Proceedings of the 4th African International Conference on Industrial Engineering and Operations Management Lusaka, Zambia, April 4-6, 2023

Harmonizing Design, Risk, Metrology and Standardization in Managing the Development of Drugs using Nanotechnology

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Abstract

Irritable bowel disease is typically situated towards the end of the human gastrointestinal tract thus, challenging and restricting the efficacy of traditional drugs. Nanotechnology, regarded as a game-changer in the modern pharmaceutical world has shown the advancement of drug performance in extraordinary ways up to laboratory scale. Failure of standardized protocols, potential toxicity, inability to up-scale practice, among others have been mooted to prevent the advancement of novel drug development using nanotechnology to commercialization. This study was Qualitative. Data was collected using an Integrative Review of 144 articles. Specific quality control was adopted to ensure that Validity (saturation) and Reliability (trustworthiness and repeatability) was established. This paper culminated in a series of schematic frameworks of fundamental key strategies to advance the development of nano-enabled drugs, responsibly, demonstrating mitigation strategies for hazard characterization, risk evaluation, risk reduction and quality control along the lifecycle of product development for nano-enabled drugs.

Keywords
Nanotechnology, Innovation Drug Development, Risk Management and Quality Management

1. Positioning nanotechnology in drug development

In this highly competitive and technology driven world, the medical and pharmaceutical fraternity is constantly searching for smarter technologies and novel and innovative ways of developing, manufacturing and managing drug development towards clinical trials and commercialization (Safari et al. 2014).

Nanotechnology, viewed as a disruptive technology in the era of the Fourth Industrial Revolution(4IR) has been regarded as the solution and game-changer to produce cutting-edge drugs with smarter solutions and predictable performance that have minimal side-effects, are cost-effective and environmentally friendly (Seifirad et al. 2016; Sardo et al. 2019; Ahadian et al. 2020 & Kazemzadeh et al. 2022). Nanotechnology refers to materials with at least one dimension in nanometers (1-100nm) and displays extraordinary features, from their counterparts, that are attributed to their small size, large surface area, reactive surface structure, versatile chemical composition, unique solubility and variable shape (Hartwig 2021; Zhang 2020; Kazemzadeh 2022). These nano-derived components in drug delivery, present an improved rate of dissolution and adsorption in the human body and are used in the form of polymers, dendrimers, liposomes, micelles, solid-lipid nanoparticles (NPs), hydrogels, metallic NPs, semiconductors, carbon nanotubes and nanocrystals (Zhang et al. 2020). Nanoparticles are favoured in the pharmaceutical industry because they can control and regulate the pharmacodynamics (PD) and pharmacokinetics (PK) of drugs (Zhang et al. 2020) relative to the extracellular matrix, inflammation, tissues and therapeutic action (Yang et al. 2011) better than systems using the same materials as macromolecules, and deliver them to different parts of the body for a sustained period (Hartwig et al. 2021).

The nano- particles are useful because they can accumulate at the inflamed tissue thus delivering 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 minimizing the systemic effects as is experienced with traditional drugs (Ovadje et al. 2015; Chaudhari et al. 2020, Jain & Parkhe 2020, Zhang et al. 2020 & Hadji & Bouchemel 2022). Another promising feature favouring nanoparticles is their ability to protect drugs that are usually prone to degradation

in the body by allowing them to stay intact for extended periods and allowing controlled release of the active ingredient, providing stability and higher concentrations of the active components that are able to penetrate epithelial and inflamed cells making it a promising tool for inducing and maintaining prolonged remission or curing disease (Hartwig et al. 2021; Kazemzadeh et al. 2022).

Irritable bowel syndrome is widespread in most societies, is incurable in some forms and can be deadly if not monitored and controlled. Typically, treatment options are used to induce and maintain remission of the disease (Hua 2015; Jain and Parkhe 2020).

1.1 Problems with nano-enabled drug delivery systems

Current drug delivery systems face many challenges like long transit times from administration to reach the site of active disease, the different regions and their dynamics on route and premature release of the drug, to name a few. Acknowledging the promising features of nanoparticles there have been many initiatives to improve drug delivery to the colon (Pertuit et al. 2007 and Seifirad et al. 2016 and Sardo et al. 2019).

