SITUATION ANALYSIS STUDY ON NANOMEDICINES REGULATION AND ASSESSMENT PRACTICES IN ZAZIBONA ACTIVE COUNTRIES

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Keywords

Nanomedicines

Regulatory challenges in Southern Africa

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Abstract

Nanomedicines are loosely defined as medicines that seek to apply nanotechnology. Currently, nanomedicines are available for clinical use, including treatments for cancer, high cholesterol, hepatitis, COVID-19 vaccination, among other uses (Patra *et al.*, 2018; Gao *et al.*, 2021). Most of the nanomedicines meet the definition of medicines according to various national legislations. Consequently, these products are regulated as medicines. Nanomedicines present major differences in biological details and increased complexity of clinical use. They integrate different technology subsets from therapeutics to imaging and integrated non-invasive diagnosis (Gaspar, 2007). These complexities require extra regulatory effort.

In the resource-poor context of low- and middle-income countries (LMICs) many National Medicines Regulatory Authorities (NMRAs) still lack the resources and capacities to assure the quality of medicinal products circulating in their territory because they have weak legal and regulatory oversight of the pharmaceutical sector (Ravinetto, Pinxten and Rägo, 2018). With emerging trends in innovative technologies, including nanotechnology, this burden may be worsened. The need to overcome regulatory challenges that ultimately hinder patient access to healthcare products drove the formation of a work sharing initiative in the Southern African Development Community (SADC), by four countries Zambia, Zimbabwe, Botswana and Namibia, the ZAZIBONA initiative in 2013 (Gwaza *et al.*, 2014). To date, nine countries; Zambia, Zimbabwe, Botswana, Namibia, South Africa, Democratic Republic of Congo, Mozambique, Malawi and Tanzania contribute to assessments in ZAZIBONA (MCAZ, 2020).

The aim of this study was to establish the regulation status of nanomedicines in the ZAZIBONA active countries. The main objective was to obtain an overview of the assessment practices of the products in the countries, with a view to identify any challenges faced as well as documenting future priorities areas for capacity building. A study sample consisting of regulatory authorities active in the ZAZIBONA joint assessments was used in the questionnaire based, cross-sectional exploratory study.

Results of this study show that in as much as ZAZIBONA active regulatory authorities are aware of the existence of nanomedicines and have legal mandates to regulate nanomedicines, there are no regulatory documents that cover assessment of nanomedicines. Most of the NRAs

do not have specific technical committees or committee members with expertise in nanomedicines for consideration of advanced drug delivery systems including nanomedicines. Collaboration with external experts or organisations in the regulation of nanomedicines is also lacking and there is need for training and capacity building in the area of assessment of nanomedicines as well as incorporation of nanomedicines in regional harmonisation activities.

Declaration

I declare that this thesis titled *Situation Analysis Study on nanomedicines regulation and assessment practices in ZAZIBONA* active countries is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

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Signed: 

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I am extremely grateful to my supervisors, Prof. Admire Dube and Prof. Star Khoza for their invaluable advice, continuous support, and patience during my research study.

Dedication

This work is dedicated to my daughter, Rue. You have made me stronger, better and more fulfilled than I could have ever imagined.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
AMA	African Medicines Agency
AMRH	African Medicines Regulatory Harmonization
AU	African Union
AUDA-NEPAD	African Union Development Agency -New Partnership for Africa's Development
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
GMP	Good manufacturing practices
GAMP	Good automated manufacturing practice
HIV	Human immunodeficiency virus
LMICs	Low- and middle-income countries
LNPs	Lipid nanoparticles
MRI	Magnetic Resonance Imaging
mRNA	Messenger ribonucleic acid
NCE	New chemical entities
NPs	Nanoparticles
NMRAs	National Medicines Regulatory Authorities
NRAs	National Regulatory Authorities
REC	Regional Economic Community
SADC	Southern African Development Community
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
UK	United Kingdom
USA	United States of America
USFDA	United States Food and Drugs Administration
WHO	World Health Organisation
ZAZIBONA	Pilot of collaborative registration procedures involving Zambia, Zimbabwe, Botswana and Namibia

CHAPTER ONE: INTRODUCTION

1.1 Nanomedicines

Nanoparticle-based medicines (also usually referred to as nanomedicines) are defined as therapeutic or imaging agents which comprise a nanoparticle in order to control the biodistribution, enhance the efficacy, or otherwise reduce toxicity of a drug or biologic (Bobo *et al.*, 2016). The European Science Foundation defines nanomedicines as the science and technology of diagnosing, treating, and preventing disease and injury, of relieving pain, and of preserving human health, using molecular tools and knowledge of the human body (European Science Foundation, 2005). Currently, nanomedicines are available for clinical use, including treatments for cancer, high cholesterol, autoimmune disease, fungal infections, macular degeneration, hepatitis, among other conditions (Patra *et al.*, 2018). Additional applications include use in vaccinations, magnetic resonance imaging (MRI) contrast agents, fluorescent biological labels, pathogen detection, protein identification, DNA structure probing, tissue engineering, drug- and gene-delivery agents, and the separation of biological molecules and cells (Ventola, 2012; Pelaz *et al.*, 2017; Ali *et al.*, 2021).

The first generation of nanomedicines, mainly liposomes and nanoparticles, were first marketed in 1990. The USFDA approved the first adenosine deaminase enzyme modified by covalent conjugation with polyethylene glycol (PEGylated deaminase enzyme) in 1990 (Ventola, 2012). Most of the currently approved nanomedicines consist of relatively simple nanoparticles and build on the success of well described nanoparticle systems and prior approved drugs, e.g. PEGlyated liposomes. There has been both a broadening in nanoparticle types and an increase in the complexity of nanoparticles within these categories over time

(Bobo *et al.*, 2016). Currently many 'follow-on' or 'next generation' nanotechnology based products are in development pipelines.

Innovations in nanotechnology for intracellular delivery and advances in nanomedicine production have recently been used in the production of mRNA-based vaccines for emergency use in vaccination against COVID-19 (Gao *et al.*, 2021). Of the twenty-two COVID-19 vaccines that have been granted emergency use authorization world-wide, the two vaccines that have shown the most promising efficacy results in preventing COVID-19 infection are composed of messenger ribonucleic acid (mRNA) strands encapsulated in lipid nanoparticles (LNPs) (Craven, 2021; Hou *et al.*, 2021). mRNA vaccines developed by BioNTech/Pfizer and Moderna were the first mRNA vaccines to receive 'emergency use authorization' by USFDA and 'conditional approval' by EMA (Schoenmaker *et al.*, 2021). The BioNTech/Pfizer and Moderna vaccines have also been reported to have relatively high efficacy rates of 95% and 94.1% respectively (Polack *et al.*, 2020; Baden *et al.*, 2021) .

Most of the nanomedicines meet the definitions of medicines according to various national legislations. Consequently, these products are regulated as medicines and the common laws apply. For the safe evaluation and regulation of nanomedicines however, critical quality attributes (CQAs) and additional toxicological assessments have to be considered, in addition to the general requirements for medicines. This is due to the wide range of structures of the nanomedicines, their physicochemical and biological properties, and the variety of therapeutic applications which makes the generalisation of CQAs a challenge (Bremer-Hoffmann, Halamoda-Kenzaoui and Borgos, 2018). These additional considerations need to be translated into standardised and regulatory accepted test methods, testing strategies, guidelines and policies. It has also been discussed that albeit a significant number of nanomedicines having

been approved, there was still lack of specific general protocols for preclinical development and characterization of these products (Sainz *et al.,* 2015). Global regulatory trends are yet to be defined, despite the several attempts already made (Dorbeck-Jung and Chowdury, 2011). On the contrary, the European Medicines Agency (EMA), AdHoc Informal Group, 2009 highlighted that new set of guidelines was not necessary; rather integration in the existing regulatory framework needed to be considered (EMA, 2009).

1.2 Regulatory challenges associated with nanomedicines

Due to the lack of extensive and deep scientific knowledge as well as tools and techniques related to nanomedicines, several challenges are anticipated in their regulation. The definition of nanotechnology is not universally agreed upon. In addition, there is no harmonisation with respect to what an acceptable limit for a nanomedicines is. The US National Nanotechnology Initiative (NNI) considers the dimension from 1-100 nm. The U.K. Royal Society and Royal Academy of Engineering proposed a range of 0.2-100 nm (The Royal Society, 2004; US National Nanotechnology Initiative, 2021). In practice, the metric definition of 1-1000 nm is usually used and several nanomedicines products under development are over the size range of 100 nm, with sizes ranging approximately between 200 and 300 nm (Rajneesh Kumar Gaur, 2013). Considering the fact that the size of nanoparticles is a determinant factor of the physicochemical properties, pharmacokinetic & pharmacodynamic properties, toxicity and biosafety levels, this disharmony in definition poses a serious challenge.

As a result of the differences in definitions, a product may be regarded as a nanomedicine in one jurisdiction and not a nanomedicine in another. Products may also be classified differently by different jurisdictions thus making it difficult for manufactures to use common submissions.

Different classifications may also bring about additional concerns related to their potential toxic and deleterious effects (Sainz *et al.*, 2015). In addition, it will be difficult to harmonise the regulatory requirements of these products among different jurisdictions and authorities.

Nanomedicines are also complex in their structure, with major differences in biological details and increased complexity of clinical use. They integrate different technology subsets from therapeutics to imaging and integrated non-invasive diagnosis (Gaspar, 2007). These complexities will require extra regulatory effort, perhaps tying together medicine and medical devices regulations and requirements. Their properties can easily be altered by slight changes in raw materials and small modifications in manufacturing processes. Although these changes might result in minor alterations in the structure, the biological properties and biodistribution patterns may be significantly altered (Sainz *et al.*, 2015).

Issues to do with clinical safety of nanotechnology products also require careful consideration. The impact of nanomaterials and some manufacturing processes involved in the production of these nanoparticles in humans need to be carefully understood and well-regulated so as to prevent unintended impacts.

In terms of manufacturing practices; a full review of production processes, diverse raw materials, unique in-process critical steps and the link to appropriate industrial standards is needed. Good manufacturing practices (GMP), good automated manufacturing practice (GAMP) and other current industrial requirements need to be adapted to a new technological level for these nanotechnology-based medicines.

1.3 Narrowing regulatory challenges to SADC (ZAZIBONA)

It has been reported that in the resource-poor context of low- and middle-income countries (LMICs) many National Medicines Regulatory Authorities (NMRAs) still lack the resources and capacities to assure the quality of medicinal products manufactured, imported or circulating in their territory because they have weak legal and regulatory oversight of the pharmaceutical sector (Ravinetto, Pinxten and Rägo, 2018). This predicament has been exacerbated by the emergence of nanomedicines. Nanomedicines are complex and require extensive and deep scientific knowledge. Moreover, these products are not similar to the current conventional medicines, as such current guidelines and regulations are not likely to cover their requirements.

In Africa, pharmaceutical regulatory challenges include weak or non-coherent regulatory standards and requirements among countries; lengthy medicine registration processes that lead to delays in approval decisions; technical capacity and capability; overall resource constraints (Ndomondo-Sigonda *et al.*, 2018). Many NMRAs in LMICs still lack the resources and capacities to assure the quality of medicinal products manufactured, imported or circulating in their territory (WHO, 2008, 2010b). In addition, unclear policies and challenges with high staff turnover as well as lack of competent regulatory professionals are common features in many African NMRAs (Ncube, Dube and Ward, 2021). With emerging trends in innovative technologies, including nanotechnology which are highly inter-disciplinary in nature, encompassing physics, chemistry, engineering, biotechnology, health sciences, cell and molecular biology, pharmaceutical sciences and biomedicine, the burden may be worsened for pharmaceutical regulators in LMICs.

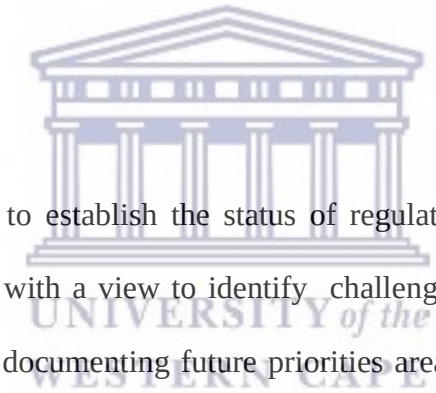
1.4 The ZAZIBONA initiative

The need to overcome regulatory challenges that ultimately hinder patient access to healthcare products drove the formation of a work sharing initiative in SADC. NMRAs in Zambia, Zimbabwe, Botswana, and Namibia (acronym ZAZIBONA) with support from the WHO Prequalification Team-medicines (WHO-PQTm) agreed to cooperate in the assessment of applications for registration of medicines and inspection of product manufacturers for compliance with good manufacturing practice (Gwaza *et al.*, 2014). As an initiative, ZAZIBONA received formal endorsement from SADC Ministers of Health & Ministers Responsible for HIV & AIDS in 2014 resulting in the initiative being recommended for expansion to other SADC Member States beyond the 4 founding Member States (Sithole *et al.*, 2020). As of 2021, a total of thirteen (13) countries (including the four founding members) have now joined the initiative with different membership status including; South Africa, (active), Democratic Republic of Congo (active), Mozambique (active), Malawi (active), Tanzania (active), Eswatini (non-active), Angola (non-active), Seychelles (non-active) and Madagascar (non-active). Angola, Seychelles, Eswatini, and Madagascar participate in ZaZiBoNa as non-active members and Comoros Islands, Lesotho, and Mauritius are the few remaining SADC countries not yet participating in the initiative. To be granted active member status, a country should have legislation mandating the registration of medicines as well as in-house capacity to perform assessments. Countries that do not meet these criteria but are willing to participate in this initiative are granted observer status and do not actively contribute to the assessment of registration dossiers (Sithole *et al.*, 2020).

