes ranging up to sizes ranging up to 1 micrometre (1,000 nm), such as gene therapy or vaccine products – unless also present in the product is a material that has been deliberately manipulated to have dimensions from 1 to 100 nm or to exhibit dimension-dependent properties or phenomena up to 1 micrometre. (This may be present, for example, as a carrier or an inactive ingredient.)

Others

Some drugs fall between the biological and non-biological categories. Antibody-drug conjugates, for example, are a combination of both a biological and a small molecule. Classification as biological or non-biological varies around the globe (examples treated differently include low molecular weight heparins and albumin-bound nanoparticles) (de Vlieger and others, 2019b).



Summary

In summary, from a regulatory standpoint, complex products broadly include all biologicals, any product that contains a complex API, is administered via a complex route of delivery, is considered a complex dosage form/formulation, is a complex drug-device combination, or other product whose approval pathway is considered complex or uncertain, plus a subset of non-biologicals termed NBCDs and ADCs. This is illustrated schematically in Figure 2. Yet the Medicines Discovery Catapult considers this definition too broad. The following further explores the specific technologies included within each category and discusses the merits of including them within a proposed Medicines Discovery Catapult definition of 'complex medicines'.

ADCs = antibody drug conjugates

Figure 2: How regulatory bodies classify complex drugs

3 | Refinement of the definition of complex medicines

While it is appropriate in a regulatory setting to separate biologicals and non-biologicals (partly driven by organisational structure), the Medicines Discovery Catapult is free from such constraints.

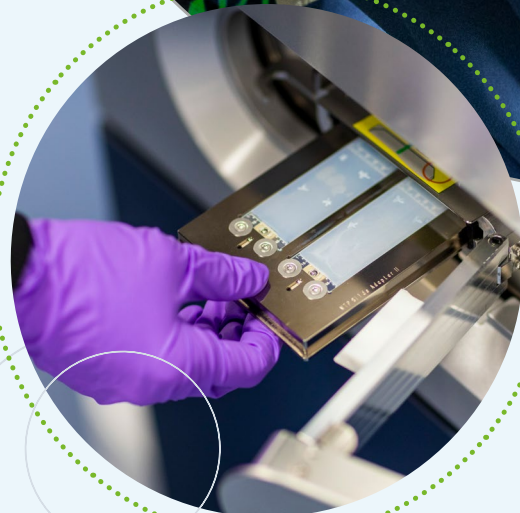
As such, it is appropriate that both biologicals and non-biologicals are included where appropriate. We would propose broadening the FDA 'small' molecule-focused classification of complex drugs to also include biologicals if certain other criteria are met. Within the complex drugs classification seen in Figure 1, we propose excluding categories 4 and 5 (complex drug-device combination products and other products). Within category 1, we propose refining the term complex API to reflect agents (biological or non-biological) that are chemically conjugated to a targeting moiety to intentionally alter the biodistribution of the naked drug and target to a specific tissue. In contrast to the regulatory framework where all biologicals are termed 'complex', a biological product would thus be considered within scope only if conjugated to a targeting moiety, delivered via a complex route or in a complex dosage form. This is to avoid the automatic inclusion of biologicals such as monoclonal antibodies, recombinant peptides/proteins and vaccines, which can often be delivered in a simple solution formulation for systemic activity.

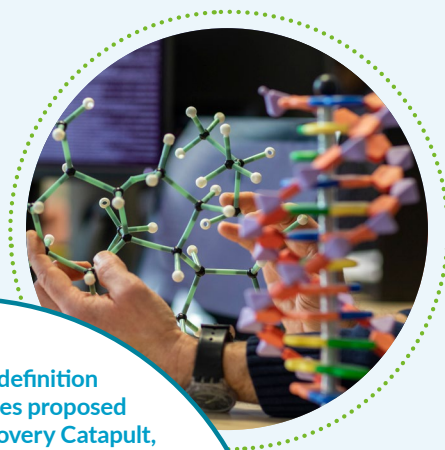
Traditional small molecules (typically under 900 g/mol), if administered via a standard formulation via a standard route – simple intravenous solution, for example, or a drug blend in a capsule for oral administration – would be considered out of scope. Traditional small molecules may move within scope if they are in some way conjugated to a targeting moiety (making them a complex API), delivered via a complex route or in a complex dosage form.

