

RESEARCH ARTICLE:

## An Integrative Review to Progress the Responsible Development of Nano-Drugs

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Received: 29 November 2022 | Revised: 24 April 2023 | Published: 22 May 2023

Reviewing Editor: Dr. Francis Akpa-Inyang, Durban University of Technology

### Abstract

*There has been extensive research on improving and innovating current treatments for irritable-bowel-syndrome using nanotechnology. However, there are growing challenges to progress these drugs to clinical trials and commercialisation. This study sought to develop a framework to manage key features, overlooked in current studies, to improve the development of drugs. An integrative literature review was used to extract themes by using a summative content analysis to interrogate information. Validity was established when saturation of information was achieved. Reliability focussed on the repeatability of key information. Absorption, distribution, metabolism, excretion and toxicity, quality by design attributes, metrology, and standardisation of practice emerged as important themes. These themes together among others, were used to develop the framework to manage the drug development process: Knowledge-based society, Foresight planning, Multidisciplinary approach, Unified definition, Adapt to existing standards and guidelines, Precautionary principle, Case-by-case approach, Quality-by-design, Scale-up and Training. The framework provided reflections that no study has considered. The framework will ensure that drug development will be approached strategically to avoid duplication of research-designs, including risk mitigation, quality at the source and supplier-chain management to progress drug development to clinical trials and beyond.*

**Keywords:** nanotechnology; drug-delivery; irritable-bowel syndrome

### Introduction

This paper used an integrative review to conceptualise and sensitise stakeholders along the pharmaceutical value-chain of the multidisciplinary considerations that have not been included in current initiatives that could be undertaken to manage nano-enabled drug development responsibly. There are many frameworks and guidelines advising on traditional drug development, however there is not much information on drug development using nanomaterials that considered the value-chain. Pilot work was undertaken to establish possible common themes to develop the framework proposed in this study. Moreover, past studies concentrated on one or two themes, for example, studies focused either on the drug design, drug release and/or particle behaviour without consolidating their interactions and interrelationships within the human body that enabled a holistic understanding of the drug and its performance. Therefore, the novelty of this paper brings all the emerging themes and processes from literature and consolidates them into a streamline activity. This study will be beneficial to provide insights to nanotechnology scholars, researchers, regulatory bodies, consulting laboratories and pharmaceutical manufacturers.

In the modern era of the Fourth Industrial Revolution (4IR), automation, cyber-systems and predictive manufacturing, industries including the medical and pharmaceutical fraternity are constantly seeking better options for optimising their current practice. To stay competitive these sectors, have to operate with speed and vigour to develop innovative products ahead of their competitors to achieve better performance and to up-scale and market

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their products cost-effectively. Moreover, the recent pandemic with its concomitant restrictions have evoked a new consciousness on the way we do business with the resources available, especially on the level of human dependence, access to raw-materials and resilient production processes to provide traditional and novel products. From a South African (SA) perspective, businesses are further challenged with constant power-cuts, water restrictions and social violence. All these instances have forced us to rethink our business under the current circumstances and for the future in the face of the 4IR and artificial intelligence.

The pharmaceutical industry like other industries is tirelessly investigating possibilities to be at the forefront of producing effective drugs that use more socially favourable and appealing constituents, improve drug performance, minimise drug dose with fewer induced side-effects and improve patient adherence (Pertuit *et al.*, 2007, Sardo *et al.*, 2019 and Ahadian *et al.*, 2020, Hmar *et al.*, 2020 and Hussain *et al.*, 2021; Vakar *et al.*, 2021 and Iswandana *et al.*, 2022). For example: inflammatory bowel disease (IBD) is widespread in our modern society. If not controlled IBD in the form of Ulcerative colitis (UC) can escalate to colon cancer and thus there is a constant impetus to overcome the complexities of the human gastro-intestinal tract (GIT) to control the progression of UC to more deadly forms of disease (Hmar *et al.*, 2020 and Vakar *et al.*, 2021). There is no cure for UC thus forcing drugs to induce and maintain remission of the disease. The long-transit from the mouth to the colon exposes the drugs to many different environments thus complicating the development and efficiency of drugs. In view of the long-transit and changing environment, large doses of medication are administered to ensure that a therapeutic dose of the drug is delivered to the site of disease (Hadji and Bouchemel, 2022). In the current forms, between 20-80% of the active ingredient of the drug is released prematurely on route to the site of disease, inducing many side-effects and leaving only a small percentage of the active ingredient for treatment (Pertuit *et al.*, 2007, Sardo *et al.*, 2019 and Ahadian *et al.*, 2020, Hmar *et al.*, 2020 and Hussain *et al.*, 2021; Vakar *et al.*, 2021 and Iswandana *et al.*, 2022).

Nanotechnology, mooted as a disruptive technology in the 4IR, represents materials with at least one dimension in nanometers (1-100nm) (Hartwig *et al.*, 2021). These nanomaterials in the form of nanoparticles (NPs) display unusual properties, based on features like small size, improved surface area, reactive surface structure, robust chemical composition, good and selective solubility and varied shape (Banderas *et al.*, 2012 and Kazemzadeh *et al.*, 2022). In the pharmaceutical industry, these properties are favourable because formulations including them are able to better control and regulate the pharmacodynamics (PD) and pharmacokinetics (PK) of drugs (Zhang *et al.*, 2020) and deliver them to different parts of the body, specifically at the active site of the disease over a sustained period (Hartwig *et al.*, 2021). According to Seifirad *et al.* (2016) and Hua *et al.* (2015) this happens because NP have the ability to accumulate at the inflamed tissue and thus transforms the pharmacokinetics step of therapies (Viscido *et al.*, 2014). Hence, this enables better patient compliance and the delivery of the drug directly to the active site of the disease via muco-adhesion, muco-penetration, passive targeting of inflamed tissue and capturing of immune cells over a prolonged period while minimising the systemic effects as is experienced with macro molecule drugs (Ovadge *et al.*, 2015; Chaudhari *et al.*, 2020, Jain and Parkhe, 2020, Zhang *et al.*, 2020 and Hadji and Bouchemel, 2022). When these materials are compared to the same materials in macro-form, they are able to better control and regulate the properties of the drugs (Zhang *et al.*, 2020) and deliver them to different parts of the body for a sustained period (Hartwig *et al.*, 2021). This is a “double-edged” sword because these properties may also make nanoparticles potentially toxic thus raising some scepticism around its use in pharmaceutical products.