To this end, ZAZIBONA is one of the regional projects under the African Medicines Regulatory Harmonization (AMRH) initiative intended to improve the fragmented regulatory system for product registration in Africa by changing from a country-focused approach to a

collaborative regional and simplified one. The AMRH's intended end result is a reduced registration cycle time starting with generics and extending to other product categories such as new chemical entities (NCEs), vaccines and diagnostics (Ndomondo-Sigonda et al, 2018). The AMRH initiative is also intended to form the basis for the establishment of the African Medicines Agency (AMA) (African Union, 2020; Ncube, Dube and Ward, 2021). AMA is expected to address the challenges faced by the African continent in medicine regulation by enhancing capacities of member states and regional economic communities and developing common standards and regulations (AUDA-NEPAD, 2019; African Union, 2020).

1.5 Conclusion



The purpose of this study is to establish the status of regulation of nanomedicines in the ZAZIBONA active countries with a view to identify challenges specific to nanomedicines being encountered as well as documenting future priorities areas for capacity building. It is anticipated that the results of the study will inform priority areas to be addressed under the AMRH initiative whose intention is to extend to other product categories such as NCEs, vaccines and diagnostics, in addition to the generic products.

CHAPTER TWO: LITERATURE REVIEW

2.1 Nanotechnology and nanomedicine

Nanotechnology is the science of the nanoscale objects around a nanometer in size (Booth and Baker, 2017). The U.S. Environmental Protection Agency (EPA) defines nanotechnology as research and technology development at the atomic, molecular, or macromolecular levels using a length scale of approximately one to one hundred nanometers in any dimension (EPA, 2007). It involves the creation and use of structures, devices, and systems that have novel properties and functions because of their small size (Khare, Williams and Gokulan, 2014). Common words associated with nanotechnology include nanoparticles and nanomedicines.

Nanoparticles (NPs) are nanosized structure with one or more of its "dimensions," that is, length, width, or thickness in the nanometer range of 1–100 nm (Ray *et al.*, 2020). They have several properties such as chemical reactivity, energy absorption, and biological mobility that distinguish them from bulk materials by virtue of their size (Murthy, 2007). These properties enable use of nanoparticles in modern medicine in a variety of ways ranging from imaging of cells and tissues, sensing, targeted drug delivery, gene delivery and artificial implants (Nasimi and Haidari, 2013; Nieto *et al.*, 2021). The use of nanoparticles for such applications is commonly achieved by packing active pharmaceutical ingredients (APIs) into nanoparticles with the intention to (Precision Nanosystems, 2021):

i) Protect the API;

ii) Control API release;

iii) Alter the biodistribution;

iv) Target drug delivery to the site of disease and

v) Enhance solubility and bioavailability

These nanotechnology-based drug delivery platforms vary, examples of which are depicted in figure 1 below.

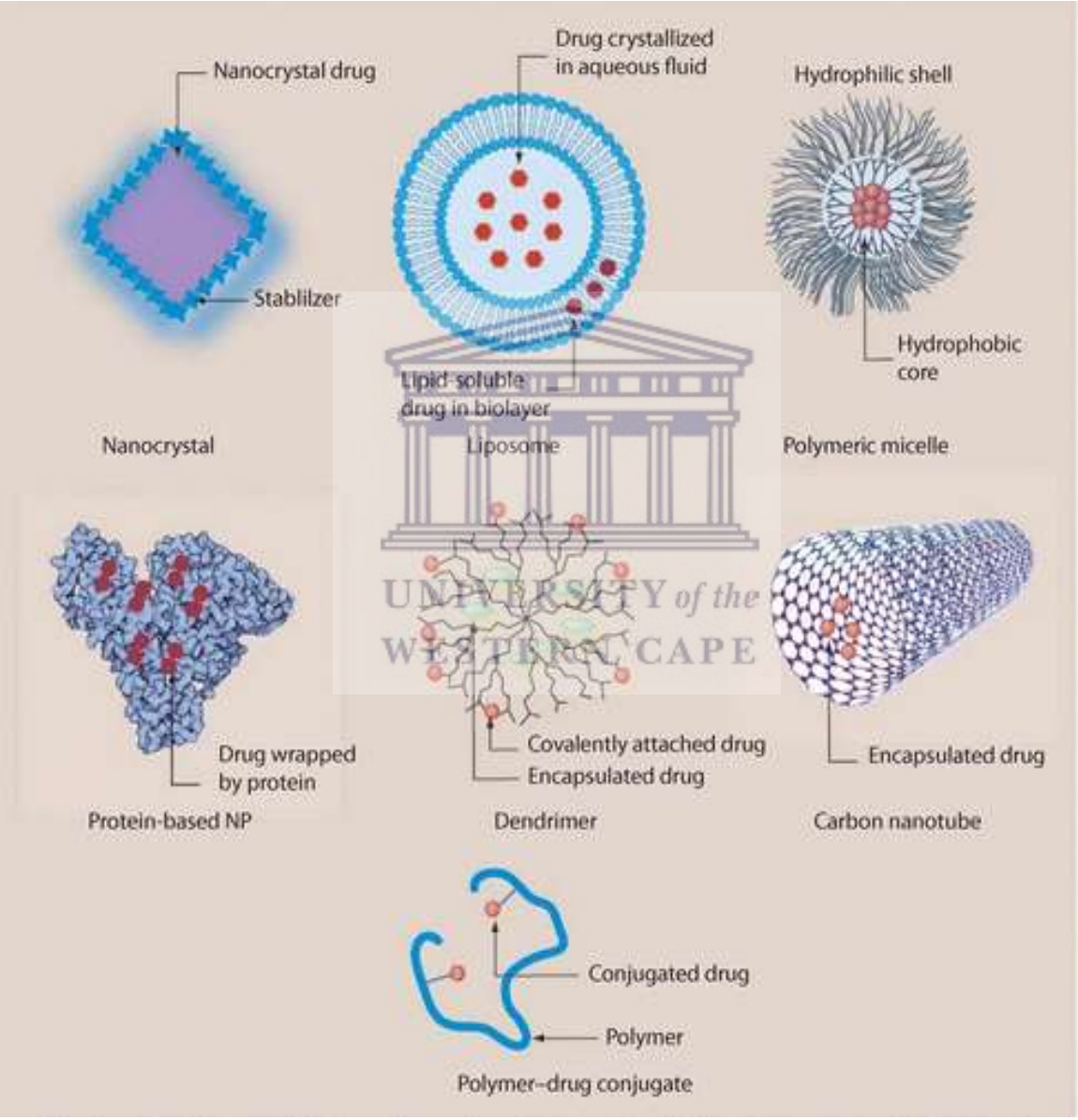


Figure 1: Examples of nanotechnology-based drug delivery platforms (source: Bamrungsap *et al.*, 2012)

Nanotechnology has opened a new category of medicines called nanomedicines where the medicine is reduced to the nanoscale size, hoping to enhance its physicochemical properties. Nanomedicines are defined as the use of nanotechnology for medical therapeutics by developing nanoscale agents for the treatment of various kinds of diseases (Schlachetzki *et al.*, 2004). These medicines have brought hope in the area of innovation and medicines development as they are opening new treatment options for several diseases and conditions (Farjadian *et al.*, 2019; Germain *et al.*, 2020). The use of nanoparticles in nanomedicines has been achieved through various techniques. These include integration of efficacious molecules that otherwise could not be used because of their high toxicity, exploitation of multiple mechanisms of actions, maximisation of efficacy and reduction in dose and toxicity, drug targeting, controlled and site specific release, favouring a preferential distribution within the body and improved transport across biological barriers (Soares *et al.*, 2018).

According to their chemical and physical characteristics, nanoparticles are classified into three main groups as indicated in figure 1 below: organic nanoparticles (liposomes and polymers), inorganic nanoparticles (metals, metal oxide, ceramic, and quantum dots), and carbon-based nanoparticles (De Matteis and Rinaldi, 2018).

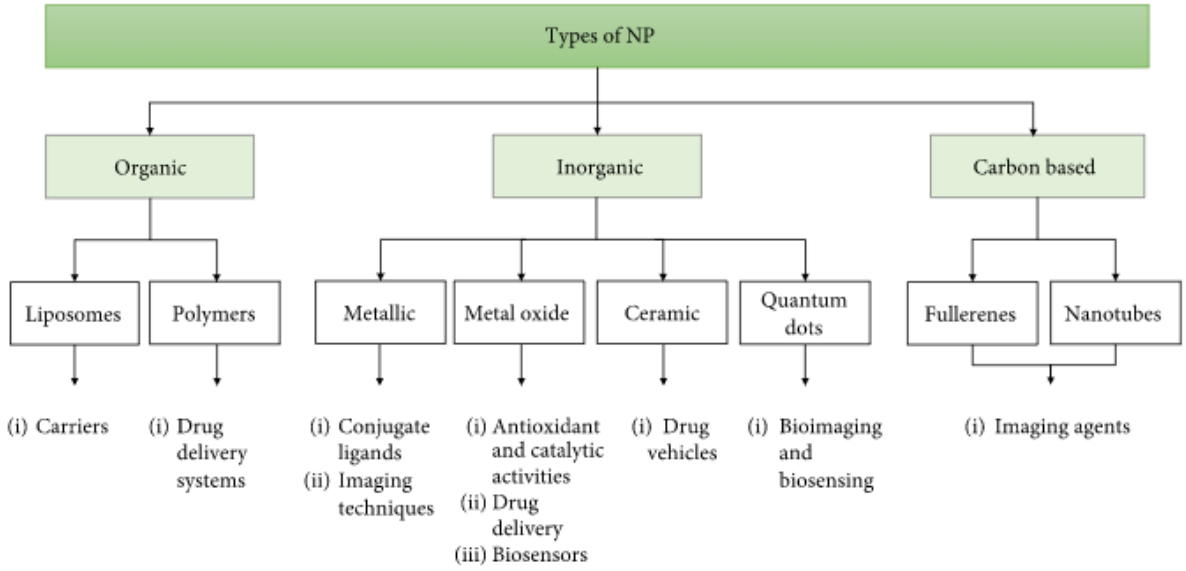


Figure 2: Generalized diagram of the types of nanoparticles and their main biomedical applications (source: Mauricio *et al.*, 2018).

2.1.1 Polymeric NPs

Polymeric NPs are defined as sub-micron (1 to 1000 nm) colloidal particles comprising active pharmaceutical ingredients encapsulated within or adsorbed to macromolecular substances (Mehanna, Mohyeldin and Elgindy, 2014). They are regarded as the simplest form of soft materials for nanomedicine applications owing to their simple synthesis and wide applicability across all aspects of the nano-field (Bobo *et al.*, 2016). Polymeric NPs are also regarded as advantageous because of their potential use for controlled release, their ability to protect drug and other molecules with biological activity against the environment thus improving bioavailability and therapeutic index (Zielińska *et al.*, 2020). Feasibility of scale-up under GMP, stability of polymeric nanoparticles in biological fluids, the opportunity to functionalise their surfaces and to modulate polymer degradation have also been discussed as significant benefits of polymeric NPs (van Vlerken, Vyas and Amiji, 2007; S.Venkatraman, 2010; Goodall, Jones and Mahler, 2015). The matrix of polymeric NPs consists of natural, semi-synthetic or synthetic polymers. These can be biodegradable or non-biodegradable. Synthetic

polymers, like aliphatic polyesters, such as poly(lactic-co-glycolic acid) (PLGA), poly(glycolic acid) (PGA) and poly(lactic acid) (PLA), have been approved by the US Food and Drug Administration (FDA) (Caballero-George, Marin and Briceño, 2013). Natural polymers can be proteins such as collagen, albumin, zein, gluten and polysaccharides such as chitosan, hyaluronate, cellulose, alginate, and starch (Nieto *et al.*, 2021).

Polymer nanomedicines are usually categorised into polymer-drug conjugates for increased drug half-life and bioavailability, and degradable polymer architectures for controlled release applications (Bobo *et al.*, 2016). Polymer-drug conjugates, which are also known as polymeric prodrugs, are drug delivery systems that are formulated for the incorporation of therapeutic agents into polymers of choice (Pang, Yang and Zhai, 2014). They are composed of three units: solubilizing unit, targeting moiety, and a therapeutic agent covalently incorporated into the polymer backbone (Alven *et al.*, 2020). Biodegradable polymers are polymers that can be cleaved into small polymer fragments in vivo (Quan *et al.*, 2018).

Neulasta® (PEGylated granulocyte colony stimulating factor) is an example of an approved nanomedicine that is based on polymeric NPs. PEGylation of the active substance resulted in a significant increase in biological half-life in plasma, 15–80 hours versus 3–4 hours for the plain filgrastim (Ho and Gibaldi, 2013). Another example is Eligard® which was formulated based upon incorporation of leuprolide (a testosterone inhibiting drug) into a polylactide-co-glycolic acid (PLGA) nanoparticle (Bobo *et al.*, 2016).

2.1.2 Lipid-based NPs

Lipid-based nanoparticles such as liposomes, solid lipid nanoparticles and nanostructured lipid carriers are nanoparticles composed of lipids (García-Pinel *et al.*, 2019). The use of these nanoparticles has been extensively explored as they can transport hydrophobic and hydrophilic molecules, display very low or no toxicity, prolong half-life thus increasing the time of drug action (Ozpolat, Sood and Lopez-Berestein, 2014). In addition, lipid nanosystems can include chemical modifications to avoid the detection by the immune system or to improve the solubility of the active substance. They can also be prepared in formulations sensitive to the pH in order to promote drug release in an acidic environments (R. Rama *et al.*, 2016).

PEGylated liposomal doxorubicin (Doxil®), is an example of a liposomal nanoparticle drug, which was proven effective in the reduction of cardiotoxic side effects of doxorubicin treatment (Bobo *et al.*, 2016; Batty, Eric M. Bachelder and Ainslie, 2021). Use of lipid-based nanoparticles has also recently been in the spotlight as they have been incorporated as significant components of COVID-19 messenger ribonucleic acid (mRNA) vaccines (Tenchov *et al.*, 2021). The mRNA vaccines developed by BioNTech/Pfizer and Moderna are composed of mRNA strands encapsulated in lipid nanoparticles (Schoenmaker *et al.*, 2021).