Nucleic acids – for example, siRNA, mRNA, self-amplifying RNA (saRNA), ASOs and synthetic proteins/peptides are neither biologicals nor traditional small molecules, and would be excluded if delivered in a simple solution formulation via a traditional route of administration. Again, nucleic acids would move within scope if conjugated – N acetylgalactosamine (GalNAc)-siRNA conjugates for delivery to the liver for example – or if delivered in a complex dosage form (encapsulated into lipid nanoparticles for example) or via a complex route.

Products administered via a complex route of delivery should also be considered within scope, such as those administered via a non-standard route for targeting to a particular tissue (ASOs administered via intratumoural injection for example).

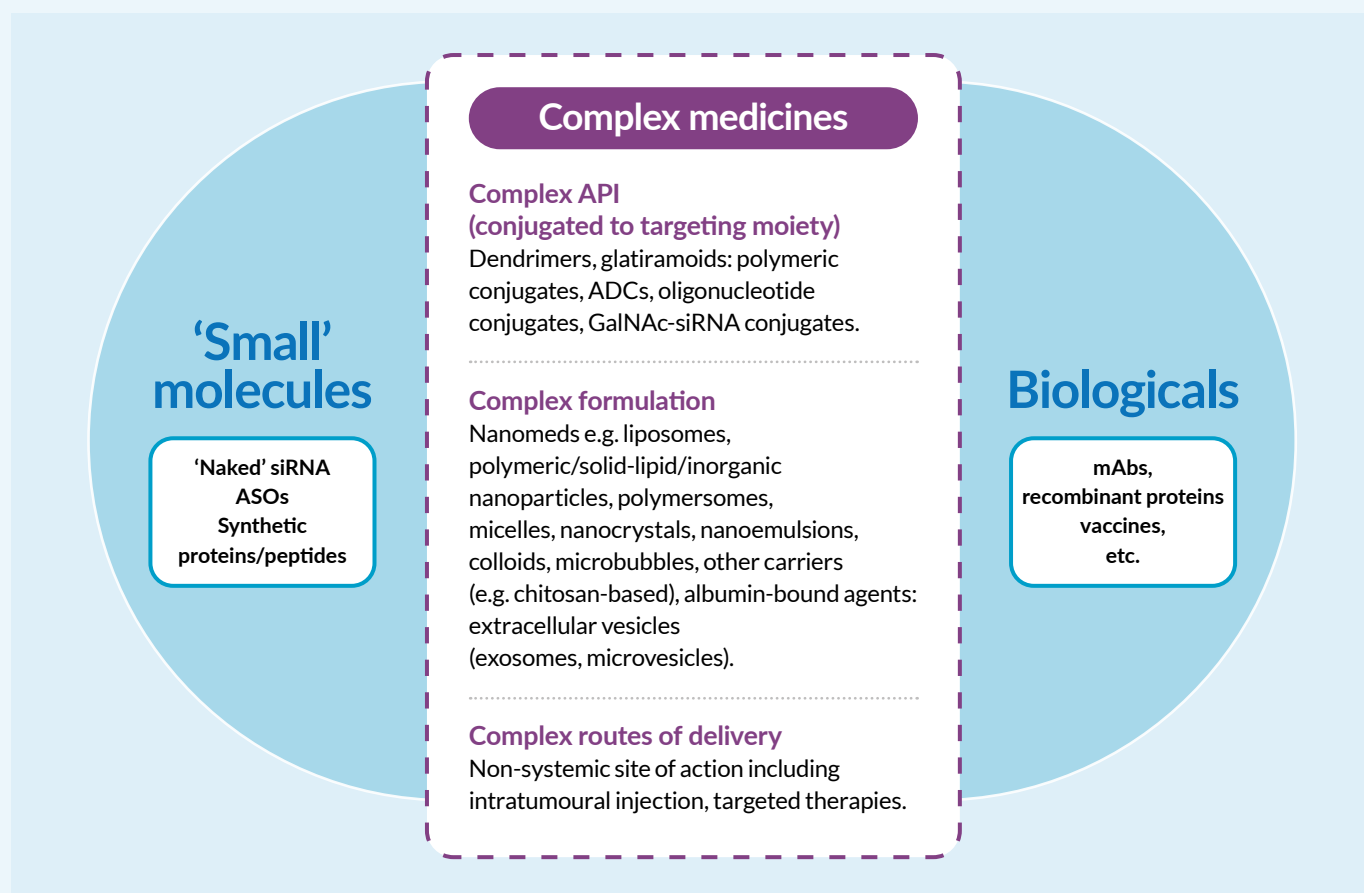
In terms of complex dosage form/formulation, the Medicines Discovery Catapult proposes that all nanomedicines should be within scope. Examples include liposomes, polymeric/solid-lipid/inorganic nanoparticles, nanocrystals, colloids, microbubbles, other carriers (chitosan-based for example), albumin-bound agents and extracellular vesicles (exosomes, microvesicles). Such examples are discussed further below.