Even though large volumes of research from laboratory tests in petri-dishes and animal models have suggested that nanoparticles will improve the drug response and drug delivery in the body (Hua 2015; Seifirard 2019; Iswandana 2022; Kazemzadeh 2022), very few drugs reach clinical trials, scale-up and commercialization to the market (Doxil, Caelyx, Myocet and Abraxne) (Ahadian 2020; Zhang 2020) while others like: Ferrugose and Resovit have been recalled because of safety concerns (Zhang et al. 2020).

It has been advised that there is safety and toxicity concerns that arise from using such small sizes nanoparticles because they are capable of crossing the blood brain barrier (Vijayaraghavan and Nalini (2010) and Narayanan and Sakthivel (2010) as cited in Abbasi et al., 2015].

Moreover, the risks that arise from using these nanoparticles are inconclusive as determined by the tests that are presently available. The lack of standardized protocols, particularly in risk and laboratory management, regulatory oversight, poor repeatability in scale-up initiatives and low consistency between batches of drugs produced in research affects the validity of drug performance and complicates the understanding of drug interactions in the human body [Ahadian et al. 2020 and Kazemzadeh et al. 2022].

1.2 Objectives

This paper will explore and propose some keys factors to manage colonic drug delivery initiatives, to progress development beyond laboratory practice by offering risk and laboratory management mitigation strategies to ensure that nano-enabled drug formulation is undertaken with responsible attention to the patient, the employees and the environment along the value-chain.

2. Literature Review

From the review of literature, particularly Zhang et al. (2020) it was apparent that there has been overwhelming and ongoing focus on innovative drug development and not much focus on exploiting the data and findings from existing studies. Moreover, not much attention was given to governance (poor repeatability during scale-up trials), risk management (poor understanding of particle interactions), monitoring (lack of standardized protocols and regulations) and control (low consistency between batches) which was mooted as some of the constraining factors preventing these drugs from being commercialized (Savolainen et al. 2013, Zhang et al. 2020, Berger 2021 and Rose et al. 2021). The review also demonstrated that there is a reasonable about of information that is well documented in terms of transport, physical and chemical properties of components for drug delivery systems with more focus required in understanding nanoparticle behaviour, monitoring and its recovery in-vivo.

Based on the concerns of researchers, manufacturers and regulators, the concept of a Precautionary Approach has been mooted. This approach allows the development of nano-enabled products with the adoption of precautions concomitant with the level of mitigation that is required to develop the product responsibly by the developer or manufacturer without harm to society and the environment (Mathua 2011). Although, this approach has been in the public domain for many years it has failed to guide nanotechnology to reach its full potential. An assessment of this approach and research by Yerlikaya et al. (2013); Patwardhan and Asgarzadeh (2014); Bansal and Asthana (2016) and Ahadian et al. (2020) suggests that manufacturers strategically develop product plans to examine the drug

formulation, process related aspects and risks from product conceptualization, design and development to commercialization. Safety from chronic exposure, process optimization of particles and their interaction in drug formulation, control of variability, measurement and measurement uncertainties could influence cost-effective ease of scale-up.

Consequently, they believe that this will improve the standardization of protocols and processes to provide reliable manufacturing and scale-up initiatives where NPs will demonstrate their stability and dispersibility with standardized surface functionalization before proceeding to clinical trials. According to Zhang et al. (2020), a systematic understanding of the processes associated with absorption (A), distribution (D), metabolism (M), excretion (E) and toxicity (T) of NPs is required in-vivo to grasp the behaviour of these particles in the human biome to ensure safe and efficient drug release and treatment (Kazemzadeh et al. 2022).

3. Methods

An integrative literature review was used to collect data from 144 articles obtained via an appropriate keyword of 16 data bases. Each article had to satisfy on a set pre-defined criterion relevant to information sought for developing suitable drug management strategies. These criteria were aligned to material science, compliance to regulations, pharmacology, research methodology and human anatomy and its biome.

Validity was established by assessing the methodological quality of articles and saturation of information between articles, for their suitability to provide information to develop the envisaged quality and risk mitigation strategies (Vieira et al. 2022). Reliability focused on repeatability of information and focused on credibility, dependability, transferability and confirmability of the facts between articles in literature (Goddard and Melville 2006; De Souza et al. 2010 & Synder 2019). Pilot work was used to establish theories/themes in drug delivery, particle behaviour in the body and quality of design attributes.