2.1.3 Metallic and Metal oxide NPs

Metal nanoparticles are submicron scale entities made of pure metals (e.g., gold, platinum, silver, titanium, zinc, cerium, iron, and thallium) or their salts (e.g., oxides, hydroxides, sulfides, phosphates, fluorides, and chlorides (Piñón-Segundo, Mendoza-Muñoz and Quintanar-Guerrero, 2013). The modification and functionalization of these nanoparticles with specific functional groups allow them to bind to antibodies, drugs and other ligands thus

making them suitable for use in nanomedicines (García-Pinel *et al.*, 2019). Metallic nanoparticles are nontoxic and biocompatible, and their surface can be modified with other biomolecules due to their negative charge (Patra *et al.*, 2010).

2.1.4 Ceramic NPs

These are inorganic compounds with porous characteristics that are used as vehicles for drugs (Mauricio *et al.*, 2018). They are capable of transporting molecules such as proteins, enzymes, or drugs without swelling or compromising their porosity due to the external effects of pH or temperature (Singh *et al.*, 2013).

2.1.5 Quantum dots NPs

Quantum dots are known as semiconductor nanocrystals with diameter range from 2 to 10 nm (Patra *et al.*, 2018). Examples of semiconductor cores used for quantum dots are cadmium–selenium, cadmium–tellurium, indium–phosphate or indium–arsenate, overcoated with a shell (e.g., zinc sulfide (ZnS)) to improve their optical and physical properties and to prevent leaking of the toxic-heavy metals (Mauricio *et al.*, 2018).

2.1.6 Carbon-based NPs

Fullerenes and carbon nanotubes represent two major classes of carbon-based NPs (Khan, Saeed and Khan, 2019). Fullerenes are l carbon allotropes with a polygonal structure made up exclusively of 60 carbon atoms while carbon nanotubes are normally manufactured from chemical vapor deposition of graphite (Mauricio *et al.*, 2018). Carbon-based nanoparticles are valuable due to their physical properties, including high electrical conductivity and excellent mechanical strength (Miglietta, Rametta and Di Francia, 2009).

2.2 Nanomedicines in clinical use

Nanoparticles have made an impact in the treatment of various types of diseases. Organic and inorganic nanoparticles have been approved for a variety of clinical indications and several others are being investigated in current clinical studies for additional indications (Anselmo and Mitragotri, 2019). Doxil® was one of the first nanomedicines approved by the USFDA in 1995. It was first approved for the treatment of AIDS-related Kaposi's sarcoma and later for refractory ovarian cancer and multiple myeloma (Ventola, 2012). Two of the top 10 best-selling medicines in the US in 2013 were nanotechnology-based polymeric drugs, Copaxone® and Neulasta® (Duncan, 2014).

A clinical area where nanoparticles have made a significant impact is in the treatment of cancer. Paclitaxel a water-insoluble anticancer agent was formulated to be administered as a solution in ethanol (Taxol®), administered together with a solvent, polyoxyethylated castor oil (Cremophor® EL) (Murthy, 2007). Due to the side effects associated with Cremophor®, a different form of paclitaxel, Abraxane® loaded within nanoparticles of a natural polymer, albumin, using a high-pressure emulsification process was developed (Zhang *et al.*, 2005; Micha *et al.*, 2006). In addition to the elimination of side effects, the albumin carrier used in Abraxane® is reported to have the benefit of improving transport of the drug from the bloodstream to the tumor site and allows higher drug dosing compared with Taxol® (Ibrahim *et al.*, 2002).

Another formulation of paclitaxel was also developed to overcome the problem of multidrug resistant associated with Abraxane® and Taxol® by loading paclitaxel into emulsifying wax nanoparticle (Koziara *et al.*, 2006; Murthy, 2007). Other nanotechnology based formulations have been approved such as Daunorubicin® and Myocet®. Virosomes are also licensed for use in clinical settings in some countries, for example in the Philippines the use of

Rexin-G® for solid tumours has been used since 2007 due to its ability to specifically target exposed collagen which is commonly found in metastatic tumours (Weissig, Pettinger and Murdock, 2014)

Use of nanoparticles has also been explored to overcome the challenge of drug delivery to the central nervous system, in the area of HIV/AIDS, ocular and respiratory diseases (Cafaro *et al.*, 1999; Schlachetzki *et al.*, 2004; Garcia-Garcia *et al.*, 2005; Ludwig, 2005; Koziara *et al.*, 2006). For pain management, DepoDur®, was approved in 2004 (Gerancher and Nagle, 2008). In the formulation, morphine sulphate is encapsulated within multivesicular liposome, which results in a more sustained drug release (Chawla *et al.*, 2010). This was intended to reduce opiod treatments to single dose formulations, in order to prevent misuse, addiction and overdose (Foulkes *et al.*, 2020).

Information on nanotechnology-based products already approved by the USFDA and EMA has been provided in various literature (Weissig, Pettinger and Murdock, 2014; Bobo *et al.*, 2016; Patra *et al.*, 2018; Anselmo and Mitragotri, 2019, 2021). The USFDA and EMA are part of the six of the world's most preeminent medicines regulatory bodies (Gaffney, 2015). They are considered stringent regulatory authorities and in addition to Japan, are the founding members of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (WHO, 2017; ICH, 2021). Nanomedicines approved by these agencies are therefore likely to be submitted for approval in the ZAZIBONA active countries. A list of the USFDA and EMA nanomedicines approved for marketing in the US and EMA are shown in Table 1.

Table 1: A list of the USFDA and EMA nanomedicines approved for marketing in the US and EMA.

Nanomedicine	**API and material description**	**Therapeutic indication**
Abelcet®	Amphotericin B complex 1:1 with DMPC and DMPG (7:3), >250 nm, ribbon like structures of a bilayered membrane	Treatment of a variety of serious fungal infections.
Adagen®	PEGylated adenosine deaminase. One enzyme molecule is modified with up to 17 strands of PEG, MW 5,000, 114 oxymethylene groups per strand	Enzyme replacement therapy for the treatment of severe combined immunodeficiency disease (SCID) associated with a deficiency of adenosine deaminase.
AmBisome®	Amphotericin B encapsulated in liposomes (60–70 nm)composed of hydrogenated soy phosphatidylcholine, cholesterol, and distearoyl phosphatidylglycerol (2/0.8/1 molar)	Treatment of serious, life-threatening fungal infections including leishmaniasis, or a certain form of meningitis in people infected with HIV (human immunodeficiency virus).
Amphotec®	Amphotericin B complex with cholesteryl sulfate (1:1). Colloidal dispersion of disc-like particles, 122 nm ×4 nm	Treatment of a variety of serious fungal infections.
Cimzia®	PEGylated antibody (Fab' fragment of a humanized anti-TNF-alpha antibody)	Reduction of signs and symptoms of moderate to severe

		rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis, and Crohn's disease.
Comirnaty ®	lipid nanoparticle encapsulated COVID-19 mRNA Vaccine	Vaccine for prevention of coronavirus disease.
Copaxone®	Polypeptide (average MW 6.4 kDa) composed of four amino acids (glatiramer)	Treatment of multiple sclerosis.
DaunoXome®	Daunorubicin citrate encapsulated in liposomes (45 nm) composed of distearoyl phosphatidylcholine and cholesterol (2/1 molar)	Treatment of advanced HIV-associated Kaposi's sarcoma.
DepoCyt®	Cytarabine encapsulated in multivesicular liposomes (20 μm; classified as nanopharmaceutical based on its individual drug containing "chambers") made from dioleoyl lecithin, dipalmitoyl phosphatidylglycerol, cholesterol, and triolein	Used alone or in combination with one or more other medications to treat leukemia and lymphoma.
DepoDur®:	Morphine sulfate encapsulated in multivesicular liposomes (17–23 μm; per se not a nanopharmaceutical – classified as such based only on its individual drug	Treatment of pain after major surgery.

	containing “nano-sized chambers”) made from dioleoyl lecithin cholesterol, dipalmitoyl phosphatidylglycerol, tricaprylin, and triolein	
Doxil®	Doxorubicin hydrochloride encapsulated in Stealth® liposomes (100 nm) composed of N-(carbonyl- methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3-phosphoethanolamine sodium, fully hydrogenated soy phosphatidylcholine, and cholesterol	Treatment of AIDS-related Kaposi's sarcoma, breast cancer, ovarian cancer, and other solid tumors.
Eligard®	Leuprolide acetate (synthetic GnRH or LH-RH analog) incorporated in nanoparticles composed of PLGH copolymer (DL-lactide/glycolide; 1/1, molar)	Treatment of symptoms of Advanced Prostate Cancer, Endometriosis, and Uterine Leiomyomata (Fibroids).
Emend®	Aprepitant as nanocrystal	Prevention of nausea and vomiting that may be caused by surgery or cancer chemotherapy.
Genexol®	Paclitaxel in 20–50 nm micelles composed of block copolymer poly(ethylene glycol)-poly(D,L-lactide)	Treatment of breast cancer, pancreatic cancer, and non-small cell lung cancer.

Inflexal® V	Influenza virus antigens (hemagglutinin, neuraminidase) on surface of 150 nm Liposomes	Inactivated influenza vaccine.
Macugen®	PEGylated anti-VEGF aptamer	Treatment of wet age-related macular degeneration.
Marqibo®	Vincristine sulfate encapsulated in sphingomyelin/cholesterol (60/40, molar) 100 nm liposomes	Treatment of Acute Lymphoblastic Leukemia (ALL: Philadelphia chromosome-negative), relapsed.
Megace ES®	Megestrol acetate as nanocrystal	Treatment of symptoms of loss of appetite and wasting syndrome in people AIDS-Related Cachexia, breast cancer or endometrial cancer.
Mepact™	Mifamurtide (synthetic muramyl tripeptide-phosphatidylethanolamine) incorporated into large multilamellar liposomes composed of 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine and 1,2-dioleoyl-sn-glycero-3-phospho-L-serine	Treatment of high-grade non-metastatic osteosarcoma (a type of bone cancer).
Mircera®	PEGylated epoetin beta (erythropoietin receptor activator)	Treatment of anemia (low red blood cell count) in people with long-term serious kidney disease (chronic kidney disease).

Myocet®	Doxorubicin encapsulated 180 nm oligolamellar liposomes composed of egg phosphatidylcholine/cholesterol (1/1, molar)	Treatment of metastatic breast cancer in adult women (aged 18 years or over).
Neulasta®	PEGylated filgrastim (granulocyte colony-stimulating factor)	Prevention of neutropenia caused by receiving chemotherapy.
Oncaspar®	PEGylated L-asparaginase	Treatment of acute lymphocytic leukemia (ALL), especially in patients who are allergic to L-asparaginase.
Opaxio®	Paclitaxel covalently linked to solid nanoparticles composed of polyglutamate	Treatment for: Non-Small Cell Lung Cancer, Ovarian Cancer, Glioblastoma Multiforme, Head and Neck Cancer.
Pegasys®	PEGylated interferon alfa-2b	Treatment of chronic hepatitis C.
PegIntron®	PEGylated interferon alfa-2b	Treatment of chronic hepatitis C.
Rapamune®	Rapamycin (sirolimus) as nanocrystals formulated in tablets	Immunosuppressive agent used to prevent the body from rejecting a transplanted kidney.
Renagel®	Cross-linked poly allylamine hydrochloride, MW variable	To control phosphorus levels in people with chronic kidney disease who are on dialysis.
Somavert®	PEGylated human growth hormone receptor antagonist	Treatment of acromegaly.

Spikevax®	lipid nanoparticle encapsulated COVID-19 mRNA Vaccine	Vaccine for prevention of coronavirus disease.
Tricor®	Fenofibrate as nanocrystals	Reduction of symptoms of cholesterol and triglycerides (fatty acids) in the blood.
Triglide®	Fenofibrate as insoluble drug-delivery microparticles	Reduction of cholesterol and triglycerides (fatty acids) in the blood and is used to treat high cholesterol and high triglyceride levels.
Visudyne®	Verteporfin in liposomes made of dimyristoyl-phosphatidylcholine and egg phosphatidylglycerol (negatively charged); lyophilized cake for reconstitution	Treatment of blood vessel disorders in the eye caused by macular degeneration and other eye diseases.
Zinostatin stimalamer®	Conjugate protein or copolymer of styrene-maleic acid and an antitumor protein NCS	Treatment of hepatocellular carcinoma.

(References: Debasis Bagchi *et al.*, 2013; Weissig, Pettinger and Murdock, 2014; Sainz *et al.*, 2015; Shetab Boushehri, Dietrich and Lamprecht, 2020; Khurana *et al.*, 2021; Nieto *et al.*, 2021)

The World Health Organisation (WHO) proclaimed pandemic caused by SARS-CoV-2 has resulted in the use of nanotechnology to develop vaccines to assist in easing the pandemic (Dube, Egieyeh and Balogun, 2021). Nanoparticles and viruses function at the same scale in terms of size; therefore, nanoparticles have an ability to enter cells to enable expression of antigens from delivered nucleic acids (mRNA and DNA vaccines) and/or directly target

immune cells for delivery of antigens (subunit vaccines) (Chung *et al.*, 2020). As such, vaccine technologies that employ these techniques by encapsulating genomic material or protein/peptide antigens in nanoparticles such as lipid nanoparticles (LNPs) or other viruses such as adenoviruses are being used. The BioNTech/Pfizer and Moderna SARS-CoV-2 vaccines involve encapsulation of mRNA vaccines within lipid nanoparticles while the University of Oxford/ Astrazeneca Astrazeneca) and CanSino incorporate antigen-encoding sequences within the DNA carried by Ads of nanoparticle dimensions (Chung *et al.*, 2020; Jackson *et al.*, 2020; Mulligan *et al.*, 2020). The Novavax vaccine deposits recombinant S proteins of SARS-CoV-2 onto their proprietary virus like particle (VLP) nanoparticles (Precision Vaccinations, 2021). In addition, nanotechnology offers an opportunity for the co-delivery of SARS-CoV-2 antigens and adjuvants. The three main methods are (i) co-delivery through encapsulation within or conjugation onto a nanoparticle, (ii) direct antigen-adjuvant conjugation, and (iii) utilizing the delivery vehicle as an adjuvant (Pati, Shevtsov and Sonawane, 2018; Wang and Xu, 2020).