Nanotechnology projects have demonstrated theoretically and at small laboratory-scale to improve drug-delivery when compared to traditional practice in the pharmaceutical fraternity, but like many other applications using nanotechnology, it has not reached its full potential or realisation. A number of nanotechnologies inspired drug systems have been researched with positive results at the laboratory scale and fewer of them have been trialled clinically with some failing due to premature drug release, poor targeting ability and high toxicity (Zhang *et al.*, 2019 and Yang *et al.*, 2011). This failure has been attributed to the vast challenges faced by the drug on-route to the colon and to a poor grasp of drug absorption, distribution, metabolism, excretion, toxicity (ADMET), drug processes and a partial understanding of pharmacokinetic activities (Zhang *et al.*, 2020). The most cited reason for the poor commercialisation of nano-enabled drugs for colonic delivery is a lack of standardised protocols, regulations and standard-operating procedures (Berger, 2021), poor scale-up initiatives and their lack of repeatability and low consistency between batches of drugs produced (Ahadian *et al.*, 2020 and Kazemzadeh *et al.*, 2022), thus complicating their acceptance for large-scale production. It was also found after a review of the literature that most

of the research conducted focused on the applied science (experimental work only) and either invitro or animal tests to prove drug release, drug concentration at the site of disease and nanoparticle characteristics (size and shape) (Zhang *et al.*, 2020) with very few studies focussing on toxicity, clinical responses or scale-up initiatives.

From this narrative it was reasonable to explore better ways of using nanotechnology in drug development to establish sufficiency of measurement, long and short-term product stability and manufacturing sustainability, traceability, appropriate handling and control, reliable test methods and reference materials to mitigate any bias. This paper will delve into the nuances of nano-enabled drugs, particularly in colonic-drug delivery and provide a mechanism for pharmaceutical organisations to produce nano-enabled drugs responsibly by mitigating and addressing salient points that emerge from using nanoparticles to optimise drug development for the treatment of colonic disease. By implication, for this to occur, there needs to be greater uniformity of practice during the conceptualisation and manufacturing processes associated with acceptable standards, quality control and codes of conduct. Governments around the world have high-hopes for nanotechnology to solve their countries' challenges to meet their sustainable development goals and key imperatives and have concomitantly established National Nanotechnology Strategies via the Department of Science and Technology to manage the process. In South Africa (SA), the Department of Trade, Industry and Competition (DTIC) and industry partners are sanctioned to advance various nanotechnology initiatives (National Planning Commission, 2015). To achieve this, South Africa boasts a national footprint in the form of three Research Councils (Mintek, The Medical Research Council and The Water Commission) and three University partners [University of Johannesburg (Water); University of Western Cape (Bio-labelling) and Rhodes University (Health sensor)] to provide analytical services and mentorship to the stakeholders (DSI, 2007). These bodies have been established to improve development in the nano-enabled applications and encourage entrepreneurship in SA.

## Methodology

This section will present the approach that was undertaken to acquire data. Due to the challenges highlighted above, particularly the absence of validated protocols and regulatory practice in nanotechnology this paper adopted a qualitative and theoretical strategy by using an integrative peer-review research methodology and content summative analysis. This methodology was used to establish theoretical frameworks, acceptable protocols, current thinking and practice in this area of interest to develop the framework presented in this paper. The integrative review sought evidence from literature, assessed and critiqued current practice to synthesise knowledge to assimilate themes for the framework. Content analysis analysed features and relationships based on keywords evident from the literature (Liberati *et al.*, 2009; Tranfield *et al.*, 2003; Wong *et al.*, 2013 in Snyder, 2019).

Integrative reviews, developed by an epidemiologist was used for data collection because it was regarded as an evidence-based practice and provided the most robust of all literature approaches and styles to facilitate clinical care based on evidence (facts and proof), knowledge and its quality because it allowed for the flexibility of analysing both theoretical (non-experimental) and non-theoretical (experimental) work (De Souza *et al.*, 2010). Snyder *et al.* (2019) advises that integrating different findings and perspectives from a variety of empirical studies (literature) that addresses a particular research question, "has the power that no single study has" to highlight areas that are dissimilar and interdisciplinary. Thus, Table 1 highlights the data-bases that were used for data collection. These data-bases were selected because they appeared to be active publishers in both traditional and nano-drug-delivery research.

**Table 1:** Data-bases used to seek literature

Pub-med	Science Direct
Dove Press	Wiley
Dove Press – Medical	International Journal of Pharmaceutical Science Review and Research
Elsevier	International Journal of Research publications and Reviews
Springer	Royal Pharmaceutical Society
Taylor and Francis	US Food and Drug Association
Frontiers in Chemistry	South African Bureau of Standards
Creative commons	American Association of Pharmaceutical Science

Table 2 provides the research focus area of the articles that were sought. This was to ensure that key points and themes that were pertinent to drug-development and drug-delivery covered all the aspects that were required to demonstrate intensive and robust methodological quality and that there was consistency of research design and

practice between the articles reviewed from literature during the evaluation process. A summative assessment was made to evaluate the strengths, weaknesses, deficiencies and contribution of each article within the scope of Tables 2 and 3.

**Table 2:** Focus areas from journal articles

Journal focus	
Polymer Science	Medical, gastroenterology, digestive matters, nanomedicine
Drug Delivery and advanced drug delivery	Pharmaceutical science, pharmacology
Macromolecules	Microbiology
Alternative medicine	Research methods
Biomaterials	Related Regulatory bodies

Table 3 provides the inclusion criteria, specifically representing the characteristics sought to select each article. Each article was evaluated to determine if it satisfied these criteria. Articles that did not satisfy the inclusion criteria in Tables 2 and 3 were not evaluated. It was important to adhere to these inclusion and exclusion criteria to ensure that all articles were assessed fairly and uniformly. It also ensured consistency of practice in data collection, reliable themes and later the ability to generalise findings.