In summary, the definition of complex medicines proposed by the Medicines Discovery Catapult, and illustrated in Figure 3, is:

"A complex medicine is one that requires the application of novel technologies for the delivery and targeting of drugs, through the modification of the active pharmaceutical ingredient (drug-dendrimer complexes for example) or of the formulation (liposomes for example) and/or through novel routes of delivery (intratumoural delivery for example)."



ADCs = antibody drug conjugates; **API** = active pharmaceutical ingredient; **ASOs** = antisense oligonucleotides; **GalNAc** = N acetylgalactosamine; **mAbs** = monoclonal antibodies; **siRNA** = short-interfering RNA

Figure 3: The proposed Medicines Discovery Catapult classification of complex drugs

4 | Specific technology examples

The following discusses selected examples of products that would be considered within the scope of the current proposal.

Antibody drug conjugates

An antibody-drug conjugate (ADC) combines an inherently complex antibody with a small synthetic drug molecule (payload) via a linker to create a complex large molecule. Despite the relatively small addition in molecular weight, the small molecule drug has a profound impact on the characteristics and properties of the conjugate (Leung and others, 2020). Due to the combination of the biological portion (antibody) and its small molecule linker and payload, an ADC is both a drug and a biological, and FDA approval follows a collaborative review process (Miksinski, 2013). Ideally, ADC payloads are inactive in the circulation while conjugated to the antibody via the linker, and remain so until the conjugate reaches the target of interest. When the conjugate-target complex is internalised, the active payload is released inside target cells after lysosomal degradation of the linker or of the antibody itself. The stability of the conjugate is critical for specific delivery and distribution of the payload to the target tissue, in addition to reducing off-target effects. Conjugation sites, chemistries and linker designs, coupled with drug-to-antibody ratio, greatly affect plasma stability, biophysical properties and so the pharmacokinetics of the conjugate (Leung and others, 2020).

CRISPR-Cas9 nanoparticles

Clustered regularly interspaced short-palindromic repeats (CRISPR) associated protein 9 (CRISPR Cas9) is a gene-editing technology that relies on Cas9/single guide RNA ribonucleoprotein complexes (RNPs) to target and edit DNA. Many therapeutic targets cannot be accessed, however, due to the current lack of carriers able to systemically deliver RNPs. Complex delivery systems such as modified lipid nanoparticles are needed to efficiently deliver RNPs into cells to edit targets in tissues such as muscle, brain, liver and lungs (Wei and others, 2020).

Drug nanocrystals

Drug nanocrystals are nanoscale particles of API often formulated in suspension with excipients that stabilise against aggregation by electrostatic repulsion and steric hindrance. The manufacturing process is either bottom-up (precipitation for example) or top-down (milling for example), or a combination of the two. The ratio of amorphous to crystalline drug form in the nanoparticles, the particle size distribution and the extent of stabiliser adsorption to the nanocrystal surface must be controlled during the manufacturing process to assure product quality, clinical performance and safety. Several nanocrystal products have been approved by the EMA and FDA through a conventional regulatory framework, which may improve in its sensitivity to nanomedicine issues. No generic or similar products of nanocrystal formulations have yet been developed (Borchard, 2015).