2.3 Medicines regulation in southern Africa

A consistent supply of safe, efficacious, good quality and affordable medical products is key to the promotion of public health and patient care (Ndomondo-Sigonda *et al.*, 2017). To protect the public health and well-being, the pharmaceutical industry is one of the highly regulated industries, with many enforceable rules and regulations (Handoo *et al.*, 2012). This mandate is carried out by medicines regulatory agencies in the respective countries.

Modern medicines regulation started in the 19th century (Rägo and Santoso, 2008). In the United States Federal Food, Drug and Cosmetic Act with the premarket notification

requirement for new drugs was introduced in 1938 (Ndomondo-Sigonda *et al.*, 2017). In the United Kingdom, a Committee on the Safety of Drugs was started in 1963 followed by a voluntary adverse drug reaction reporting system in 1964 (Rägo and Santoso, 2008). The activities involved in medicines regulation incorporate integrated reinforcing activities all aimed at promoting and protecting public health. These activities include medicines registration (marketing authorization), licensing of activities related to medicines supply, import and export control, inspections, quality control, market surveillance (product quality monitoring, pharmacovigilance, control of promotion and advertising) and oversight of clinical trials (WHO, 2010a). With respect to medicines registration, medical products are required to conform to certain standards on safety, efficacy and quality before they can obtain registration. This requires submission of medicines information in the form of a dossier. The information on the product is then assessed to ascertain if the risk-benefit balance is favourable in the quality, safety and efficacy.

In Africa, all countries with the exception of Sahrawi Arab Democratic Republic have either a regulatory agency or a unit within the ministry responsible for health that is responsible for issues related to the regulation of medicines (Sithole *et al.*, 2020). Medicines regulatory systems and capacities to regulate medical products among these regulatory agencies or units vary, are largely uneven and are heavily dependent on financial and technical support from international donors (Pezzola and Sweet, 2016). The WHO in 2010 reported that 7% of the 46 sub-Saharan African countries have moderately developed medicine regulatory capacity and more than 90% have minimal or no capacity (WHO, 2010a). The relatively low capacity of the NMRAs can be attributed to shortages of human resources, technical capacity, and funding (Goñi, 2016).

In order to strengthen medicines regulation in Africa, several efforts have been made; the key being establishment of the African Medicines Regulatory Harmonisation (AMRH) initiative in 2009 (Ndomondo-Sigonda *et al.*, 2017). The goal of the AMRH initiative is to achieve a harmonized medicines registration process in countries belonging to the RECs, based on common documents, processes, and shared information systems (Goñi, 2016). It also aims at creating more effective, efficient and transparent regulatory mechanisms in various African markets through collaborative regional mechanisms that, among others, achieve faster medical product approvals (Ndomondo-Sigonda *et al.*, 2018; Ncube, Dube and Ward, 2021). The intention of the AMRH is to expand its scope of work gradually, commencing with generic medicine registration and moving towards oversight of registration of new chemical entities among other medical products (Ndomondo-Sigonda *et al.*, 2017, 2018). It is envisioned that a single African Medicines Agency (AMA) will be established from the foundation set by the AMRH (Ndomondo-Sigonda and Ambali, 2011). As of September 2021, 15 African Union Member States had ratified the treaty for the establishment of AMA (Huihui Wang, Patricio V. Marquez, 2021). The intended purposes of AMA are coordination of on-going regulatory systems, strengthening and harmonizing efforts of the African Union-recognized RECs, provision of regulatory guidance and enhancement of collaboration and contribution to improving patients' access to quality, safe and efficacious medical products and health technologies on the continent (African Union, 2021a).

In an effort to promote consistency of policy and legal frameworks, AUDA-NEPAD and key stakeholders developed the AU Model Law on Medical Products Regulation. The law was endorsed by the AU Heads of State and Government in 2016, to act as a reference guide to AU Member States as they update or enact national law (Ndomondo-Sigonda *et al.*, 2017). Since inception of the AMRH, major progress has been made with regards medicines

regulation harmonization among Regional Economic Communities (RECs). RECs are regional groupings of African states which were developed individually to facilitate regional economic integration between members of the individual regions and through the wider African Economic Community (African Union, 2021b). The African Union recognises eight RECs;

- Arab Maghreb Union (UMA)
- Common Market for Eastern and Southern Africa (COMESA)
- Community of Sahel–Saharan States (CEN–SAD)
- East African Community (EAC)
- Economic Community of Central African States (ECCAS)
- Economic Community of West African States (ECOWAS)
- Intergovernmental Authority on Development (IGAD)
- Southern African Development Community (SADC).

Of these communities; EAC, ECOWAS, ECCAS, IGAD and SADC have made strides towards medicines regulation harmonisation. The East Africa Community Medicines Regulatory Harmonization Programme was launched on 30th March 2012 by the EAC Council of Ministers in Arusha, United Republic of Tanzania (EAC, 2021). In West Africa, the Economic Community of West African States officially launched the Medicines Harmonisation Regulations project in February 2015 in Accra, Ghana (AUDA-NEPAD, 2016). To initiate activities in the Central Africa region, AUDA-NEPAD, in collaboration with the Organization of Coordination for the Fight against Endemic Diseases in Central Africa (OCEAC), ECCAS and WHO, developed a collaborative framework to spell out activities with clear roles and responsibilities for partners involved in the implementation of the harmonisation activities.

Furthermore, a mapping exercise was carried out in 2016 to establish the status of regulatory systems in Member States (Magubane and Robles, 2017).

In April 2016, the IGAD Member States signed the Khartoum Declaration to Call for Action towards the implementation of a regional medicines regulatory collaboration and harmonisation programme (Owusu-Danso, 2019). This call for action further stipulated the support for the development of an overarching regional pharmaceutical policy and the adoption of modern legislative frameworks based on the AU Model Law (AUDA-NEPAD, 2021). SADC is a REC comprising 16 member states: Angola, Botswana, Comoros, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe (SADC, 2021). In 1999, the SADC Protocol on Health in which heads of states agreed that member states shall "cooperate and assist one another in the harmonization of procedures of pharmaceuticals, quality assurance, and registration was developed (SADC, 1999). Subsequently, a SADC Pharmaceutical Business Plan, which is reviewed and renewed periodically was established. Strengthening of regulatory capacity by supporting and actively encouraging joint inspections and registrations among SADC Member States was included as one of the strategic priority areas for the 2015–2019 plan.

The ZAZIBONA collaborative medicines registration initiative was established in 2013 by four countries, Zambia, Zimbabwe, Botswana, and Namibia, with technical support from the WHO Prequalification Team (PQT) (Gwaza *et al.*, 2014). In 2014, the initiative was formally endorsed by the SADC Ministers of Health & Ministers Responsible for HIV & AIDS and was recommended for expansion to other SADC Member States beyond the 4 founding Member

States (Sithole et al., 2020). Successively, in 2015, the SADC region joined the Medicines Regulatory Harmonization (MRH) project. The objectives of the SADC MRH project are to:

- ensure that at least 80% of member states have NMRAs that meet minimum standards
- ensure regional harmonization of medicines regulatory systems and guidelines,
- facilitate capacity building of medicines regulatory authorities in member states through implementation of quality management systems (QMS) and
- develop and implement national and regional integrated information management systems (IMS) to facilitate decision-making and sharing of knowledge among member states and stakeholders."
- strengthen and expand areas of technical cooperation among member NMRAs through initiatives such as ZAZIBONA (SADC, 2011)

Participation in the ZAZIBONA initiative is voluntary and any SADC country wishing to participate in the initiative should submit a request to join to the Heads of Agencies (Sithole *et al.*, 2020). Depending on the availability of legislation mandating the registration of medicines as well as in-house capacity to perform assessments, countries requesting to participate in the work-sharing initiative are designated as either as active or non-active members. The countries actively participating in ZAZIBONA and their year of joining the initiative are depicted in the figure below.

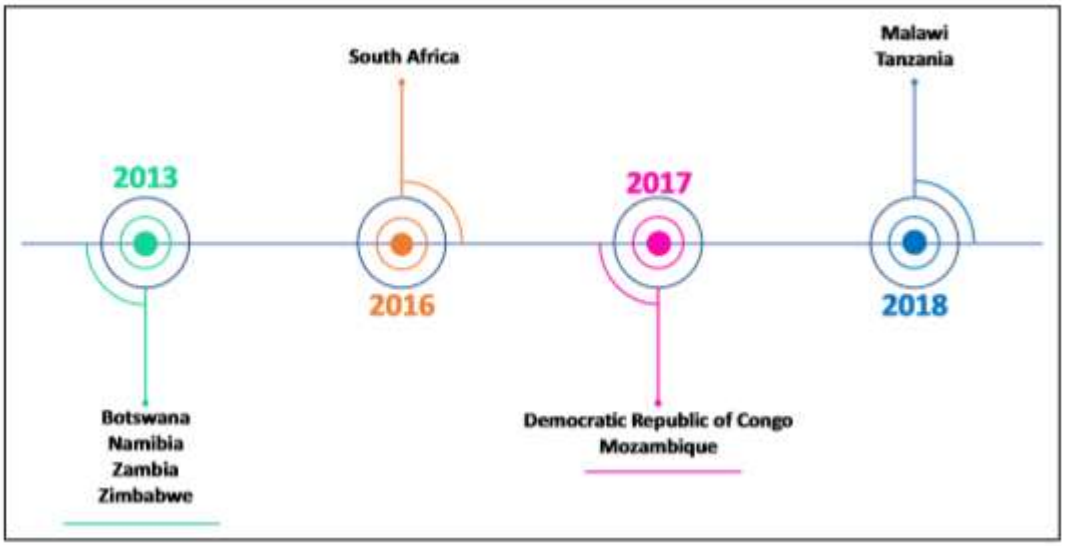


Figure 3: ZaZiBoNa active members and their initiation date (source: Sithole *et al.*, 2020).

The ZAZIBONA registration procedure has yielded substantial success; as of October 2019, 24 assessment sessions had been held and a total of 289 products had been considered under the initiative (Sithole *et al.*, 2020). ZAZIBONA assessment sessions are held quarterly. Products eligible for assessment under the ZAZIBONA initiative consist of all essential medicines and medicines used in the treatment of the SADC priority conditions. In addition, other products can also be considered if they are important from a public health perspective.

2.4 Regulation of nanomedicines and related challenges

As with all medical products, nanomedicines are subject to regulation and monitoring and must undergo extensive characterization, toxicity assessment and clinical trials before their full potential is realized for the benefit of patients. They also have to be granted marketing authorisation before they can be marketed. This responsibility usually lies with medical product regulatory authorities in the countries. Due to the complexity of nanomedicines, regulators are faced with the challenge of attempting to balance the need for timely patient access and the

promotion of innovation against the need to protect the public's health by guarding against potentially unsafe emerging medicines (Harris, 2009). In addition, issues to do with classification of these products are not easy as most of them have multiple functions (Morrison, 2008). For example, a nanomedicine can be used to unclog arterial walls, which would render it a device, but this same product can also administer a cancer-fighting treatment, which would make it a medicine (Harris, 2009). An example of such a scenario is SilvaGard®, an antimicrobial nanoparticle silver that provides an effective, broad-spectrum antimicrobial functionalization to the surface of devices. This prevents biofilm formation, which typically serves as the reservoir for pathogens that cause recurrent infections associated with indwelling devices (Elrod, 2008). Furthermore, due to the constant changes in nanotechnology, it may not be possible for regulators to maintain an adequate level of scientific expertise to assess the safety and efficacy of nanomedicines.

The clinical use of nanomedicines is strongly dependent on in-depth assessment, characterization and understanding of crucial properties such as size variability, morphology and charge (Sainz *et al.*, 2015). This raises scientific and analytical concerns in the context of nanomedicines regulation. Firstly, nanomedicines have brought about the need for new quality control assays and robust methods that have to be developed in order to effectively monitor and characterize not only their physicochemical properties, such as size and size variability, morphology and charge, but also to assess their performance in relation to drug release, biodistribution, metabolism, protein binding and cellular uptake (Tinkle *et al.*, 2014). Secondly, nanomedicines are known to interact with immune cells and to adsorb plasma proteins. As such there is need for appropriate assessment of toxicity during the development studies meant to optimise dosage regimen, therapeutic index, administration route and targeted disease environment (Dobrovolskaia and McNeil, 2013). Nanoparticles also have the potential

to induce toxicity due to their material composition and any surface functionalization (Karnik *et al.*, 2008). The change in the physicochemical and structural properties of engineered nanoparticles with enhanced surface area to volume ratio could be responsible for the interactions that could lead to toxicological effects (Liu, 2014). Increased penetration of nanoparticles within the lungs causes airway blockage leading to alveoli dysfunction (Maynard, Warheit and Philbert, 2011).

Another difficulty associated with the regulation of nanomedicines is the nature of information to be provided before and during the product life cycle, requiring *in vivo* animal and clinical studies (Sainz *et al.*, 2015). The mechanism of action for nanomedicines involves delivery of drugs locally in high doses at a particular cellular site. This mechanism of drug delivery requires extensive safety data at as it might lead to a number of adverse effects. Furthermore, due to the small size of these medicines, they possess exceptional mobility quality; as a result, they may cross the blood brain barrier (Rajneesh Kumar Gaur, 2013).

With regards GMP, complications relating to facilities design and infrastructure and its limitations, as well as the impact of nanomaterials in the environment which are dependent both on reported physical characteristics and available information from the biologic effects of specific nanomaterials need to be considered (Gaspar, 2007). There is also need to carefully assess cross-contamination among different products manufactured in the same facility, since physical properties vary from conventionally manufactured materials that are manufactured in the same facilities. Concerns have been raised on the ability of the innovative manufacturing processes to consistently produce similar batches as well as their scale-up potential, mostly due to the extensive diversity of properties of the materials used for synthesis (Gaspar, 2010).