**Table 3:** Characteristics sought in research articles

Characteristic sought in each journal article	
Involved CDDS	Methodology was clear and reasonable
Used to NPs but not essential	Was there a focus on risk assessment?
Drug used is mesalamine or related	Was design of experiment discussed?
In vivo-results reported but not essential	Was compliance to regulatory considerations discussed?
Invitro studies were reported but not essential	Was metrology discussed?
Important variable contributing to responses were highlighted	Was there evidence of quality assurance or quality control?
Results were interpreted and discussed	Were appropriate models used?
Mathematical models were used but not essential	Was mathematical or computational modelling used or discussed?
Was Absorption, distribution, metabolism, excretion and toxicity (ADMET) discussed?	Was the formulation commercialised?
Were measurements discussed?	Were findings conclusive?
Particle size and charge was discussed	Was validity and reliability demonstrated in the study?
Encapsulation was discussed?	Statistical analysis was conducted

(Adapted from Snyder, 2019 and Vieira *et al.*, 2022)

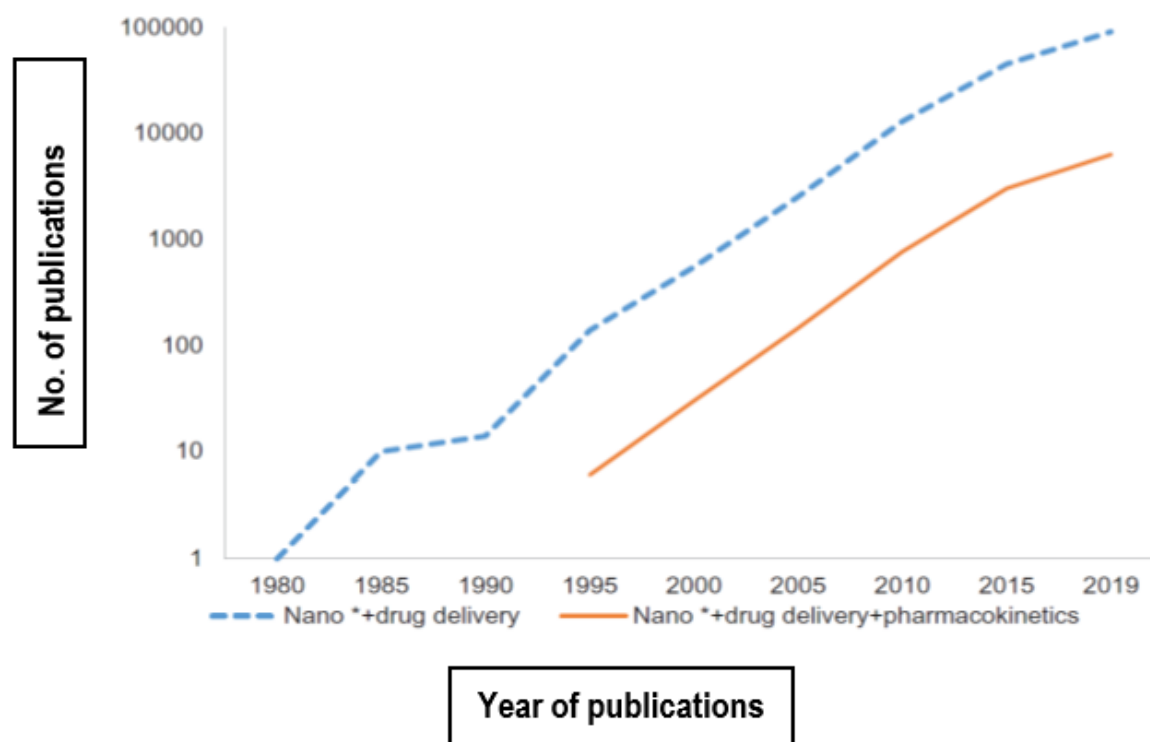
For validity purposes, the methodological quality of the articles was assessed (Vieira *et al.*, 2022) until saturation of information between these articles was established. This exercise was undertaken to verify the appropriateness of the information to inform the development of the envisaged framework. Reliability focussed on the repeatability of the findings derived from the various articles. This established the credibility, dependability, transferability and confirmability of the facts that emerged from the review of literature (Table 3) (Goddard and Melville, 2006 and De Souza *et al.*, 2010). Sound validity and reliability practices were considered as an important activity to ensure that a representative review was undertaken and that it provided accurate information, demonstrated the depth of knowledge and rigour that could be replicated by an external scholar (Snyder, 2019).

From a cursory evaluation of selected papers Pertuit *et al.* (2007); Yerlikaya *et al.* (2013) and Patwardhan and Asgarzadeh (2014) it became evident that ADMET, QbD and metrology were important considerations in the development of drugs. Thereafter, appropriate keywords as indicated were used to conduct the wider literature search: [ADMET(Colonic drug delivery, Pharmacodynamics, Pharmacokinetics and 5-Aminosalicylic acid and UC); QbD (Risk assessment, Risk control, Risk identification, Design of experiments and Troubleshooting), metrology (Measurement, Calibration references, Test methods, Standard operating practice and Validity, Reliability) and standardisation (Legislation, Regulation, Technical Reports, Standards and Guidelines)]. One-hundred and thirty-four salient articles that spanned from 2007-2022 were evaluated. After screening these articles with explicit inclusion and exclusion criteria (Tables 2 and 3) relevant information was collected. Each article was read, key thoughts were assimilated and analysed to establish emerging themes. Forty-three articles were applicable to this paper.

Pilot work (in the form of the cursory evaluation) was undertaken to establish the theoretical framework and extract relevant themes, theories and practices from the literature (Snyder, 2019). The following papers were studied in depth to explore mechanism for drug delivery and the components required for drug formulation was established from Pertuit *et al.* (2007), the ADMET was established from Zhang *et al.* (2020), while the Quality-by-design (QbD attributes) were established from Patwardhan and Asgarzadeh (2014). After an evaluation of approximately twelve articles in ADMET and four articles in QbD. These features formed the themes for the development of the Framework proposed in this paper and illustrated the technical approach for the supporting resources and infrastructure to sustain the management of drug-development in a nano-enabled milieu. At the time of this study, we were not aware of any research that incorporated ADMET, QbD, pharmacokinetics, metrology and standardisation has been proposed experimentally or theoretically for the development of colonic drug delivery. The ADMET concept is an understanding of the behaviour of a drug in terms of its absorption, distribution, metabolism, excretion and toxicity within the human body. Quality-by-design represents a systematic way of developing a product by considering product inputs in relation to understanding and controlling processes based on science that governs it and the associated risks. Pharmacokinetics signifies the interactions that emerge in the body when it is being exposed to the drug. Metrology is an understanding of measurement in relation to quality. Standardisation promotes the uniform activities and/or compliance to a standards or technical guidelines (Zhang *et al.*, 2020 and Patwardhan and Asgarzadeh, 2014). These themes were evaluated and critiqued to consolidate information from the literature and the nuances of NPs in drug development.