4. Data Collection

The research design of each article reviewed from literature was assessed for soundness of practice in terms of experimental design, metrological reflection, models used, demonstration of validity and reliability, statistics and commercialization (Table 1). This removed any potential bias and ensured that each article was assessed equally before being used to demonstrate consistency in the information obtained.

Given the nature and composition of nano-enabled pharmaceuticals, Table 1 illustrates the cognizance of the multidisciplinary contribution of material science, biotechnology, pharmaceutical science, medicine and compliance monitoring.

Table 1. Journal focus area

Journal focus area	
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

An appreciation of each of the interactions derived from these components with each other and the human-biome was thus apparent and considered in the development of the frameworks proposed in the study.

Table 2 describes the fundamental quality control that was used to ensure that very specific reflections to colonic drug delivery systems (CDDS) was present in each article from literature so that relevant articles and information could be gathered.

Table 2. Characteristics for purposeful selection of articles (Adapted from Synder, 2019 & Vieira et al., 2022)

Journal focus area	
Involved CDDS	Methodology was clear and reasonable
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 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

5. Results and Discussion

The Process Analytical Technology Framework (PAT), supported by the International Conference on Harmonization (ICH) provided the pharmaceutical industry sound practice over the years that has consolidated chemical, physical, microbiological, mathematical, risk assessment and regulatory insights to provide a navigation tool for strategic development and implementation of manufacturing and quality assurance. The salient features included are: a risk management and quality systems to maintain the quality of the system, access to latest technologies and developments, reviews and inspection activities, regulatory reflections and, health and safety (US FDA 2004; Orzechowski et al. 2018; Saydam and Takka 2018).

Although the PAT Framework has worked positively for the traditional pharmaceutical industry, it could not address some of the challenges experienced with innovative drug development and innovations, particularly using nanotechnology. In view of the current challenges experienced by the nanotechnology fraternity, it was apparent from research that better management and control for the scale-up of nano-enabled drug development and delivery is required and can be achieved by interactions on the entire value-chain from drug conceptualization, to drug development, manufacture and commercialization (Ahadian *et al.* 2020; Iswandana et al. 2022).

Based on this discourse it was reasonable to deduce that a strategy that incorporated both the PAT recommendations and nuances of nanotechnology be proposed. Therefore, the Table 3 was developed to highlight salient points that have been selected for the adaptation of the traditional PAT framework to nanotechnology inspired formulations.

Table 3. Salient features to adapt PAT Framework to nanotechnology

Salient factors	Approach
Responsible practice	Appropriate rules of engagement
Surface characteristics, reactivity, particle size & particle shape	Understand fate of nanoparticles
Manage uncertainties & risks	Hazard identification
Manage exposure routes	Hazard evaluation
Risk and waste management options	Hazard reduction
Quality assurance & quality control	Validity, reliability, traceability & conformity
Sound laboratory, occupational & environmental practice	ISO 17025, GLP, ISO 14001

Facilities, resources & responsible practice	Compliance with standards

The reasoning, as indicated in Table 3, was to preserve the features from the PAT Framework that is required for development and regulatory compliance and to concentrate on the features like particle surface chemistry, risk management, environmental and occupational management and quality assurance. The inclusion of these additional features was inspired by literature to account for the uncertainties and concomitant toxicity and risks arising from nanoparticles.

This series of strategies and protocols in the form of individual frameworks were contemplated to address governance from the perspective of risk and quality management in nano-enabled CDDS, which is what was highlighted as major concerns in literature (Iurian et al. 2017; Beg et al. 2019 & Rahman et al. 2021). These outlined the practices that covered the various stages of drug development from the establishment of multi-disciplinary teams along a value-chain representing the various stages of drug development from conceptualization, process management, occupational and environmental management, pharmacology science, risk management to commercialization.

5.1 The influence of key factors on CDDS development

An appreciation of the lifecycle of the formulation according to Figure 1 addresses the call by researchers for an understanding of the occupational processes in the product development. This is useful because it will provide a map of relevant activities that should be considered to ensure that the drug formulation is optimized not only to meet the requirements of the patient but also be safe from the design and processing aspects from conceptualization to production.

The development of Figure 1 was inspired by the works of Rahman et al. (2021) who suggested the route of systematically developing high quality, robust drugs while taking cognizance of the potential risk factors and managing and controlling sources of error and variation (Iurian et al. 2017) to facilitate continuous improvement (Beg et al. 2019).