Regulators internationally are also being challenged with the new wave of 'nanosimilars' which bring issues of appropriate comparability studies with the innovator nanomedicine (Haubenreisser, 2014). Nanosimilars are follow-on products which are similar to an innovator product for which the patent has expired (Ehmann *et al.*, 2013). Some of the first-generation nanomedicines that to come off patent were iron–carbohydrate (iron–sugar) drugs, a number of liposome products, and glatiramoids (Hussaarts *et al.*, 2017). Like for simple pharmaceutical molecules, authorization of these generic products is based on showing pharmaceutical equivalence and bioequivalence to the listed reference innovator product thus demonstrating therapeutic equivalence and suitability for interchangeability or substitutability (Astier *et al.*, 2017) . However, due to the complexity of nanomedicines, showing equivalence has proven to be challenging for nanosimilars (Ehmann *et al.*, 2013). Consequently, due to lack of demonstration of molecular and functional similarities, reduced requirements for clinical studies cannot be implemented thus implying the possible need for Phase I-IIA clinical trials (Halamoda-Kenzaoui, Box, *et al.*, 2019). Following approval for use of iron-sucrose nanonosimilars, which were approved on the basis of physicochemical comparability to the iron–sucrose originator (Venofer R®) but without considering the nano-colloidal character of the products, efficacy and safety issues were observed during clinical use (Rottembourg *et al.*, 2011; Lee *et al.*, 2013; Agüera *et al.*, 2015). For example, in a certain practice, the use of iron sucrose similar was discontinued owing to safety concerns outweighing the theoretical cost benefit. The question on the appropriateness of approval process for complex drugs and if these can be substituted without appropriate clinical testing, both for efficacy and most importantly safety, in routine clinical practice was raised (Lee *et al.*, 2013).

Regional differences in acceptance of nanosimilars also demonstrates challenges associated with nanosimilars. For example “Doxorubicin SUN" was accepted as a generic drug of the reference product "Doxil" by the USFDA. The same nanosimilar was presented in Europe as a generic liposomal formulation of doxorubicin referring to the European innovator product. Caelyx®. However, the product was not recommended for authorisation in the European Market due to major non-clinical and clinical objections (Bremer *et al.*, 2016; Halamoda-Kenzaoui, Holzwarth, *et al.*, 2019). Major concerns regarding the reliability of the data and signals of a lack of equivalence between the two products were raised (European Medicines Agency, 2004).

These challenges are likely to be worse in the African region due to the weak or absent medicines regulatory systems, unclear regulatory policies, lack of competent regulatory professionals in National Medicines Regulatory Authorities (NMRAs) as well as incomplete or incoherent regulatory frameworks (Ndomondo-Sigonda *et al.*, 2018; Ravinetto, Pinxten and Rägo, 2018; Ncube, Dube and Ward, 2021). Efforts are therefore needed to put in place regulatory frameworks and guidelines for nanotechnology based products so as to ensure that these are adequately regulated.

2.5 EMA and USFDA approach to regulation of nanomedicines

Regulation of nanomedicines by the USFDA was included under the already existing statutory and regulatory structure rather than establishment of a separate framework for regulation of such products. To complement the existing structure to the requirements for nanomedicines, the USFDA maintained its policies for product-focused, science-based and product-specific technical assessments, taking into account the effects of nanomaterials in the particular

biological and mechanical context of each product and its intended use. In addition, attention to nanomaterials was incorporated into existing procedures (FDA, 2013). Specific guidelines have also been developed to discuss the use of nanotechnology or nanomaterials in FDA-regulated products. These include:

- Guidance for Industry - Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives
- Guidance for Industry - Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology
- Guidance for Industry - Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation
- Guidance for Industry - Safety of Nanomaterials in Cosmetic Products
- Guidance for Industry - Use of Nanomaterials in Food for Animals
- Draft Guidance for Industry - Drug Products, Including Biological Products, that Contain Nanomaterials

With regards safety and efficacy data for nanomedicines applications, the requirements are the same as for non-nanobased products with the obligation to provide evidence of safety and efficacy resting on the sponsor. In addition, due to presence of nanoscale materials which are responsible for high reactivity, and unique mechanical and magnetic properties a sponsor should provide additional safety and efficacy information of nanomedicines (Rahman *et al.*, 2018).

In Europe, the responsibility for the regulation of nanomedicines has also remained with the European Medicine Agency (EMA) as well as national regulatory agencies of each member state as for all medicines. To provide clearer guidance, the European Union has published a definition of nanomaterials and has also provided confirmation that nanotechnology-based drugs follow the standard process for the assessment of any other medicines, as well as its toxicological assessment (Tobler and Rocha, 2020). The EMA has also published several scientific guidelines and reflection papers on nanomedicines and these include.

- Guidance document on data requirements for intravenous iron-based nano-colloidal products developed with reference to an innovator medicinal product
- Guidance document on data requirements for intravenous liposomal products developed with reference to an innovator liposomal product
- Guidance document on development of block-copolymer-micelle medicinal products
- Guidance document on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products
- Reflection paper on general issues for consideration regarding the parenteral administration of coated nanomedicines
- Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product
- Reflection paper on the development of block-copolymer-micelle medicines , jointly developed by the Agency and the Japanese Ministry of Health, Labour and Welfare
- Reflection paper on the data requirements for intravenous iron-based nanocolloidal products developed with reference to an innovator medicine

2.6 Harmonisation in regulatory practices of nanomedicines

Today's medicines regulation system is characterized by increasing levels of harmonization – from collaboration on selected topics, to Mutual Recognition Agreements (MRAs), all the way to full integration, as with the European Union (Strachan, 2017). Harmonization of regulatory requirements has many benefits to the regulators, applicants for marketing authorisation as well as the public (WHO, 2019). It ensures constructive marketing conditions that promote early access to medicinal products, promotes regulators' efficiency, and reduces unnecessary duplication of work (Ndomondo-Sigonda *et al.*, 2021). In the area of nanomedicines, progress has been made towards harmonisation of regulatory practices. The International Pharmaceutical Regulators Programme (IPRP) created in 2018 to promote convergence of regulatory approaches for pharmaceutical human medicinal products established a Nanomedicines Working Group (NWG) (IPRP, 2021). The NWG was established to discuss nanotechnology related issues relevant to regulated products that may contain nanoscale materials. It works on the exchange of non-confidential information on nanomedicines and nanomaterial in drug products and borderline and combination products (IPRP, 2020). IPRP Members and Observers participating in the NWG as of October 2019 are:

- National Administration of Drugs, Foods and Medical Devices, Argentina
- Agência Nacional de Vigilância Sanitária, Brazil
- Federal Committee for Protection from Sanitary Risks, Mexico
- European Commission /European Medicines Agency, Europe
- Food and Drug Administration, United States
- Health Canada, Canada
- Health Sciences Authority, Singapore
- Ministry of Food and Drug Safety, Republic of Korea

- Ministry of Health, Labour and Welfare/ Pharmaceutical and Medical Device Agency, Japan
- Swiss Agency for Therapeutic Products (Swissmedic), Switzerland
- Taiwan's Food and Drug Administration (TFDA), Chinese Taipei
- Therapeutic Goods Administration, Australia

To date, the NWG has conducted some work including conducting surveys on liposomes, mapping nanomedicines terminology in the regulatory landscape and identification of regulatory needs for nanomedicines (IPRP, 2020). With regards the survey conducted on liposomes, the working group intended to map and exchange regulatory requirements and research needs for medicines that contain liposomal products amongst stakeholders. The survey noted that nearly all jurisdictions responding to the survey, indicated that a critical challenge is the assessment of nanosimilar liposomal products. In addition, as all respondents used either a classical or scientific definition for liposomes it was concluded that it may be possible to produce a common definition that would be acceptable to all respondents (IPRP, 2018).

In 2016, a mapping survey on nanomedicine terminology in the regulatory landscape was conducted by the NWG. The aim of the survey was to understand and demonstrate the actual complexity and large amount of terminology used to describe nanotechnology applications in the health sector. The study was also intended to support the discussion towards a harmonised terminology that may foster the clinical translation of emerging nanomedicine products (IPRP, 2016). The working group also conducted a survey with the aim to get a general overview on the status and regulatory needs of nanomedicines and indicate some trends on future requirements. The survey confirmed that some regions were more advanced in marketing nanomedicines than others. These regional differences called for a close collaboration of

various regulatory bodies in order to share experiences in the assessment of nanotechnology based products (Bremer *et al.*, 2016)

CHAPTER THREE: WORK PLAN

3.1 Statement of the problem

The development of 'follow-on' nanotechnology based products is a clear indication that nanotechnology will continue to be utilised in medicines development and may actually be the basic technology of pharmaceutical products in the foreseeable future. To promote safe and effective use of nanomedicines, there is need for high standards of regulation with clear regulatory frameworks. This will promote better access to such new technology-based products. Lack of training, expertise and inadequate knowledge regarding nanomedicines behaviour, lack of understanding on different mechanisms and how the nanoparticles are presented to organs, cells and organelles may present regulatory challenges to African regulatory agencies. Furthermore, lack of guidelines, policies and good assessment practices specific for nanomedicines may result in irregularities in the overall review process, poor quality reviews, reduced efficiency which may have a negative impact on public health.

Due to the complexity of these products, development of such frameworks may require a regional integrated approach, so as to maximise on the limited expertise that may be available for such products. Possibilities for international harmonisation and convergence are to be explored with the aim for better regulation of these complex products.

3.2 Study Aim

The aim of this study was to establish the status of regulation of nanomedicines in the ZAZIBONA active countries, i.e. Botswana, Democratic Republic of Congo, Malawi,

Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe. The study focused on ZAZIBONA active countries as these are the countries with in-house capacity to perform assessments.

3.3 Study objectives

The main objective was to obtain an overview of the assessment practices of nanomedicines in the countries, with a view to identify any challenges faced as well as documenting capacity building needs, being cognizant of the AMRH initiative whose intention is to extend to other product categories such as NCEs, vaccines and diagnostics, in addition to the generic products.

The objectives of the study were to:

a) Determine regulatory experience with nanomedicines among the ZAZIBONA active countries
b) Analyse legislation, guidelines and policies with a focus on nanomedicines registration
c) Review the assessment practices implemented in establishing safety, efficacy and quality of nanomedicines before granting them marketing authorization
d) Identify challenges, barriers and constraints regarding regulation of nanomedicines and exploring opportunities for possible harmonisation among ZAZIBONA active countries
e) Document perceived needs for capacity building with regards to nanomedicines

CHAPTER FOUR: METHODS

A cross-sectional exploratory study design with qualitative techniques was used. A study sample consisting of regulatory authorities active in the ZAZIBONA joint assessments was used in the questionnaire based, cross-sectional study.

4.1 Study Setting

All nine countries participating actively in ZAZIBONA joint assessments were included in the study. These are Botswana, Democratic Republic of Congo, Malawi, Mozambique, Namibia, South Africa, Tanzania, Zambia and Zimbabwe.

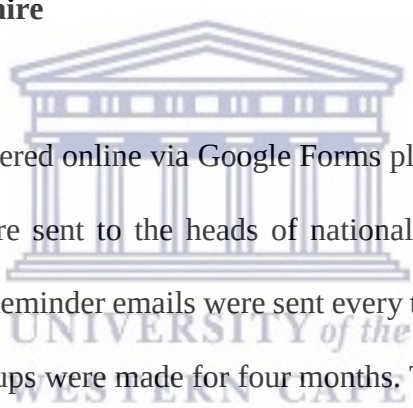
4.2 Development and piloting of Questionnaire

A questionnaire was formulated based on the objectives set for the study. Questions to gather information on awareness of nanomedicines, existence of legal mandate and regulatory framework to regulate nanomedicines were included in the questionnaire. In addition, questions to ascertain regulatory experience with nanomedicines; and areas that were perceived as important for process improvement in the regulation of nanomedicines were included in the questionnaire. The questions included if the regulatory agencies had specific definitions for nanomedicines, legal provisions that cover regulation of nanomedicines, guidance documents for submission and assessment of nanomedicines applications, existence of specific technical committee for consideration of advanced medicines including nanomedicines, in-house assessment templates for nanomedicines and if any regional harmonisation activities the

NMRAs participated involved nanomedicines applications. A copy of the questionnaire is attached in appendix A.

The tool was piloted with one country participating in ZAZIBONA as a non-active member, i.e. Eswatini. The tool was assessed for volatility, ease of use and comprehensiveness. The pilot country was chosen as it is regularly involved in the ZAZIBONA assessment activities. Although the country does not participate in ZAZIBONA with an active status, Eswatini has been involved with the initiative since November 2016, participating in all relevant meetings. Findings of the pilot study with Eswatini are therefore representative of the active countries.

4.3 Distribution of Questionnaire



The questionnaire was administered online via Google Forms platform. Emails containing the link to the online platform were sent to the heads of national regulatory authorities of the ZAZIBONA active countries. Reminder emails were sent every two weeks, if no response was received. Further email follow-ups were made for four months. Thereafter, if no response was received, it was assumed that the country was unwilling to participate in the study.

4.4 Data Analysis

Thematic and descriptive analysis were used. Thematic analysis is the "method for identifying and interpreting patterns of meaning across qualitative data" (Clarke and Braun, 2014). Descriptive analysis is a type of data analysis that helps describe, show or summarize data points in a constructive way such that patterns might emerge that fulfil every condition of the data (Rawat, 2021). Responses were coded into thematic categories for interpretation. Trend

analysis was conducted, involving an in-depth analysis of patterns and compared according to country perspective.

4.5 Ethics

The methodology and ethics of the research project was approved by the Humanities and Social Science Research Ethics Committee of the University of the Western Cape, ethics approval number HS20/3/8. Written consent was also received from participants in the questionnaire. A copy of the ethics approval letter is attached in Appendix B.

Confidential and proprietary information was not collected in the study. Consent was also sought to have individual NMRA's responses shared and their names unblinded in any publication resulting from the study.

CHAPTER FIVE: RESULTS AND DISCUSSION

The study was intended to obtain an overview of the assessment practices of nanomedicines applications in the ZAZIBONA active countries, with a view to identify any challenges faced as well as documenting for capacity building needs, being cognizant of the AMRH initiative's vision to extend its scope to other product categories, in addition to the generic products. An online questionnaire with qualitative multiple choice and open-ended questions was administered to the nine National Medicines Regulatory Authorities of the ZAZIBONA active countries. Seven of these NMRAs responded to the survey.

The results attained were classified into four categories: (i) awareness of nanomedicines (ii) existence of regulatory framework (iii) regulatory experience with nanomedicines; and (iv) areas for improvement in the regulation of nanomedicines.