## Findings

It was found that there was a disproportionate number of studies between those that focussed on drug development and drug delivery at laboratory-scale as opposed to the those that developed the drugs that proceeded from an evaluation of optimised practice through better design, pharmacokinetics, measurement and standardisation, with even fewer of the studies referring to toxicity and actions for scale-up initiatives. For example, there were approximately twenty papers that dealt with drug development, four included QbD and two risk explicitly.



**Figure 1:** Nano-enabled publications for the last thirty years (Zhang *et al.*, 2020)

This can be corroborated by Zhang *et al.* (2020) who showed in Figure 1 the disparity between the number of studies that focussed on drug development as a standalone research and those with drug delivery and pharmacokinetic considerations. For example, in 2019 the number of research articles that investigated nano-enabled drug delivery was approximately 100 000 while for the same period nano-enabled drug delivery that



considered pharmacokinetics were just under 10 000. From this figure it is reasonable to assume that the difficulties experienced by nano-enabled drugs to move beyond the laboratory and to reach clinical trials and commercialisation could be attributed to the limited focus and lack of discourse on pharmacokinetics and other salient features like, toxicity and the finer QbD attributes. Moreover, it was found that review-type of articles reached saturation and were repeatedly citing the same studies and findings (Hua *et al.*, 2015; Seifirad *et al.*, 2016 and Sardo *et al.*, 2019). Although many review-type articles were evaluated in this study, the five review-type papers that spanned from 2021 and 2022 were considered as the final acceptance criteria as an indication of the latest information on the salient features pertinent to this study (Hartwig *et al.*, 2021; Hussain *et al.*, 2021; Vieira *et al.*, 2022; Iswandana *et al.*, 2022 and Kazemzadeh *et al.*, 2022). It can be reasoned that studies in drug-delivery have either reached their threshold in terms of research design and innovation or that the same role-players are investigating this focus area.

It was deduced that currently, most of the research focus is on discovering new innovations either in components and research design with little consideration placed on consolidating knowledge from research already undertaken. There was little to no impetus or engagement for drug development sensitised towards clinical trials nor related initiatives to advance drug development to move beyond the laboratory towards scale-up and commercialisation. Moreover, there was very little to no deliberations around ethical matters that may arise from nano-induced materials in a therapeutic setting, interaction of nano-enabled drugs with society and funders, in occupational health and safety and environmental management and regulatory management associated with drug development (Savolainen *et al.*, 2013 and Rose *et al.*, 2021).

Of concern, there was no consensus among authors about the potential movement of the drugs across the blood-brain barrier, its accumulation in the liver or its toxicity (Zhang *et al.*, 2020). Of great importance, Satakar *et al.* (2016); Miah, (2017); Mitter and Hussey, (2019); Kappel and Holmen, (2019), Joubert *et al.* (2020) and Zhang *et al.* (2020) caution that the gaps of knowledge around the use of nano-enabled products emerging from studies confined to the laboratory stage, those that the lack of scale-up activities and potential safety concerns if not addressed quickly and appropriately may lead to poor public perception, decreased funding opportunities and potential moratoriums against nano-enabled products, as seen with other new technologies like genetically-modified foods and stem cell research. These repercussions could be very detrimental to public acceptance of nanotechnology and thus manufacturers and investors should consider the balance between what is the public's right to know and their need to know.

Zhang *et al.* (2020) provided an appreciation that there is sufficient knowledge and understanding available about the understanding of transport, physical and chemical properties of components of drug delivery systems. The main constraint in drug-development, they admit, is the failure of applications to progress to clinical trials or failure within the clinical trials because it was difficult to understand the behaviour, monitoring and recovery of small nanocarriers within the human body. Beg *et al.* (2019) purport that because drug development consists of many continuous stages with their own variability, it will be beneficial to designate practices into manageable sizes so that they could be controlled so that inconsistencies can be minimised.

### **A framework to progress colonic drug-development**

In considering the forgoing narrative, Figure 2 demonstrates the salient features, addresses the deficiencies and novel considerations in drug development to strategically establish and approach nano-enabled drug development to progress beyond the laboratory bench-top. The features were reasoned after an evaluation of the discourse in literature with particular focus on management and scale-up considerations. These features are knowledge-based development, knowledge-based society, use foresight planning, establish a multidisciplinary approach, decide on a unified definition for nanomaterial, adapt to existing regulatory standards and guidelines, Adopt Precautionary principle, adapt case-by-case approach, recognize the formulation relationship to ADMET, establish optimized research QbD approach, Consider Product Scale-up facility and commercialization and Training, competency, and development.

1.	<b>Knowledge-based Development</b>
• Understanding contemporary research	
2.	<b>Knowledge-Based Society</b>
• Deliberate guided product development	
3.	<b>Use Foresight Planning</b>
• Sustainable, safe & ethical development	
4.	<b>Establish a Multidisciplinary Approach</b>
• Inclusiveness, openness and respect	
5.	<b>Decide on a Unified definition of Nanomaterial</b>
• Point of Departure, facilitate legislation & support funding opportunities	
6.	<b>Adapt to Existing Guidelines, Standards and Regulations</b>
• Excellence, integrity, uniformity of practice, conformity	
7.	<b>Adopt the precautionary Principle</b>
• Accountability	
8.	<b>Adapt to a Case-by-Case Approach</b>
• Anticipate potential risks & mitigation strategies	
9.	<b>Recognise the formulation relationship to ADMET</b>
• Understanding the human-biome to facilitate optimisation	
10.	<b>Establish Optimised research design approach</b>
• Employee Creativity, innovation & best practice	
11.	<b>Consider Scale-Up Facility &amp; commercialisation</b>
• Flexibility/Agility of practice, patents	
12.	<b>Training, Competency Testing &amp; Development</b>
• Employees & Society - trust & awareness	