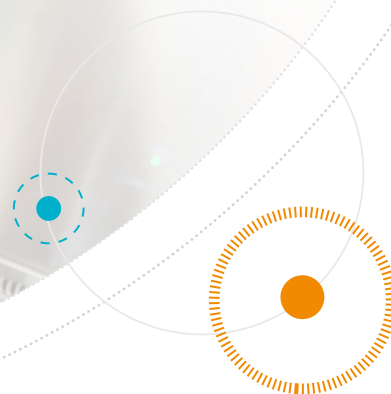
Glatiramoids

Glatiramoids are a family of synthetic copolymer mixtures comprising the four amino acids, L-glutamic acid, L-alanine, L-lysine and L-tyrosine, in a defined molar ratio. Glatiramer acetate was the first glatiramoid approved for treatment of relapsing-remitting multiple sclerosis. Glatiramoids are complex and heterogenous in nature. The clinically active epitopes within the mixture cannot be identified and the consistency of polypeptide sequences within the mixture is dependent on a tightly controlled manufacturing process. Although no two glatiramoids can be proved identical, it is possible to differentiate among members of the glatiramoid class using analytical methods and immunological and biological markers. Even slight differences in the distribution of molecular masses or in the composition of antigenic polypeptide sequences among glatiramoids can significantly influence their efficacy, toxicity and immunogenicity profiles (Varkony and others, 2009).

Iron carbohydrate complexes

Iron carbohydrate complexes for intravenous therapy consist of nanosized particles with a polynuclear Iron(III) oxyhydroxide core and a carbohydrate shell. The iron carbohydrate nanoparticles interact with cells of the innate immune system for uptake and release of iron into the physiological iron metabolic pathways. They are NBCDs – that is, they show polydispersity (non-homomolecular structures), cannot be fully characterised and are highly dependent on a well-controlled manufacturing process. Iron carbohydrate complexes are regarded as nanomedicines whose properties are key to their specific disposition, which also influences their pharmacodynamics and therefore their efficacy and safety (Mühlebach and Flühmann, 2015).





Liposomes

Liposomes are vesicular, (phospho)lipid-based drug-carrier systems in the nanometre/micrometre range. The therapeutic performance of these 'composite' drug products heavily depends on their supramolecular structure. They are heterodisperse, difficult to fully characterise by physicochemical means and are produced via complex manufacturing processes. A liposome is a spherical vesicle having at least one lipid bilayer. The immunogenicity of a liposomal vaccine relies heavily on physicochemical factors such as size, surface charge and lipid content (Marasini and others, 2017).

Messenger RNA

Messenger RNA (mRNA) may be delivered to target cells in the body via different modalities, including vaccines against viruses, cancer vaccines, intratumoural immuno-oncology and localised regenerative therapeutics (Moderna, 2020). In vivo administration usually needs formulation of mRNA into nanoparticles to protect against degradation by ubiquitous ribonucleases. Moreover, formulation is required to direct the mRNA to the desired target cells and for their efficient transfection (Schlake and others, 2019). Moderna's candidate vaccine mRNA 1273 encodes the stabilised prefusion SARS CoV 2 spike protein, delivered in a lipid nanoparticle formulation (Jackson and others, 2020).

Microbubbles

Micron-sized, lipid-stabilised bubbles of gas have been used in the medical world as contrast agents for ultrasound imaging. Much interest has been shown recently in combining microbubbles' imaging and therapeutic properties, such as by producing drug delivery vehicles for targeted chemotherapy, and a number of academic institutions are investigating this potential (Peyman and others, 2014).



Nanoparticle albumin-bound anticancer agents

Nanoparticle albumin-bound (nab) technology is a nanoparticle drug delivery platform that uses the unique transport and binding properties of albumin to achieve enhanced tumour penetration and accumulation of albumin-bound, poorly soluble hydrophobic drugs. It can eliminate the need for toxic co-solvents (Abraxane for example). Nanoparticles of nab-paclitaxel are complex three-dimensional constructs that require careful design and engineering, detailed orthogonal analysis methods, and a reproducible scale-up and manufacturing process to achieve a consistent product with the intended physicochemical characteristics, biological behaviour and pharmacological profiles. Due to its complexity, the safety and efficacy may be influenced by minor variations in the physicochemical properties or the manufacturing process. Preclinical and clinical studies thus need to examine safety and efficacy carefully (Desai, 2015).