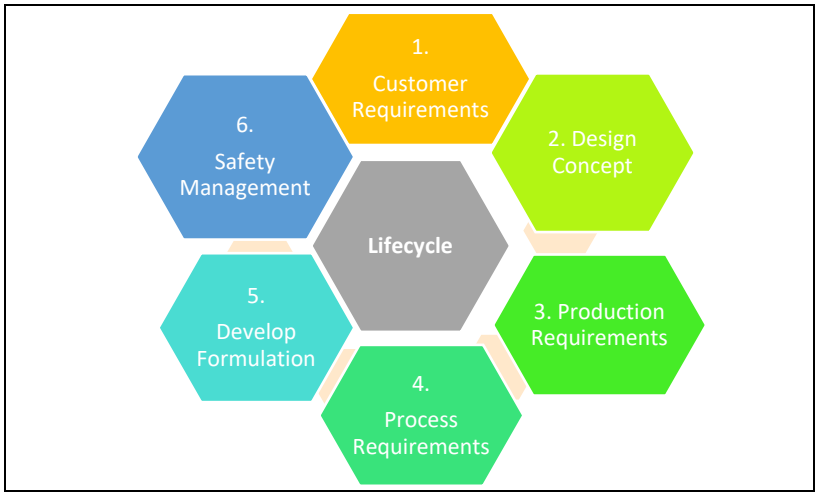

Figure 1. Lifecycle of CDDS Development (Adapted form Iurian et al., 2017, Beg et al., 2019 & Rahman et al., 2021)

This map will also assess and highlight the different regions along the lifecycle of the product so that the concomitant attention to quality production, safety and risk management can be addressed during the entire development and production process.

Yerlikaya et al. (2013) and Wang et al. (2014) considered the contribution of Cause and Effect analysis on the stability of processing. Saydam and Takka (2018) worked on the importance of process capability and variability. Orzechowski et al. (2018) worked extensively on laboratory practice, customer requirements, and product development and reiterates that goal of laboratories is to produce reliable, accurate and traceable analytical results with known

uncertainty to progress patient treatment. These concepts were not only useful for process optimization but also for a deeper understanding of nanoparticle behavior in the human milieu.

Thus, Figure 2 and 3 considered features that were aligned to poor standardization of protocols. By default, these figures offer the resources and facilities that are required for product development, monitoring and control during manufacturing. This can be achieved by developing appropriate process mapping and standard operating practices (SOP) with the input of trained personnel. It also accommodates for quality control and quality assurance so that the efficacy of the formulation is consistently produced and patient requirements are maintained. This structured approach of practice can support the reproducibility and replication that is required.

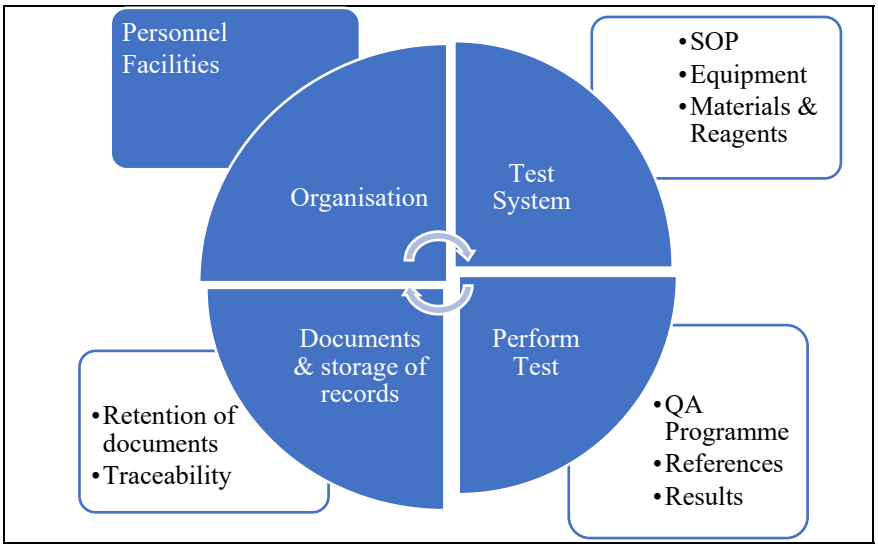

Figure 2. Integration of GLP guidelines and ISO 17025 standards (Adapted by Researcher)