**Figure 2:** Framework for nano-enabled drug development

### **Knowledge-based development**

The coordinated global assimilation and dissemination of information and management of human-behaviour during the Covid-19 pandemic and its concomitant lock-downs confirm that we are a society that can be driven and guided by cutting-edge knowledge derived from science and technology. During this period, the global collaboration between scientists, science-councils, laboratories and governments to successfully produce a vaccine to manage the Covid-19 virus showed us that a coordinated effort which is very different from traditional practice can be useful to produce a desired and favourable outcome in pharmaceutical development and production in a short-time. Drawing from this, it can be prudent that a coordinated effort to share information from global research initiatives can facilitate and accelerate drug development, drug acceptance, scale-up and commercialisation in the field of nanotechnology. By implication, the plethora of laboratory research already undertaken globally can be used to derive appropriate knowledge and research that is available at the laboratory scale to form a base-line of practice (Zhang *et al.*, 2020). This information could be used to initiate a universal data-base where data can be input at the end of each project by the different research groups and research centres conducting related literature, globally.

The criteria for conducting experimental work consistently between the various groups and for updating the data-base can be stipulated at the outset so that all stakeholders can practice uniformly when using the data base. For example: the experimental design, quality control procedures, scope and presentation of findings can be predetermined to harmonise documentation and data collection between all the research groups. The motivation behind this is that before embarking on a study, researchers could view this data-base and scaffold their knowledge from what is already known. This will alleviate the repetition of experiments, as is evident currently, and improve knowledge acquisition, to facilitate experiments to improve them after each undertaking to add-value to the knowledge base to accelerate the development of nano-enabled drugs. Furthermore, it will also provide a platform

for consultation, inclusiveness, guidance from experts and exposure and mentorship to develop researchers and research groups and an establishment of a registry for potential funders and venture capitalists.

### **Knowledge-based society**

Nanotechnology can be a game-changer to improve societal challenges in food security, medicine, construction, manufacturing, and so much more. However, the uncertainty regarding risks in nanotechnology can place it in jeopardy of public acceptance. Potential job losses and harm can encourage the spread of false-information and cause panic that could obstruct its development. It is reasonable to thus deliberate with society transparently via open dialogues to drive out fear to exploit maximum benefit that nanotechnology can offer (Miah, 2017).

### **Foresight planning**

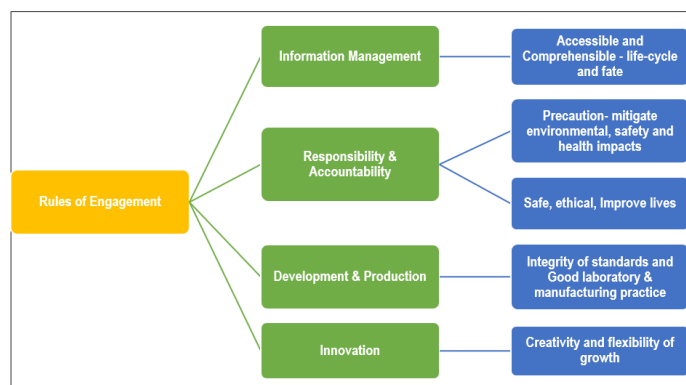
The over-riding benefit of foresight planning is that it can endorse a coordinated formation of milestones over a five and ten-year period that is informed by the most appropriate focus of topics that can be undertaken, particularly picking up from where the preceding experiments concluded. This will ensure continuity in the knowledge that is developing and provide a global understanding of the status and evolution of the vagaries of that particular experiment or research focus. Thus, Foresight planning can be used as a gauge to establish and monitor the maturity of nano-enabled drug development in real-time (Masara *et al.*, 2021). Moreover, it could augment the identification of gaps of knowledge and where more focus is required for potential improvement and innovation. This will inform current practice and will stimulate future research, in tandem, strategically. For example: key role players and expertise can be easily identified, potential opportunities for future collaborations can be undertaken with resource-sharing, mentorship support and expanding the research scope of drug development in a focussed and coordinated way. This would avoid the duplication we see currently because the increase in the knowledge base will improve the understanding and insights that is required for the evolution of drug development in real-time.

### **Multidisciplinary approach**

Based on the information derived from foresight planning, it is plausible to assume that a universal data-base can be established to serve as a repository for research to provide “open-access” information to scientists, public, entrepreneurs, funders, industry, academia and governments, globally. This will enable the formation of multidisciplinary teams to facilitate product development from concept to innovation and patents to commercialisation. The establishment of a multidisciplinary team will not only inform the activities on the immediate value-chain from an operational perspective but will inform the communication that is required to facilitate public awareness, understanding and acceptance of nano-enabled products. Arising from this, the contribution of each role-player in the multidisciplinary team will inform future engagement on the value-chain. Their contribution should not be under-estimated particularly the role of the consumers and funders and their appreciation and awareness of the product (drug developed). This approach will also provide support for underdeveloped and poorly developed research groups both in terms of access to resources and guidance of practice.

The multidisciplinary approach provides informed engagement for stake-holders regarding the product development and it will encourage expert input on customer requirements, design and development concepts, production, processing, safety, waste-management and community engagement. It might be sensible to introduce some form of standardisation of practice for all contributors of the repository to ensure that there is consistency of practice, and related validity and reliability so that a comparison of findings and generalisation is plausible. There are certain inputs that supports the standardisation of practice. These include an in-depth understanding of the: Rules of engagement; the Life-cycle in product development, the Fate and behaviour of NPs, Hazard Characterisation; Integration of GLP, Standards, QA and Risk Assessment Evaluation and Reduction (SANS ISO/TR 12885: 2008; Hasselov *et al.*, 2008; Thomas *et al.*, 2010; CRO Briefing, 2010; ISO/TR 13121:2011 and Tolmachev, 2012). The details of each of these inputs is a major contributor to the management of nano-enabled materials and products and requires further discussion with its own focus and is thus out of the scope of this paper. The Rules of engagement will be discussed as it contributes to the behavioural understanding associated with the management of the importance of a unified definition and precautionary implications of nanomaterials. Figure 3 proposes the “rules of engagement”.