Polymeric micelles

Polymeric micelles are nanoparticles formed on the self-assembly of amphiphilic (block co-)polymers in aqueous solutions. The typical result is a spherical nanoparticulate structure with a hydrophobic core that acts as a reservoir for poorly soluble drugs, and a hydrophilic shell that provides colloidal stability and limits protein adsorption and opsonisation, and so lengthening in vivo circulation times. The physicochemical properties, and ultimately the in vivo distribution, safety and efficacy, of the final drug product are highly dependent on the chosen polymer chemistry and manufacturing process (Crommelin and de Vlieger, 2015).

Self-amplifying RNA

Derived from an alphavirus genome, self-amplifying RNA (saRNA) encodes the alphaviral replicase and a gene of interest, which enables the replication of the RNA on delivery to the cytoplasm. saRNA encapsulated in lipid nanoparticles could be of vital importance in the context of the SARS CoV 2 pandemic as it is possible to encode any antigen of interest and requires a minimal dose compared with mRNA (McKay and others, 2020).



Small interfering RNA

Small interfering RNA (siRNA) is a class of double-stranded RNA molecules, 20–25 base pairs in length. siRNA can be chemically modified to alter its physicochemical properties and to increase its in vivo stability for improved circulation time. The first siRNA therapy (patisiran) was approved under the NDA (as opposed to the BLA) process by the FDA in 2018, and is administered as a lipid nanoparticle formulation for intravenous infusion, for the treatment of hereditary transthyretin-mediated amyloidosis (Center for Drug Evaluation and Research, 2018).

The potential efficacy of siRNA-based treatments has been demonstrated in multiple oncology indications. Their development as systemic therapeutics has been hampered, however, by limitations, including the development of a proper delivery system to carry siRNA specifically to its target cells (Resnier and others, 2013). Unmodified (naked) siRNAs are rapidly degraded and cleared by nucleases, which results in a short half-life, and typically have a large molecular weight (around 13 kg/mol) and high negative charge, which greatly reduces cellular membrane permeability. GalNAc-siRNA conjugates are a simple solution to the siRNA delivery problem for liver hepatocytes (Springer and Dowdy, 2018). The encapsulation of siRNA into lipid nanoparticles protects it from enzymatic degradation, facilitates its uptake by the tumour cells and promotes its escape from the endosomal compartment after delivery, resulting in efficient cytoplasmic delivery (Zhang and others, 2014). Other siRNA delivery systems in clinical trials include cyclodextrin nanoparticles, LODER polymer for intratumoural administration, and dynamic polyconjugates (Xu and Wang, 2015).

Targeted antisense oligonucleotides

Antisense oligonucleotides (ASOs) are short, synthetic, single-stranded oligodeoxynucleotides that can alter RNA and reduce, restore or modify protein expression through several distinct mechanisms (Rinaldi and Wood, 2018). Like other nucleotides, ASOs require intracellular delivery for activity, which is the major barrier to effective ASO activity within target cells (Rinaldi and Wood, 2018). Targeted delivery of therapeutic oligonucleotides through conjugation to a homing ligand enables modulation of disease targets in specific cell types that are inaccessible to small molecules and antibodies. The homing ligand can be a small molecule, peptide, carbohydrate or aptamer. The linker chemistry is designed so that the conjugate cleavage occurs in the desired cell type to deliver the drug where it can modulate the disease-causing target (Anderson, no date).



5 | Other types of medicine considered out of scope

Advanced therapy medicinal products

Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells. They offer groundbreaking opportunities for the treatment of disease and injury. They are generally considered outside the scope of this definition of complex medicines unless delivered in a complex carrier such as a CRISPR Cas9 nanoparticulate delivery system.

ATMPs can be classified into three main types: gene therapy medicines, somatic-cell therapies and tissue-engineered medicines (Medicines and Healthcare products Regulatory Agency, 2015).

Gene therapy medicines contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting recombinant genes into the body, to treat a variety of diseases, including genetic disorders, cancer or long-term diseases.