5.1 Awareness of nanomedicines

In order to ensure the respondents had an understanding of nanomedicines, they were asked if they were aware of the existence of nanomedicines. One respondent indicated that they were not aware of the existence of nanomedicines while the majority (n=6) of the respondents were aware of the existence of nanomedicines. The high level of awareness by medicines regulators of the ZAZIBONA active countries could be explained by the fact that at least one person in each agency received training on assessment of advanced drug delivery systems including nanomedicines in five of the seven organisations. This opinion is further discussed below.

For the one respondent that indicated that they were not aware of nanomedicines, it was

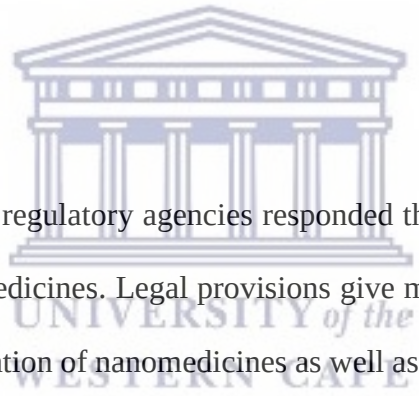
observed that there was no person in their agency that had received training on assessment of advanced drug delivery systems including nanomedicines. This could also explain why the respondent was unaware of nanomedicines. Another reason for unawareness by this respondent could also be lack of exposure to nanomedicines since the same respondent also indicated that they had not received any applications for approval of any of the EMA or USFDA approved nanomedicines.

The results of this study are not very similar to those of other studies that have been conducted on awareness of nanotechnology, although not necessarily specific to NRAs. A 2010 Eurobarometer survey conducted in 32 European countries, revealed that about 45% of the population had heard of nanotechnology. 45% of Europeans said they had heard of nanotechnology, and 60% expressed their support for nanotechnology applications (Gaskell *et al.*, 2005). Similarly, in an online survey conducted in Austria, 26.1% of the participants indicated that they were not aware of nanotechnology and reported that they had no related knowledge, 60.7% reported to know a little about nanotechnology, while 13.2% felt well or very well informed (Joubert *et al.*, 2020). In South Korea, a comparative analysis of nanotechnology awareness in consumers and experts of nanotechnology pointed out that the expert group recognized that they knew more than consumers about nanotechnology and that there was a need for relevant education in nanotechnology and nanomaterials among consumers (Kim *et al.*, 2014).

Despite all these results, there is no published literature on awareness of nanomedicines, let alone awareness by medicines regulators. Awareness of nanomedicines by medicines regulators is considered worth studying as regulators have a privileged knowledge position. As such, they are expected to be aware of trends and emerging technologies related to medicines.

Moreover; these regulators are responsible for ensuring the quality, safety and efficacy of these products. Their opinion and awareness are also likely to influence public perception and acceptability of nanomedicines by the general public. Furthermore, awareness, knowledge and understanding of nanomedicines by regulators are important prerequisites for the contribution to the development, implementation and maintenance of effective medicines regulatory systems. If the regulators are not aware of products under their jurisdiction they will not know of the need to regulate them and patients may be exposed to ineffective and unsafe nanomedicines.

5.2 Regulatory framework



5.2.1 Legal Provisions

In this study, four of the seven regulatory agencies responded that they have legal provisions that cover regulation of nanomedicines. Legal provisions give mandate to national regulatory authorities to oversee the regulation of nanomedicines as well as enforcement powers over the requirements. It is therefore expected that the NMRAs with legal provisions for the regulation of medicines are already in positions to regulate nanomedicines. With regards the details of the legislation that cover regulation of nanomedicines, the agencies pointed out to the fact that the agencies are mandated to regulate all medicines irrespective of the technology applied. As such, legislation that mandates regulation of all medicines and medical products also applies to nanomedicines.

These observations are similar to the results observed in a survey conducted in 2010 by the Organisation for Economic Co-operation and Development (OECD) Working Party on Nanotechnology. In the survey of organisations responsible for the regulation of medical

products in Canada, the European Union (European Commission and European Medicines Agency), France, Germany, Japan, Netherlands, Poland and Russia, revealed that each organization had at least one legislative act on the regulation of medical products involving nanotechnology (OECD, 2013). Furthermore, the delegations in the OECD study identified existing legislation for medical product areas as legislation that applied to products containing nanomaterial or otherwise involve the application of nanotechnology in most cases. Similar responses were also noted in this study, in which the respondents indicated that their regulatory agencies are mandated to regulate all medicines irrespective of the technology applied.

Rather than developing separate legislation specific for nanomedicines, the approach taken by the respondents of this survey as well as the OECD survey is expected to streamline and simplify the regulatory process as the nanomedicine issues are merely incorporated into the already existing structures of regulation.

The USFDA also adopted a similar approach. They indicated that nanomedicine is not different to any other new technology that is incorporated into FDA products. As such, there was no need for regulations written specifically for nano-engineered materials in the products regulated by FDA. Consequently they were content in using their existing regulatory framework (Culliton, 2008). Other schools of thought however indicate the need for development of a specific legislative framework for nanomedicines (Szabat-Iriaka and Le Borgne, 2021; Vitanov, 2021). The basis of these arguments are that current legislations for medical products are not specific for nanomedicines, neither are they sufficient to address complex issues related to nanomedicines. In addition, nanomedicines may be developed as medicines or devices or a combination of the two. In the latter case, either medical devices or conventional pharmaceutical regulatory principles will have to be applied. This will augment

uncertainty in the regulatory pathway of the products and possibly affect research and development as well as commercialization of nanomedicines (Bhatia and Chugh, 2017).

Of the three respondents that did not have legal provisions that cover regulation of nanomedicines, two had not received applications for approval of any of the USFDA and EMA approved nanomedicines listed in the questionnaire. Lack of receipt of such applications could have been because the authorities are not mandated to regulate nanomedicines. The reverse could also be considered possible; the authorities may have not seen the need to develop legislation for the regulation of nanomedicines as they have never received applications for registration of such products. For the other respondent who indicated that their regulatory agency did not have provisions that covered nanomedicines, it is observed that their regulatory agency have received the highest number of applications for nanomedicines in comparison with the other agencies in the survey. Also, the same respondent indicated that they were a member of the of the IPRP and they were in the process of developing guidance documents for applicants as well as in-house guidance documents to assist with assessment of nanomedicines. The negative response regarding legal provisions for regulation of nanomedicines could therefore have been an oversight on the respondent's part as it is unlikely to have not been possible for the regulatory agency to receive applications for market approval without the mandate. On the other hand, the NMRA could be in the process of revising their legislation such that it includes nanomedicines

5.2.2 Definition of nanomedicines

None of the respondents had a specific definition for nanomedicines. Their definition for nanomedicines falls under the general definition for medicines, which includes all products that are used in man or in animals for (a) the diagnosis, treatment, mitigation or prevention of

disease or any abnormal physical or mental state or the symptoms thereof in man or in animals; or (b) restoring, correcting or modifying any physical, mental or organic function in man or in animals. These observations are similar to the approach taken by the USFDA who does not have a formal regulatory definition for nanomaterials, nanoscale, nanotechnology or nanomedicine. Instead, the agency took a broad, inclusive approach by determining whether the products they regulate contain nanomaterials or whether they involve nanotechnology (FDA, 2020).

EMA also does not have a formal definition of nanomedicines. Like the USFDA, they have a working definition that takes into consideration if the product (i) is purposely designed for clinical applications; (ii) contains at least one component at nanoscale size; (iii) results in definable specific properties and characteristics related to the specific nanotechnology application and characteristics for the intended use (route of administration, dose) and associated with the expected clinical advantages of the nanoengineering (e.g. preferential organ/tissue distribution) and (iv) meets the definition as a medicinal product according to European legislation (Haubenreisser, 2014).

Globally, there is also no consistent and uniform definition of nanomedicines. For example, the US National Nanotech Initiative in their definition for nanomedicines clearly refer to the nanoscale (1-100nm). On the other hand, the European Science Foundation and the European Technology Platform on Nanomedicine do not refer to it (Webster, 2006). In the context of SADC medicines regulation, regulatory agencies in the ZAZIBONA active countries should consider coming up with a working definition for nanomedicines. This would considerably facilitate effective regulation of nanomedicines. With a clear definition or a working definition, the risk of miscommunication with various stakeholders is minimised. Working definitions

adopted by the other jurisdictions can be considered. Descriptions may be considered instead of definitions. For example, the IPRP NWG does not have a specific definition and instead describes nanomedicines as a rapidly emerging and evolving drug product category with the potential to provide earlier disease detection, improve the precision of diagnosis and improve patient outcomes while potentially reducing adverse reactions and health care costs (IPRP, 2020). The regulatory agencies can consider any situation that fits them best, but should in the end be able to communicate what they mean by nanomedicines with all their relevant stakeholders.

5.2.3 Guidance documents for the submission of applications for market approval of nanomedicines

None of the regulatory agencies had specific guidance documents which cover submission of quality, non-clinical/safety and clinical information for applications for nanomedicines. However, one regulatory agency indicated that it is a member of the IPRP and therefore, it applies that the principles, guidance documents and templates as laid out by the IPRP for nanomedicines. Furthermore, the same regulatory agency stated that they use guidance documents from the EMA which they rely upon. Lack of specific guidance documents which cover submission of quality, non-clinical/safety and clinical information for applications for nanomedicines in all the responding regulatory agencies is likely to impair applicants' capacity to deal with the inherent uncertainty surrounding requirements for applications of nanomedicines. Regulatory and administrative guidelines are instrumental for interpreting and providing operational clarity to regulations and requirements as they improve the quality and language of a regulatory instrument (World Health Organisation, 2021). When applicants are not aware of the information required when submitting applications for approval, the quality

of information submitted may not meet the requirements set by the regulator. As a result unnecessary time may be taken in finalisation of these applications and consequently it may take longer than necessary to make the products accessible to the public.

The absence of nanomedicines specific guidelines in the responding countries could be explained to be as a result of the relatively low number of applications of nanomedicines received in each of the countries of the responding national regulatory authority. In turn, the low number of applications could be a result of small markets for nanomedicines in these countries. Sub-Saharan pharmaceutical market's value is still relatively small, at roughly $14 billion compared with roughly $120 billion overall in China and $19 billion in India (Conway *et al.,* 2019). In order to ensure that the public have access to these innovative medicines that bring great potential for the treatment of diseases, the sub-Saharan countries could consider pool procurement of nanomedicines as a region. In addition to this, harmonised guidance documents to facilitate approval of these nanomedicines and ease the application process could be developed to assist applicants in submitting applications for registration in the SADC region. Establishment of the AMA may also possibly address such issues by implementing agreed procedures and processes and coordinating regulatory practices across the region. Such coordinated regulatory and pooled procurement efforts could motivate manufacturers and marketing authorisation holders to supply the innovative nanomedicines to SADC countries. With the use of nanotechnology based COVID-19 vaccines steadily spreading across the globe, submission of applications for emergency use authorisation of these vaccines may also prompt SADC countries to develop specific guidelines for nanomedicines.

To complement the availability of regulatory requirements, guidelines should be easily accessible. Once guidelines for nanomedicines have been developed, regulatory agencies

should ensure that nanomedicines specific regulatory guidelines are easily accessible to applicants, for example by publishing on their respective websites.

Jurisdictions in other regions of the world have developed guidelines specific for nanomedicines. EMA, for example, has developed scientific guidelines on nanomedicines to assist manufacturers to prepare marketing authorisation applications for human medicines. These include specific guidelines for intravenous iron-based nano-colloidal products, intravenous liposomal products, block-copolymer-micelle medicinal products and general issues for consideration regarding parenteral administration of coated nanomedicine products (EMA, 2021). Similarly, the USFDA has issued guidance for industry to offer advice, including advice to determine the regulatory status of nanotechnology products and evaluating their safety. These guidelines include guidance on considering whether an FDA-Regulated Product involves the application of nanotechnology, guidance on safety of Nanomaterials in Cosmetic Products, guidance on liposome drug products and guidance on drug Products, Including Biological Products, that Contain Nanomaterials (FDA, 2020).

Two of the seven agencies in this study indicated that they were in the process of developing specific guidance documents for submission of information for applications for nanomedicines. One of these has received two applications for market approval for nanomedicines, while the other has received eleven applications for market approval. This could explain the agencies' progression to development of guidelines to assist applicants with the requirements for approval of nanomedicines.

5.2.4 In-house guidance documents and assessment templates for the assessment of applications for market approval of nanomedicines

None of the agencies had in-house guidance documents for the assessment of quality, non-clinical/safety and clinical aspects of nanomedicines and two agencies indicated that they were in the process of developing such guidance documents. Correspondingly, none of the agencies had assessment templates specific for nanomedicines and two were in the process of developing such guidance documents. The absence of in-house guidance documents and templates for the assessment of quality, non-clinical/safety and clinical aspects of nanomedicines in all the responding agencies could be attributed to a number of factors. Firstly, as discussed earlier, this could have been as a result of a low number of applications of nanomedicines received in each of the countries of the responding NRA. The NRAs may have not seen the need to develop templates specific for the evaluation of nanomedicines as the amount of effort needed may have not been justifiable compared to the number of applications received. Secondly, it could also be possible that the regulatory agencies deemed the current in-house documents for the conventional product streams are adequate to also cover assessment and evaluation of nanomedicines.

Although current regulatory systems allow for the assessment of many aspects of nanomedicines, there are additional scientific matters that come with the more advanced and emerging nanomedicines. Regulatory agencies should therefore develop internal guidance documents that complement the relevant existing guidelines such that pertinent issues related to nanomedicines are not disregarded. This opinion is supported by the *Agence française de securite sanitaire des produits de sante*'s position in which they considered that toxicological evaluation of nanoparticle medicinal products should not be appreciably different from conventional evaluation, but with certain specific adaptations when necessary, without modifying the basic principle (Fattal *et al.*, 2011).