**Figure 3:** Rules of engagement (Developed by the researcher)

The “rules of engagement” provide the fundamental considerations to establish a management system to initiate the manufacture of nano-enabled products. It will induct stake-holders (customers, suppliers and industry partners) on pertinent information related to the product, it will provide a code of conduct and engagement along the entire value-chain (Figure 3) satisfying social responsibility obligations and science communication such as: ethical considerations, community awareness, openness and access to information. It is anticipated that this growing public knowledge and awareness will provide the impetus to industries on the value-chain to be responsible and accountable in their practice and to take the necessary precautions to anticipate, manage and mitigate environmental, health and safety risks not only in product development but also in research development and innovation.

#### ***Unified definition of nanotechnology and nanomaterial***

Understandably, there is a belief that nanotechnology cannot be regulated because it lacks a uniform definition that prevents a common platform for fundamental beliefs and practice (Satakar *et al.*, 2016). By implication, the establishment of a multidisciplinary team and data-base will encourage the involvement of various experts and inputs from different fields/disciplines along the value-chain of drug development. In-lieu of their contribution to the development of nano-enabled materials their interaction with society should not be underrated. At this stage members on the value-chain should debate on a common definition and come to an amicable agreement on a definition that is representative and can be agreed upon between members on that value-chain. This will form the basis for fundamental uniformity that is required to initiate, encourage and formalise standardisation to harmonise practice for funding applications, patent laws, regulatory oversight, removing trade-barriers and many others.

#### ***Adapt to existing Regulations, Standards, Guidelines***

There is a suite of Technical Reports and Guidelines relevant to nanotechnology. In the absence of validated protocols specific to nano-enabled materials, laboratories adapt current Organisation for Economic Co-operation and Development (OECD) methods, Laboratory Development Methods, Good Laboratory Practice and/ or ISO 17025 as guidance documents for measurements (OECD, 2013). Of concern, there is great trepidation with this practice because it is widely known that these OECD methods have originally been established for macromolecules, while there are great deliberations that macro-counterparts behave differently from the nano-counterparts (Zhang *et al.*, 2020). Consequently, this adaptation from macro to nanoparticles is questionable, and should be cautiously approached to ensure that the nuances of the nanoparticle behaviour have been considered in the adapted methods. Thus, relevant nanotechnology guidelines and technical reports should be exploited to obtain an understanding of the nuances of nanomaterials before any adaptation of methods are undertaken. In-keeping with this, nanotechnology regulatory bodies propose the concepts of the Precautionary Principle (PP) and the Case-by-case to manage behaviour responsibly when using nanomaterials. They are of the view that these concepts can provide the guidance that is requisite to ensure that the nanotechnology inspired behaviour has been accommodated.

#### ***Precautionary principle (PP)***

The PP guides the developer or manufacturer on the requisite precautions that is required when working with nano-enabled materials or products and the concomitant mitigation that is required to ensure that they are performing their activities responsibly with the well-being of society and the environment in mind (Mathuna, 2011). The fate of

the nanoparticles especially particle size, solubility, surface area, surface coating, reactivity and dose are influential factors that have been reported to contribute to the potential toxicity of nano-enabled materials. Thus, their influence and contribution to product development should not be underrated. For example: the influence of these factors can be seen to dominate the ADMET, hydrophobicity, type of formulation, dose and movement of the NPs in the body during drug development (Iswandana *et al.*, 2022 and Zhang *et al.*, 2020). To the best of my knowledge, very few articles provided any sound discourse on toxicity and none of the articles to the best of knowledge discussed any mitigation strategies for potential users of the products being developed. A better understanding of the fate of the NPs will provide insights on the novel chemical, mechanical and optical features that may arise from these particles thus informing the level of potential toxicity and the obligatory mitigation that is required to manage the risk. A Risk Management strategy should commence with an assessment of critical control-points that arise from particle features, uncertainty risks from processing and production stages, uncertainty risks in the body, criteria for human and animal epidemiology studies and potential health effects. An evaluation of these factors will inform critical control points that should be monitored on the value-chain.

### **Case-by-case approach**

The Case-by-Case approach moots that each project according to its specific nuances, establishes baseline of practices to determine conformity, consistency and uniformity of practice (Mathuna, 2011). During this stage Risk Assessment, Risk Characterisation, Risk Evaluation and Risk Reduction is undertaken. This risk management can be undertaken in accordance with established technical guidelines or can be adapted appropriately to include further conditions aligned to the tests (ISO/TR 12885: 2008; Hasselov *et al.*, 2008; Thomas *et al.*, 2010; CRO Briefing, 2010; SANS ISO/TR 13121:2011 and OECD: GLP, Tolmachev, 2012).

### **ADMET**

An understanding of ADMET will provide deeper reflection on the fate of NPs along the life-cycle of the product. It will provide insights on appropriate particle size and concomitant features for therapeutic action, absorption, distribution and ideal criteria for drug metabolism, excretion and toxicity (Zhang *et al.*, 2020 and Iswandana *et al.*, 2020).

### **Quality-by-design (QbD)**

Once the risks, their probabilities and severity has been established the next stage would to consider the QbD, metrology and standardisation of the developmental protocols. QbD focusses on the quality attributes, it's components and parameters that govern the development of the drugs. It promotes the philosophy of quality at the source and Process Approach according to ISO 9001:2015 (SANS, 2015) to encourage the optimisation of processes. By default, QbD will foster a collaboration of a multidisciplinary team, for example: the researcher, the manufacturer, the regulator and the community. Metrology will address the measurements, uniformity of practice and the quality assurance that is required to ensure that the products meet specifications are valid and reliable (OECD: GLP, ISO 17025: 2017, ISO/TR 13121: 2011 and ISO 12883: 2008). Standardisation is progressing with various technical reports and guidelines like: SANS ISO /TS 11308: 2020- Nanotechnology- characterisation of CNT samples using TGA, ISO/TS 12885: 2018 – Nanotechnology- Health and Safety practices in occupational settings and ISO 13121: 2011- Nanomaterial Risk Evaluation, among them guidelines for Nanotechnology - Performance Evaluation, Evaluation of Nanoparticles in Powder-form and Evaluation of Physicochemical Characteristics of Engineered Nanomaterials, among others. Although some of these guidelines are applicable to carbon-nanotubes, their approach can be used for the development of other guidelines for various nano-enabled materials.