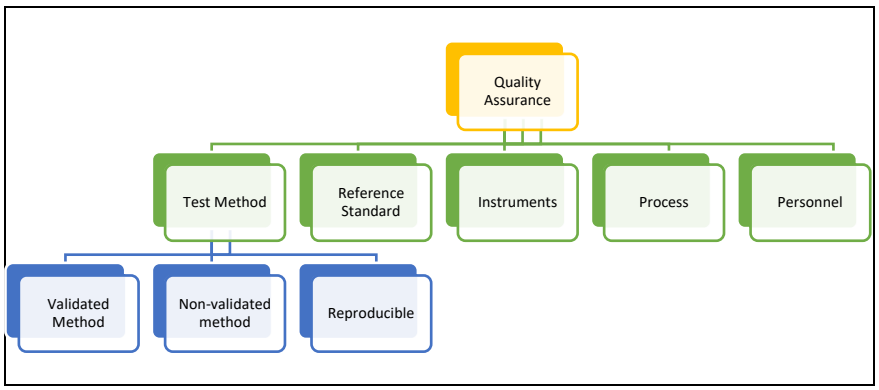

Figure 3. Quality Assurance (Adapted from OECD: GLP, ISO 17025: 2017, ISO/TR 13121: 2011 and ISO 12883: 2008)

Key aspects like document control and traceability, has been widely discussed which is so important to patient care, for example: in post treatment in terms of product recall or side-effects is also considered (ISO 2015; Nogueira et al. 2015 and Braga and Panteghini 2020). Braga and Panteghini (2020) was also an advocate of proficiency testing, method validation and appropriate management of reference materials. Thus, monitoring and control of instruments/equipment, processes and personnel are important consideration to ensure that the drug manufactured can be replicated, and that it complies with desired protocols and could remove the current problems with batch-to-batch replication that is currently evident and therefore was considered in this figure.

Nano-particle behaviour has been unanimously proposed as imperative in nano-inspired products not only for a better understanding of the particle interactions between components in the formulation but also within the human biome, particularly due to patient variability from disease, diet and medicine (Coco et al. 2013; Viscido et al. 2014; Pereira et al. 2018; Kazemzadeh et al., 2022). Hence, the features in Figure 4 have been included for consideration in this paper.

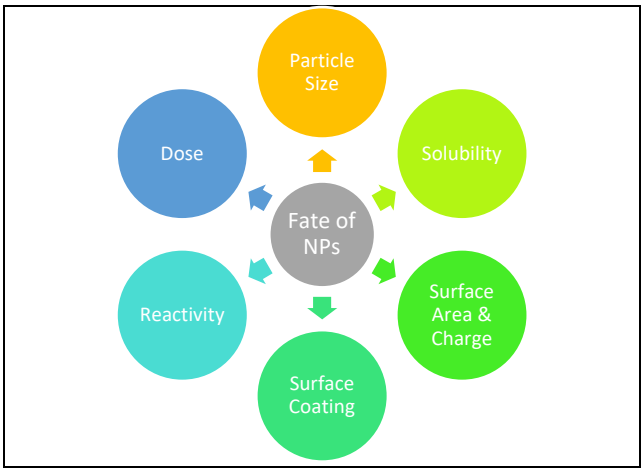

Figure 4. Features to consider for Fate of NPs

Research (Ahadian et al. 2020 and Kazemzadeh et al. 2022) has shown that particle size is important, among others, for drug encapsulation, for efficient transit through the gastro-intestinal tract (GIT) and for potential toxicity due to ability of particles to cross the blood brain barrier. Solubility is an important thought because the active ingredient has to be retained as intact in regions of the GIT where there is an absence of disease and only be released at the site of active disease, while withstanding the vast changes in the pH in the different regions and patient variability due to other disease, diet and medication. The Royal Society (2004), suggests that smaller particle sizes yield a larger surface area for reactivity. Therefore, Surface area and charge need to be optimized because this feature provides the area for contact with materials and thus the relates to the reactivity of the formulation. The surface coating has a similar function as surface area, however in this case the type of coating and its thickness influences the drug function. Reactivity ensures that the drug is able to interact with appropriate materials in designated areas. The desired dose confirms sufficient active ingredient is delivered to initiate a therapeutic action. These features are aligned to A, D, M and E which is fundamental to drug efficiency and effectiveness.