The design of highly complex nanomedicines is progressively increasing. Recently, mRNA-based vaccines have been encapsulated in lipid nanoparticles (LNPs), thus enabling delicate mRNA-based vaccines to better integrate into human cells. Such developments involve a wide variety of materials and chemicals which bring about challenges in identifying critical physicochemical parameters of nanomedicines (Gioria *et al.*, 2018). Proper assessment of the characterisation of nanomedicines is crucial as it provides extensive knowledge of the nanomedicines that could be used to ensure batch to batch reproducibility of such complex nano-based medicines (Coty and Vauthier, 2018). In addition, for the safe evaluation of nanomedicines, critical quality attributes and additional toxicological assessments have to be considered. However, these issues tend to be a challenge due to the wide range of structures of nanomedicines, their physicochemical and biological properties, and the variety of therapeutic applications. Moreover, this complexity makes the generalisation of information requirements of these attributes a challenge.

It is therefore important that these issues be included in assessment templates such that they are not overlooked. Rather than adapting and applying existing guidelines, it is proposed that regulatory guidelines that specifically apply to nanomedicines should be developed, particularly because the safety and toxicity of many nanomaterials have not been fully characterized.

With regards assessment templates that covered assessment of physicochemical and biological characterisation, characterisation methods, toxicity testing, ecotoxicology, endotoxin assessment and stability with respect to nanomedicines, one agency indicated that they have templates that cover physicochemical characterisation and stability. The other five agencies

indicated that they did not have templates that covered the above aspects with respect to nanomedicines. Due to their size related physicochemical properties and the resulting biological effects, nanomaterials can require additional quality and safety testing compared with the conventional products not using nanotechnology (Bartlett *et al.*, 2015). As such, the other regulatory agencies in the ZAZIBONA active countries should consider developing templates that cover assessment of physicochemical characterisation, biological characterisation, characterisation methods, toxicity testing, ecotoxicology, endotoxin assessment and stability of nanomedicines. The agency that indicated that it had templates that cover physicochemical characterisation and stability of nanomedicines is also the agency that applies the principles, guidance documents and templates as laid out by the IPRP for nanomedicines as well as by EMA. It is possible that this agency adopted the IPRP templates that provide for the assessment of physicochemical characterisation and stability for their use. With respect to this, the other regulatory agencies could also consider adopting templates and guidance documents as laid out by IPRP or any other jurisdictions, rather than to 'reinvent the wheel' and start developing their own. This could save them much time and effort. Furthermore, this will promote harmonisation of regulatory requirements with those of the other jurisdictions thus improving compliance by applicants.

5.2.5 Collaboration with external experts, committees and organisations

The common practice among medicines regulators is the use of technical committees to provide expert advice on subject matters. The technical committees make decisions to authorise or not authorise medicines based on available data concerning the safety, effectiveness and quality of the medicines. It is therefore important for the committees to have the necessary expertise on the product type under consideration. One agency indicated that it has a specific technical

committee for consideration of advanced drug delivery systems including nanomedicines or committee members with expertise in nanomedicines. This is the same agency that has been noted to be somewhat advanced in terms of nanomedicines assessment as it has received the highest number of nanomedicines applications for market approval, and has been involved with the IPRP.

As discussed earlier, the other responding NMRAs may have not seen the need to include nanomedicines specifics into their review processes due to the number of low applications received. Therefore, specific technical committees for consideration of advanced drug delivery systems including nanomedicines nor committee members will be absent. However, to provide expertise that may be lacking in the regulation of nanomedicines within their organizations and consequently effectively regulate nanomedicines, NMRAs could ensure that external experts involved in their marketing authorisation decision making processes include personnel who have extensive expertise in issues related to safety, efficacy and quality of nanomedicines. This could be through creating a separate committee for discussion of advanced drug delivery systems including nanomedicines. However, since the number of product applications may not justify this approach; personnel with expertise in such matters may be co-opted into the already existing committees to provide advice as and when required. On the other hand, the NMRAs may also use a system whereby external experts conduct the review of all or part(s) of the applications for nanomedicines. This will also ensure that the assessment process involves personnel with the necessary expertise.

Nanotechnology is employed in the development of most nanomedicines. For this reason, it is important for medicines regulators to collaborate and coordinate with other general nanotechnology scientists for the effective regulation of increasingly complex nanomedicines

issues. This has become more relevant now with the COVID-19 vaccines, some of which incorporate nanoparticles. None of the agencies that responded to the survey work with other external experts or organisations that assist them with the regulation of nanomedicines.

These results indicate that collaboration with external experts or organisations in the regulation of nanomedicines is lacking in the participating NMRAs. This is contrary to practices of other jurisdictions in which regulatory agencies cooperate with other relevant organisations. The USFDA for example works collaboratively with a wide variety of partners including other federal agencies, academic institutions, and international regulatory partners to build regulatory science knowledge, effectively leverage resources, facilitate innovation and coordinate policies (FDA, 2020). In view of the complexity of nanomedicines as well as the additional requirements that are different from the conventional pharmaceuticals associated with nanomedicines, the NMRAs may consider collaborating with academia, other state agencies involved in the field of nanotechnology and other relevant organisations with the necessary technical expertise for the effective regulation of nanomedicines. This collaboration is also likely to coordinate efforts necessary for the advancement of nanomedicine research and possibly production in the countries.

Regulatory cooperation and work-sharing is important, especially in the complex area of nanomedicines. In response to a question on whether nanomedicines are considered under the regional harmonization activities that the responding agencies are involved in, it was established that currently no assessments of nanomedicines applications are considered under the regional harmonization activities that the responding agencies participate in. In addition to domestic collaborations, the NMRAs could also consider interacting with regulatory bodies

in other countries so as to stay current with product development going on internationally, since these products may be submitted to their agencies for review and approval in future.

5.2.6 Regulatory experience with nanomedicines

Africa as a continent faces several health challenges. The burden of disease per population is reported to be two times higher than that of higher income countries (Confraria and Wang, 2020). It is believed that nanomedicine could potentially provide real breakthroughs in terms of improved and cost-effective healthcare, a crucial factor in making medicines and treatments available and affordable (Chang *et al.*, 2015). The emergence and use of nanomedicines could vastly assist in reducing mortality and burden of disease in the continent.

An increasing number of nanomedicines have been approved for marketing globally since the USFDA approved the first nanomedicine (Doxil®) in 1995. In Africa, however, nanomedicine is an emerging field, compared to the rest of the world (Saidi, Fortuin and Douglas, 2018). Although statistics indicate an urgent need for nanomedicines, pharmaceutical companies have lagged in marketing and distributing them in Africa. Some authors have argued that there is inequitable distribution of the benefits of nanotechnology (Saidi, Fortuin and Douglas, 2018). Most recent evidence of this dilemma is the distribution of COVID-19 vaccines. Of the total number of COVID-19 nano-vaccines procured during 2020, significantly more vaccines were procured by high-income countries. While three out of four COVID-19 vaccines procured by the rich countries by the end of 2020 were nanoparticle based vaccines, only one in ten vaccines were nanoparticle based vaccines in the procured stocks of the poorer countries (Uskoković, 2021). Overall, this has an effect that regulators in Africa will not see the need of investing the already limited resources in developing regulatory frameworks for nanomedicines. With a few

number of products marketed in their jurisdictions, the economic benefit in investing in processes for these products become minimal.

The respondents were presented with a list of USFDA and EMA approved nanomedicines and asked to identify products for which applications for registration or approval had been submitted to their regulatory agencies in the last 10 years. Four agencies responding had received at least one application for approval of nanomedicines in the last ten years whilst three responding agencies had not received any applications for registration for nanomedicines in the last ten years. One agency had received 11 applications for market approval of nanomedicines in the last 10 years, another one had received three applications, followed by an agency that had received two applications for such medicines and one agency had received one application for market approval of a nanomedicine. Figure 4 summarizes nanomedicines for which applications for marketing approval have been submitted in the regulatory agencies.

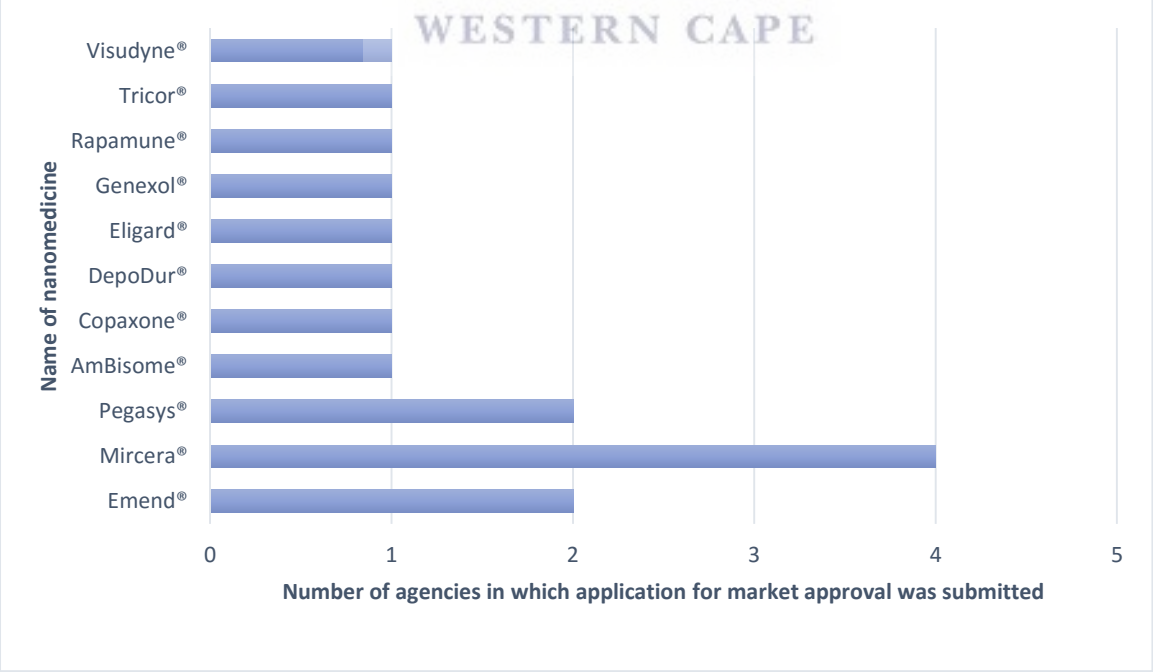


Figure 4: Nanomedicines for which applications for marketing approval have been submitted to the regulatory agencies.

The most commonly received nanomedicine is Mircera® which was received by four of the participating countries. Mircera® is a solution for injection that contains the active substance Epoetin beta (as methoxy polyethylene glycol-epoetin beta conjugate) (Shetab Boushehri, Dietrich and Lamprecht, 2020). It is available in vials and in pre-filled syringes at various strengths ranging from 50 to 1,000 micrograms per millilitre (EMA, 2014). Mircera® is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adult patients. Approximately 75% of CKD patients are reported to be anaemic in low- and middle-income countries (LMICs) (Nalado *et al.*, 2019). This could explain why Mircera® is the commonly received product for registration in the NRAs that participated in this study.

When compared to the number of approved nanomedicines, the numbers submitted to these sub-Saharan African countries appear relatively low. The USFDA is reported to have approved commercialization of 100 nanomedicine applications and products (Farjadian *et al.*, 2019). This observation could be attributed to the small financial market for nanomedicines in Africa. Medicines are more expensive in Africa (Center for Global Development, 2019). The scenario is even worse for nanomedicines which are significantly more expensive than conventional medicines (Bosetti and Jones, 2019). This situation has been proven by the accessibility of nano-based COVID-19 vaccines. Three out of four COVID-19 vaccines procured by the well-resourced countries by the end of 2020 were nanoparticle based vaccines while one in ten vaccines were nanoparticle based vaccines in the procured stocks of the middle-income countries. In addition, only one in 285 vaccine stock secured by the COVAX initiative for immunization of people in the world's poorest countries throughout the first half of 2021 were nanoparticle based vaccines (Uskoković, 2021).

The types of nanoparticles used for the nanomedicines for which applications for marketing approval were submitted in the regulatory agencies vary.

Table 2: Nanocarriers used for the nanomedicines for which applications for marketing approval were submitted in the regulatory agencies.

Nanomedicine (s)	Nanocarrier
Visudyne® **DepoDur®** **AmBisome®**	Liposome
Genexol®	Micellar dispersion
Eligard®	Polymeric nanoparticles
Copaxone®	Polypeptide (average MW 6.4 kDa) composed of four amino acids (glatiramer)
Pegasys®	PEG-interferon alpha-2a conjugate
Mircera®	methoxy polyethylene glycol-epoetin beta conjugate
Rapamune® **Emend®** **Tricor®**	Nanocrystal drug particles

The different types of nanocarriers used for the nanomedicines for which applications for marketing approval were submitted probably show that the NRAs have been exposed to a number of different types of nanomedicines. This observation also shows that different issues had to be considered during assessment of the applications submitted to the NRAs, thus supporting the fact that nanomedicines are complex and require extensive knowledge for their effective assessment.

4.4 Areas for improvement in the regulation of nanomedicines

Assessment of nanomedicines requires highly skilled scientific and technical experts. The World Health Organisation recommends that medicines assessors should have training and expertise in scientific or medical fields that relate to the assessment of medical product safety, efficacy and/or quality (WHO and World Health Organisation, 2015). In relation to this, at least one person working in the agencies that responded had received training on assessment of advanced drug delivery systems including nanomedicines in five of the seven agencies. This supports the earlier results that the respondents were aware of the existence of nanomedicines and possibly their mandate to regulate nanomedicines.

Respondents of the NMRAs that participated in the study likely appreciated their lack of expertise in issues related to the assessment of nanomedicine applications as they all agreed that there was need for training assessors on assessment of nanomedicines. To improve the internal competencies in the area of nanomedicines as well as address the rapidly evolving regulatory science challenges associated with nanomedicines, regulatory agencies should invest in nanomedicine specific trainings that bring about both practical and theoretical knowledge of nanomedicines. Additionally, the assessors should have the opportunity to attend

relevant conferences, courses and international meetings so that they are aware of international standards associated with regulation of nanomedicines. Another approach that can be taken in building the core competencies necessary for the assessment of nanomedicines is to hire assessors that are scientifically and academically trained in the area of nanomedicines.