### **Scale-up activities**

Scale-up activities have been very poorly addressed in literature (Ahadian *et al.*, 2020 and Kazemzadeh *et al.*, 2022). An assessment of the nature of the research conducted revealed that this was due to the minimalist focus only on development of drugs and the lack of investigations into the broader scope interactions of drug development. It is reasonable to accept that the framework above provides a basic infrastructure for a range of multidisciplinary considerations to initiate a value-chain with relevant stakeholders to progress nano-enabled drug development away from traditional practice and beyond the laboratory.

## **Training**

Thereafter, training and development initiatives can be put in place to inform all stakeholders of their responsibilities within their scope of work (US FDA, 2004). Adherence to standards and protocols suggested in this paper serves to consider nano-enabled content and does not preclude the products' compliance to discipline specific regulatory requirements that must be maintained, for example: those prescribed by the relevant Medical and Pharmaceutical Councils. This paper deliberates that the survival of the pharmaceutical industry in the modern era will depend on the ability of researchers and manufacturers to learn to work collaboratively and familiarise themselves with broader aspects of drug development to include all stakeholders to give the product the transparency that it requires to foster trust between competitors and collaborators on their value-chain for product acceptance. This will encourage improved performance along the entire supplier chain, more informed and faster decision making, improve the speed of research and development to subsequently fast track the product to the market.

## **Discussion**

Arising from the review of literature, it is reasonable to assume that as a fraternity we can contribute to build the body of knowledge that is required to formalise nano-enabled drug development. This section provides a narrative to highlight key features that were used to develop the Framework in Figure 2. It is envisaged that this framework could provide the infrastructure proposed by Zhang *et al.* (2020) and others, to manage, control and minimise inconsistencies in nano-enabled drug development.

From the integrative review, it was established that the success of drug delivery systems from concept to industrialization will require a deeper understanding that is different from the present thinking to augment the integration of the entire product development, manufacturing and application processes. It was realized that these sections cannot be operated as separate entities as their interactions overlap between development, manufacturers and applications. Moreover, effective management of these sections requires multidisciplinary inputs that requires a 'conversation' between all stakeholders. For example, the interaction between various departments that is required in an organization can be seen when a drug development initiative ought to include the components that make up the drug formulation (research and development, regulator and funders) and establish the design features (production, customer and regulator) that is required so that the active ingredients can be carried to the site of disease without losing its integrity. Acknowledging the distribution and transport mechanisms of the drugs in transit, their chemical and physical interactions within the human biome, the variation between patients caused by the disease and other medication cannot be overlooked and therefore their influence on each other and in-vivo will be required to demonstrate efficient drug delivery and progress to clinical trials (application).

In keeping with better communication between departments, a coordinated discourse among role-players and researchers could encourage the practice of a knowledge sharing initiative for the establishment of a data-base that can serve as a repository and be aligned to current needs to address the gaps in knowledge and develop the most appropriate formulation for world consumption. This can be monitored by a steering committee, with an ethics sub-committee and "Think Tank" comprising of national and international representation, to monitor, evaluate and coordinate efforts arising from foresight planning and the data-base to maintain focus on the outcomes of impact areas, policy development, facilitate access to start-ups and develop business models for self-funding to promote nanotechnology responsibly and transparently. Foresight planning is a useful tool to provide an understanding of the nature and outcomes of research experiments already undertaken by the various research groups. A unified definition for nanotechnology was found as challenge for all stakeholders because of poor consensus and agreement on the upper and lower limits in size to determine what constitutes a nanoparticle.

Although the QbD, in the form of the Process Analytical Technology (PAT) Framework, has been used favorably in selected studies, these have mainly been used in drug-development using macromolecules and little consideration has been given to the wider nano-enabled drug development. The PAT Framework is used to design, analyze, control processes and the manufacture of pharmaceuticals by considering critical to quality attributes of the active ingredients (US FDA, 2004). While the PAT Framework has been useful in drug development, it was deduced that it is inadequate for nano-enabled drug delivery systems in the current form and will have to be adapted and supplemented to include the nuances emanating from using nanomaterials, particularly during standardization, compliance to regulations or technical guidelines, metrology, measurement and risk management.

The concept of the Precautionary principle emerged as an important feature (Mathuna, 2011, Zhang *et al.*, 2020 and Iswandana *et al.*, 2020) although it was not approached in all the articles. This concept is very important because it assesses the level of mitigation in accordance with the precautions that have emerged from using nanoparticles. Similarly, the Case-by-case approach was also absent in the articles (Mathuna, 2011 and ISO 13121:2011). Evaluation of this concept is important to appraise each project for its specific and distinct features so that appropriate management of risk assessment, risk characterization and risk evaluation considerations could be facilitated.

Moreover, there was little discourse on the quality of raw materials and quality control aspects, yet these can have a very positive or negative influence on the progression and acceptance of drug development. Arising from this more effort could be made to understand the effects of the quality of the raw materials and their interactions on the development of drug delivery systems. Quality control, the rigorous development of unified practice and validated protocols particularly towards the development of robust standard operating procedures and measurement of the performance of processes and its stability, as this consideration has been understated in the current research milieu. These features are important to demonstrate product stability and dependability. Acknowledging this, the Framework in Figure 2 was developed to enrich the interrogation of practice proposed in drug development to provide consistency in management from drug conceptualization, design and production that will create the unity in development and the foundation for deliberate quality management and quality engineering, safety and risk management for future innovation and creativity that is practical and that demonstrates continuous improvement that scaffolds knowledge to progress towards clinical practice and commercialization.