Abbasi et al., (2015) cautions that a shortcoming of using nanoparticles, particularly smaller NP, is that it can be toxic. Understandably, intensive Risk Management is required to provide the confidence that these NP can be used safely in drug formulation. Therefore, the next series of frameworks commences with an investigation on the Hazard Characterization, it then addresses Risk Assessment and culminates in Risk Evaluation. This series is proposed for stakeholders to mitigate their risks, responsibly with the least impact to communities, employees and the environment. Studies (Yerlikaya et al. 2013, Patwardhan & Asgarzadeh 2014; Bansal et al. 2016 and Kazemzadeh et al. 2022) postulated the establishment of suitable risk and toxicological profiles for nano-enabled drug systems. Figure 5 outlines the key points that can be considered to develop a risk profile of the NPs and includes all routes of entry covering administration and occupational exposure.

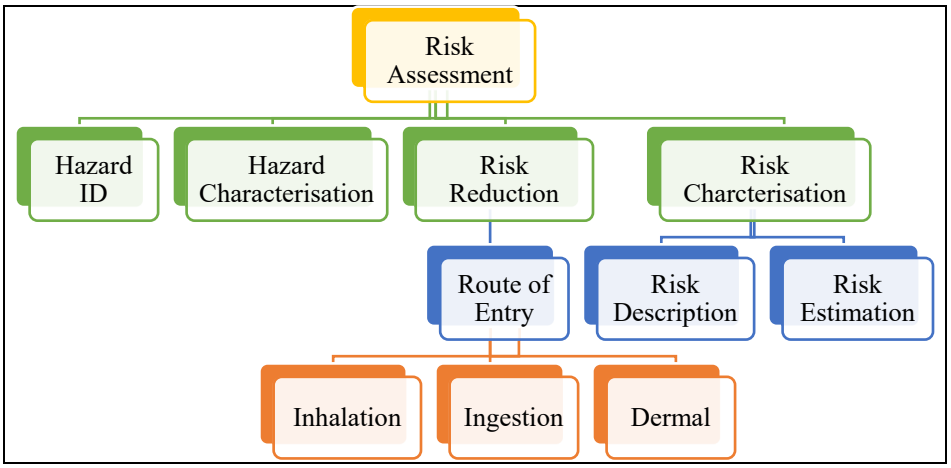

Figure 5. Risk Assessment (Adapted from ISO 13121:2011)

Arising from the potential effects of NP, Figure 6, hazard characterization reviews particles features as outlined in Figure 4 Fate and Features to seek a better understanding of the potential behavior of the drug formulation. It looks at the finer features and its role in processing and with human interaction. This will highlight the uncertainties that should be considered in processes, production, and the human body. These uncertainties can then be matched to the criteria for epidemiological studies for potential health effects to develop suitable mitigation initiatives.

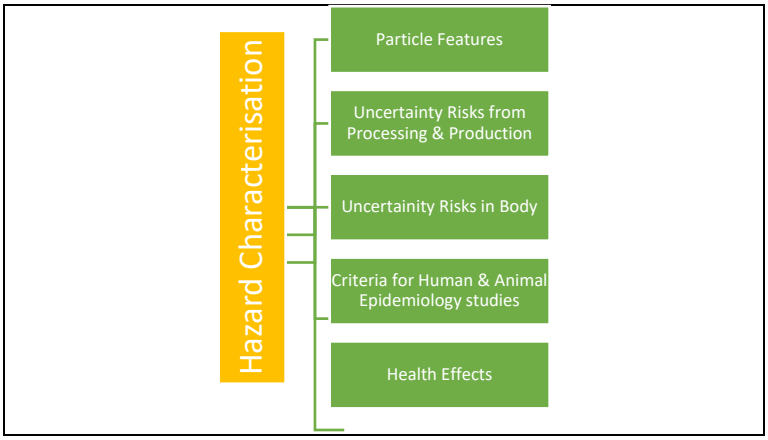

Figure 6. Hazard Characterization (Adapted from ISO 12885:2008; Tolmachev, 2012 and Karelene et al., 2012)

This framework proposes some of the key considerations in understanding the nature of particles that is responsible to intensify the risk evaluation in the ensuing activity. Thus, Risk Evaluation as outlined in figure, 7, explores a more substantial initiatives of the risk and is guided by the application of the material. It also provides a platform for ongoing evaluation (understand risk), mitigation (evaluate and act and document risk) and Continuous Improvement to ensure that processes are constantly monitored.