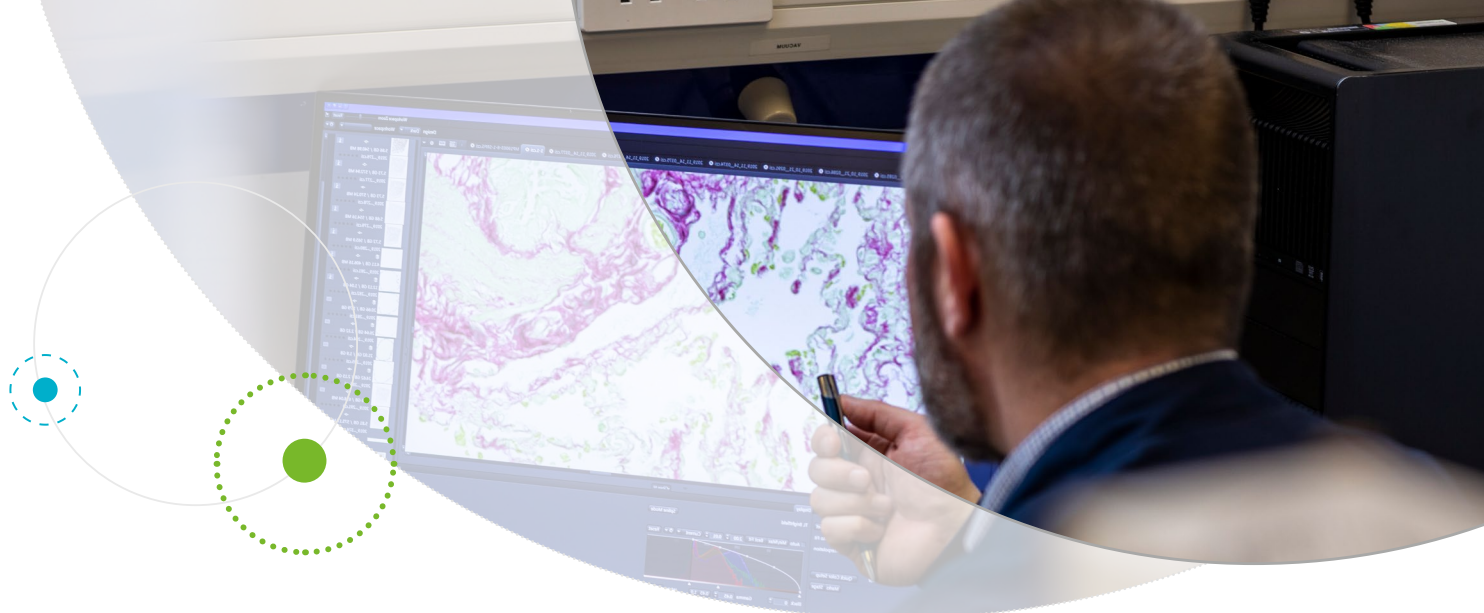
A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources. The FDA considers any use of CRISPR Cas9 gene editing in humans to be gene therapy.

Somatic-cell therapy medicines contain cells or tissues that have been manipulated to change their biological characteristics, or cells or tissues not intended to be used for the same essential functions in the body. They can be used to prevent, diagnose or cure diseases.

Tissue-engineered medicines contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

In addition, some ATMPs may contain one or more medical devices as an integral part of the medicine, when they are referred to as combined ATMPs. Cells embedded in a biodegradable matrix or scaffold are an example of this.





6 | Conclusion

From the regulators' broad umbrella view of complex drug products (incorporating biologicals, NBCDs and hybrids of the two), the Medicines Discovery Catapult postulates that the specific technologies that would benefit from innovation and support include but are not limited to any biological or non-biological drug that falls under one or more of these categories:

Complex APIs	Drug-dendrimer conjugates, glatiramoids, polymeric compounds, antibody drug conjugates, oligonucleotide conjugates, GalNAc-siRNA conjugates.
Complex dosage forms/formulations	Nanomedicines such as liposomes, polymeric/solid-lipid/inorganic nanoparticles, polymersomes, micelles, nanocrystals, colloids, microbubbles, other carriers (chitosan-based carriers for example), albumin-bound agents, extracellular vesicles (exosomes, microvesicles), extended release injectables.
Complex routes of delivery	Products with a non-systemic site of delivery, including intratumoural, targeted therapies.

Unless included under one or more of the above categories, the following are examples of medicines not considered to be within scope (not an exhaustive list):

• Naked siRNA
• ASOs
• Monoclonal antibodies/nanobodies
• Proteins/peptides
• Vaccines
• Drug-device combinations
• Medical devices
• Advanced therapy medicinal products, including gene therapy medicines such as CRISPR Cas9 gene editing, somatic-cell therapy medicines and tissue-engineered medicines (except those formulated in complex drug delivery systems)





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