In order to build capacity in the assessment of nanomedicines within ZAZIBONA, regulatory agencies should take advantage of the WHO global competency framework and global curricula being developed to support training and professional development of regulatory staff (WHO, 2019). Regulatory agencies should request that assessment of nanomedicines be included as one of the core competencies in the competency framework. In addition to individual regulatory agencies benefitting from this system, ZAZIBONA as a whole will have an internationally accepted set of competencies for the assessments of nanomedicines. This will maximize the benefits of collaboration and cooperation in medical product regulation as intended by the WHO for their global competency framework.

In response to a question regarding need for incorporation of assessments in regional harmonisation activities the respondents are involved in, all the respondents agreed that there was need, with 4 (four) out of 7 (seven) strongly agreeing that there was such need.

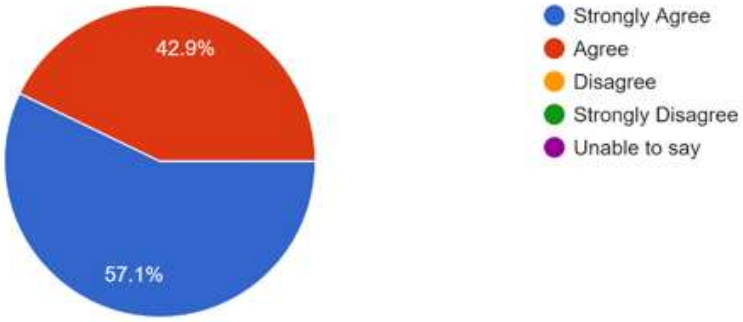


Figure 5: Opinion of the respondents on need for incorporation of assessments in regional harmonisation activities.

Regulatory cooperation and work-sharing is important, especially in the complex area of nanomedicines. To leverage resources and other NMRAs' work, as well as to prevent redundant work in the regulation of nanomedicines, the NMRAs can consider inclusion of nanomedicines into the already existing framework of the ZAZIBONA joint assessments. This will streamline the assessment of nanomedicines as well as facilitate open dialogue among the NMRAs themselves on how they can collaborate to advance scientific understanding of nanomedicines products.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

The purpose of the research was to determine regulatory experience with nanomedicines within the ZAZIBONA active countries, analyse their legislation, guidelines and policies on nanomedicines, review their assessment practices with respect to applications for nanomedicines, as well as to identify challenges and possible opportunities for harmonisation with regards to nanomedicines.

A summary of the general observations of the study are listed below:

i. The NRAs are aware of the existence of nanomedicines and at least one person working in the agencies had received training on assessment of advanced drug delivery systems including nanomedicines in five of the seven agencies.

ii. Most of the regulatory agencies reported that general regulatory approaches, including legislation applicable to other medical products are also applicable to nanomedicines.

iii. The current guidance documents and templates in the regulatory agencies do not fully accommodate the requirements for nanomedicines neither do they provide advice to applicants for marketing authorisation holders, the public, or other stakeholders. The NRAs also do not have specific definition for nanomedicines.

iv. Most of the NRAs do not have a specific technical committee for consideration of advanced drug delivery systems including nanomedicines or committee members with expertise in nanomedicines.

v. Collaboration with external experts or organisations in the regulation of nanomedicines is lacking in the participating NRAs.

vi. Respondents indicated of the need for training and capacity building in the area of assessment of nanomedicines as well as incorporation of nanomedicines assessments in regional harmonisation activities.

While the current regulatory framework in the ZAZIBONA active regulatory agencies accommodates assessment of many aspects of nanomedicines, a systematic gap still exists between the current framework and that required for the assessment of nanomedicines. It is therefore anticipated that nanomedicines specific guidance documents and templates will be implemented to complement the relevant existing guidelines and pertinent aspects will be assessed as nanomedicines applications for market approval are submitted to the regulatory agencies.

With regards study limitations, the study focused on ZAZIBONA active countries and excluded all the other SADC countries. In addition, all nine regulatory authorities of the ZAZIBONA active countries were approached to complete the survey, only seven responded. Some of the missing data from some of the NRAs may have led to the lack of a complete regional picture in aspects of this study. Follow up questions were not included in the questionnaire to further clarify responses. Respondents were not asked to further specify the number of people trained as well as the specific training topics in one of the questions. This would have assisted in ascertaining the relevance of the trainings with respect to regulation of nanomedicines as well sufficiency of people with technical expertise to assess nanomedicines product applications.

As discussed earlier, nanomedicines are complex and their regulation bring about challenges associated with this intricacy. The study respondents suggested the incorporation of assessments of nanomedicines in regional harmonisation activities the NRAs are involved in.

It is believed that the NRAs will be able to build capacity on regulation of nanomedicines as a region thus leveraging on the few resources available if they approach capacity building in the area of nanomedines as a region. The countries can leverage on the existing structure of ZAZIBONA and expand the scope of joint assessments to include nanomedicines. In addition, existing platforms such as the IPRP and the Global Summit in Regulatory Science (GSRS) could be explored.

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APPENDIX A

STUDY QUESTIONNAIRE

COVER LETTER

University of the Western Cape
P Bag X17
Bellville
South Africa

Dear Director-General,

Re: MSc mini-thesis questionnaire survey

I am a Senior Regulatory Officer with the Medicines Control Authority of Zimbabwe, currently pursuing an MSc Pharmacy Administration & Policy Regulation. As part of this programme, I am undertaking a research project titled '*Situation Analysis Study on Nanomedicines Regulation and Assessment Practices in ZAZIBONA Active Countries*'. The purpose of the study is to establish the status of regulation of nanomedicines in the ZAZIBONA active countries with an intention to obtain an overview of the assessment practices of these products in the countries, as well as to identify any challenges faced as well as documenting future priority areas for capacity building.

I believe the results will not only be of value to individual NMRAs but will also assist international organisations through the AUDA-NEPAD partnership platform to better identify the capacity building requirements for SADC. Your experience with nanomedicines and opinions on the areas that require capacity building are critical to the success of this study.

I recognise the value of your time, and sincerely appreciate your efforts.

Linda G. Mudyiwenyama

QUESTIONNAIRE

1. Name of National Medicines Regulatory Authority (or equivalent)

_____

2. Name and position of respondent

_____

PART A: REGULATORY FRAMEWORK

1. Are you aware of the existence nanomedicines? A nanomedicine is defined as a product that contains or is manufactured using materials in the nanoscale range, i.e. 1 nanometer to 100 nanometers,and includes liposomes and other engineered particles in this size range.

☐ Yes ☐ No

Nanomedicine
1. Abelcet®- Amphotericin B complex 1:1 with DMPC and DMPG (7:3), >250 nm, ribbon like structures of a bilayered membrane
2. Adagen®- PEGylated adenosine eaminase. One enzyme molecule is odified with up to 17 strands of PEG, MW 5,000, 114 oxymethylene groups per strand
3. AmBisome® - Amphotericin B encapsulated in liposomes (60–70 nm)omposed of hydrogenated soy phosphatidylcholine, cholesterol, and distearoyl phosphatidylglycerol (2/0.8/1 molar)
4. Amphotec® - Amphotericin B complex with cholesteryl sulfate (1:1). Colloidal dispersion of disc-like particles, 122 nm ×4 nm
5. Cimzia® - PEGylated antibody (Fab' fragment of a humanized anti-TNF-alpha antibody)
6. Copaxone® - Polypeptide (average MW 6.4 kDa) composed of four amino acids (glatiramer)
7. DaunoXome® - Daunorubicin citrate encapsulated in liposomes (45 nm) composed of distearoyl phosphatidylcholine and cholesterol (2/1 molar)
8. DepoCyt® - Cytarabine encapsulated in multivesicular liposomes (20 μm; classified as nanopharmaceutical based on its individual drug containing "chambers") made from dioleoyl lecithin, dipalmitoyl phosphatidylglycerol, cholesterol, and triolein
9. DepoDur® - Morphine sulfate encapsulated in multivesicular liposomes (17–23 μm; per se not a nanopharmaceutical – classified as such based only on its individual drug containing "nano-sized chambers") made from dioleoyl lecithin cholesterol, dipalmitoyl phosphatidylglycerol, tricaprylin, and triolein
10. Doxil® - Doxorubicin hydrochloride encapsulated in Stealth® liposomes (100 nm) composed of N-(carbonyl- methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3-

phosphoethanolamine sodium, fully hydrogenated soy phosphatidylcholine, and cholesterol
11. Eligard® - Leuprolide acetate (synthetic GnRH or LH-RH analog) incorporated in nanoparticles composed of PLGH copolymer (DL-lactide/glycolide; 1/1, molar)
12. Emend® - Aprepitant as nanocrystal
13. Genexol® - Paclitaxel in 20–50 nm micelles composed of block copolymer poly(ethylene glycol)- poly(D,L-lactide)
14. Inflexal® V - Influenza virus antigens (hemagglutinin, neuraminidase) on surface of 150 nm Liposomes
15. Macugen® - PEGylated anti-VEGF aptamer
16. Marqibo® - Vincristine sulfate encapsulated in sphingomyelin/cholesterol (60/40, molar) 100 nm liposomes
17. Megace ES® - Megestrol acetate as nanocrystal
18. Mepact™ - Mifamurtide (synthetic muramyl tripeptide-phosphatidylethanolamine) incorporated into large multilamellar liposomes composed of 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine and 1,2-dioleoyl-sn- glycero-3-phospho-L-serine
19. Mircera® -PEGylated epoetin beta (erythropoietin receptor activator)
20. Myocet®- Doxorubicin encapsulated 180 nm oligolamellar liposomes composed of egg phosphatidylcholine/cholesterol (1/1, molar)
21. Neulasta® - PEGylated filgrastim (granulocyte colony-stimulating factor)
22. Oncaspar® - PEGylated L-asparaginase
23. Opaxio® - Paclitaxel covalently linked to solid nanoparticles composed of polyglutamate
24. Pegasys® - PEGylated interferon alfa-2b
25. PegIntron® - PEGylated interferon alfa-2b
26. Rapamune® - Rapamycin (sirolimus) as nanocrystals formulated in tablets
27. Renagel®- Cross-linked poly allylamine hydrochloride, MW variable
28. Somavert® - PEGylated human growth hormone receptor antagonist
29. Tricor® - Fenofibrate as nanocrystals
30. Triglide®- Fenofibrate as insoluble drug-delivery microparticles
31. Visudyne® - Verteporfin in liposomes made of dimyristoyl-phosphatidylcholine and egg phosphatidylglycerol (negatively charged); lyophilized cake for reconstitution
32. Zinostatin stimalamer® - Conjugate protein or copolymer of styrene-maleic acid and an antitumor protein NCS

33. From the list of USFDA and EMA approved nanomedicines (listed above), please identify products for which applications for registration or approval have been submitted to your regulatory agency in the last 10 years? Please indicate 'None' if no applications have been received.

3. Does your regulatory agency have a definition for nanomedicines?

☐ Yes ☐ No

If you responded YES to the above question, please provide the definition

4. Does your regulatory agency have legal provisions that cover regulation of nanomedicines?

☐ Yes ☐ No

If you responded YES to the above question, please provide details of the legislation.

5. Does your regulatory agency have specific guidelines for submission of quality, non-clinical/safety and clinical information for applications for nanomedicines?

☐ Yes ☐ No

If your regulatory agency has specific guidance documents for submission of quality, non-clinical/safety and clinical information for applications, including nanomedicines, please provide links to the guidance documents, if publicly available.

If your regulatory agency does not have specific guidance documents for submission of quality, non-clinical/safety and clinical information for applications, including nanomedicines; is your regulatory agency in the process of developing such guidance documents?

☐ Yes ☐ No

6. Does your regulatory agency have in-house guidelines for the evaluation of the quality, non-clinical/safety and clinical aspects of nanomedicines?

☐ Yes ☐ No

If you regulatory agency does not have in-house guidance documents for the assessment of nanomedicines, is your regulatory agency in the process of developing such guidance documents?

☐ Yes ☐ No

7. Does your regulatory agency have a specific technical committee for consideration of advanced drug delivery systems including nanomedicines or committee members with expertise in nanomedicines?

☐ Yes ☐ No

8. Please specify other external experts or organisations that assist your regulatory agency with regulation of nanomedicines, if any.

_____

_____

_____

_____

_____

9. Have you or anyone in your organization received training on assessment of advanced drug delivery systems including nanomedicines?

☐ Yes ☐ No

10. Does your regulatory agency have assessment templates specific for nanomedicines?

☐ Yes ☐ No

11. Does your nanomedicines specific template(s) or any of your assessment templates cover assessment of the following with respect to nanomedicines? (You may tick more than one response)

☐ Physicochemical characterisation ☐ Characterisation methods

☐ Biological characterisation ☐ Ecotoxicology

☐ Toxicity testing ☐ Stability

☐ Endotoxin assessment

12. Are any assessments of nanomedicines applications considered under regional harmonisation activities you are involved in?

☐ Yes ☐ No

If you responded YES to the above question, please specify the regional harmonisation activities

_____

_____

_____

PART B: AREAS FOR IMPROVEMENT

13. In your own opinion, is there need for training assessors on assessment of nanomedicines?

☐ Strongly agree
☐ Agree
☐ Disagree
☐ Strongly disagree
☐ Unable to say

14. In your own opinion, is there need to incorporate assessment of nanomedicines into the regional harmonisation activities?

☐ Strongly agree
☐ Agree
☐ Disagree
☐ Strongly disagree
☐ Unable to say

15. Is there anything additional that you would like to mention with regards to this topic or questions above.

APPENDIX B

ETHICS APPROVAL LETTER

UNIVERSITY of the WESTERN CAPE

50 YEARS of hope, action & knowledge

15 May 2020

Ms LG Mudyiwenyama
School of Pharmacy
Faculty of Natural Sciences

Ethics Reference Number: HS20/3/8

Project Title: Situation analysis study on nanomedicines regulation and assessment practices in ZAZIBONA active countries.

Approval Period: 14 May 2020 – 14 May 2023

I hereby certify that the Humanities and Social Science Research Ethics Committee of the University of the Western Cape approved the methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report by 30 November each year for the duration of the project.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

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NHREC Registration Number: HSSREC-130416-049

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