A major challenge in the development drug-delivery strategies is to demonstrate its potential behaviour in the biological setting, in this case the human body. Generally, fruit flies, fish, rodents, dogs, pigs and non-human primates have been used in IBD studies (Hartwig *et al.*, 2021 and Hadji and Bouchemal, 2022) to determine if the new formulation will behave as desired and as predicted. These animal models have also been used to demonstrate the potential toxicity of the formulation. However, there are affirmations from researchers who caution that the efficacy of animal-models and its relationship to the human biome is not as reliable as anticipated and their use in efficacy and toxicity studies is thus worthy of further exploration and sound practice. Uweira *et al.* (2016) study, cited in Hartwig *et al.*, (2021) advise that, although, the non-human primates are most likened to humans, the innate intestinal immune system of invertebrates is similar to humans. It is worthy to note that the adaptive immune response is absent in invertebrate models and that immunological and histopathological induced IBD models in research and IBD patients vary from the source of insult and intestinal immune response, respectively. Further investigations revealed that more serious inflammation requires the input of more drugs, and these models do not represent the chronic phenotype experienced by humans (Uweira *et al.*, 2016; Gibbons and Spencer, 2011; in Hartwig *et al.*, 2021).

Fish, canine and swine models are also used because they have common human physiologic and immunologic functions related to irritable bowel conditions. Regardless of these positive traits, the efficacy of active targeting using rodent models have been brought under question. According to Jiminez *et al.* (2015) in Hartwig *et al.* (2021) rodent models are widely used because of their moderate ethical consideration by research ethics committees. Selected studies evaluated from literature in this paper used rodent models to highlight disease mechanisms, mucosal immunity, the efficiency of new formulations and their therapeutic benefits and validates their efficacy before progressing to clinical trials. For example, Mc Connell *et al.* (2008) study cited in Hadji and Bouchemal, (2022) propose that the intestinal biome of the rodent and humans are different, bringing the results derived from these tests under scrutiny. They support their claims by adding that the passive targeting in humans is much weaker than in mice, for example, when the pH of mice is 2.7 – 4.1 the corresponding location in humans can be as low as pH 1 making the function of the drug different between these media. Moreover, and of great concern, they advocate that transit times, mucus growth rate, thickness and glucan profiles, all critical to IBD, differs between humans and mice.

Furthermore, Hadji and Bouchemal, (2022) study cites Hugenholtz and Devos, (2018) that only a few percentages of bacterial genes are shared between mice and humans. Another salient contribution using animal models by Mizoguchi *et al.* (2020) study cited in Hartwig *et al.* (2021) suggested that the small size of the rodent species restricts the testing of conventional dosages that can be likened to humans. Against this backdrop, they advise that the measurements of therapeutic outcomes of animal studies and human clinical trials are recorded as different remission scores, making considerations like the route of drug administration, drug dose and biodistribution difficult



to compare and interpret. These considerations make scalability of dosage challenging and reproducibility of drug efficacy very poor and thus makes reliance on animal tests worthy of more consideration. This kind of uncertainty especially after the controversial risks associated with nanoparticles will create ambiguity in nanodrug development and their acceptance for clinical trials and commercialisation.

The lack of regulatory oversight was also evident as a barrier in progressing nano-enabled drug development because it did not encourage uniformity of practice. QbD without support from metrology practices, quality control, quality assurance and standardization may not be suitable for nano-enabled drug development and thus these considerations are warranted. Congruent with this, research initiatives did not balance moral obligations, like ethical considerations, awareness and acceptance by the public in the race for dominance. Although studies elucidated obtained ethical clearance for the use of animal models in their studies, all phases of product innovation, development and commercialisation was silent on mutual benefit, transparency, cause no harm and offer justice for all users rich and poor, all being salient points for clinical trials and commercialisation. It can be appreciated that the development and progression of the nano-enabled drugs using nanotechnology is fragmented and fails to meet clinical trial protocols because it lacks consistency in belief between role players and has ambiguity in establishing whether these drugs can be used safely and effectively in a human setting. The narrative emerging from various researchers reveal that there are uncertainties evolving from their findings around the extraordinary behavior of NPs, its concomitant unique attributes, and its potential effects, creating the impetus for further development of guidelines, standard operating procedures, validated protocols, and standards that necessitates the formalization of nanotechnology by regulatory bodies.

## **Conclusion and Recommendations**

Lessons can be learnt from the recent Covid-19 pandemic particularly during the vaccine development between countries and vaccine resistance by the public during the Covid-19 pandemic. This paper has affirmed that there has been inordinate work undertaken in the development of nano-enabled drug delivery systems to treat IBD but that it is disjointed in the current format. Regulatory compliance can be established with strong industrial relation influences and collaboration for policy development, validated protocol agreement, standardized practice and procedures in the research arena which are critical to assess daily activities in practice. Government funded institutions have been established with a national footprint to collaborate with and develop entrepreneurs to shape related projects to uplift the country by providing guidance, access to use of facilities and advice on scale-up opportunities. These institutions can be approached when such needs arise so that nanotechnology initiatives can be accessible to more individuals and progress beyond the laboratory to transfer this technology into a tangible product. This paper developed a framework to provide a mitigation strategy at various stages during the management of activities internal and external to an organisation for developing nano-enabled drugs for the treatment of IBD. It was established that this information if properly managed can serve as a data-base to provide knowledge derived from global studies obtained from peer-reviewed research to establish the current thinking and show the status of research undertaken in this field to ensure that future projects are not duplicated, they remain novel and add-value to the knowledge base in drug development using nanotechnology.

It highlighted the important themes that are required to promote consistency in practice for researchers and manufacturers with a deliberate management stance to fully understand the considerations that need to be taken, managed and/or mitigated when using nanotechnology. By implication the themes will also encourage data handling, data control and data sharing and give it the transparency that it requires to foster trust between competitors, collaborators and society on their value-chain and those researchers using the universal data-base for open access reference. The importance of engaging with the public, particularly in the transfer of the scientific knowledge meaningfully and creating a space for engagement will stimulate their appreciation of the public towards nanotechnology, was also highlighted. This will not only encourage improved performance along the entire supplier chain, more informed and faster decision making, to improve the speed of research and development but will facilitate public acceptance to fast track the product to the market. Pharmaceutical manufacturers are generally well financed and have advanced research and development centres. Perhaps if there was more collaboration between the national research council and funded-institutions, pharmaceutical manufacturers, academia and society, nanotechnology may achieve the traction to advance more nano-inspired drugs to commercialisation. This Framework was developed specifically for the pharmaceutical industry. It is hoped that it will provide the platform for a holistic approach to drug development that would include the considerations to progress the formulations



beyond the laboratory. This Framework should be tested for its applicability, thereafter way forward would be to adapt the Framework for other disciplines.

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