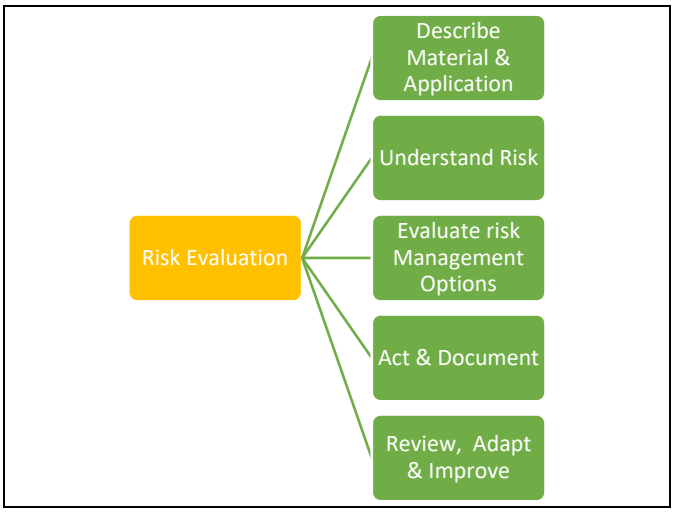

Figure 7. Risk Evaluation (Adapted from ISO 13121:2011)

Risk reduction, in figure 8, reviews the direct impact of the processes and their potential contribution to risks that could be encountered by employees. It suggests likely control points from a measurement and waste-management perspective, mitigating impacts on communities, employees and the environment.

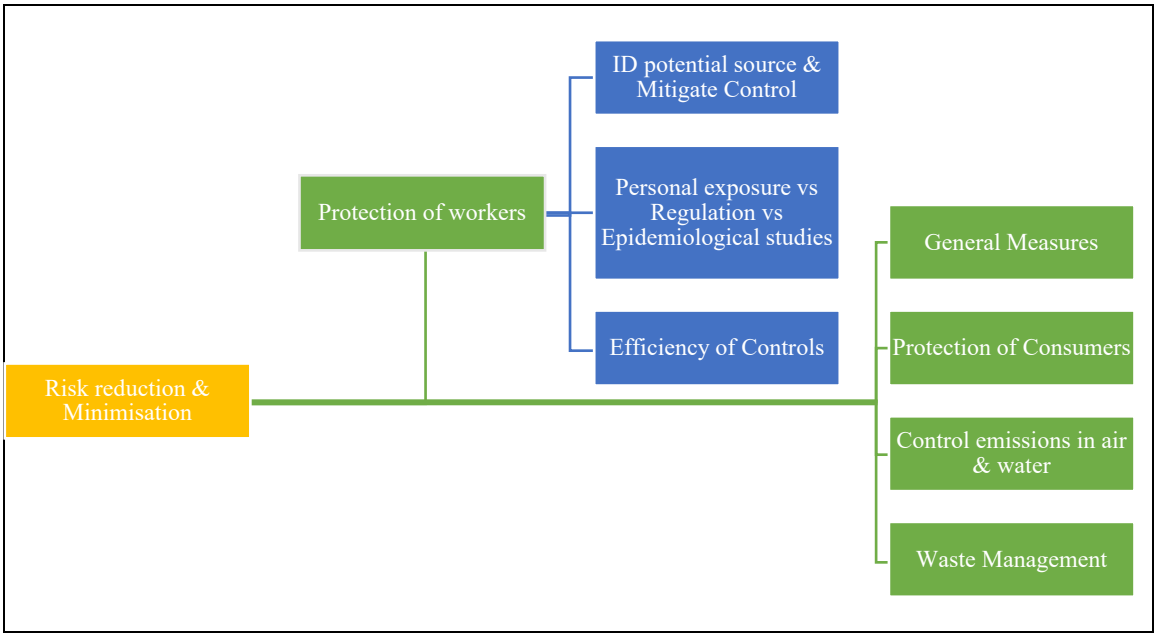

Figure 8. Risk Reduction (Adapted from ISO/TR 12885: 2008; Hassellov et al., 2008; Thomas et al., 2010; CRO Briefing, 2010; ISO/TR 13121:2011and OECD: GLP, Tolmachev, 2012)

It is anticipated that Figures 5-8 is consistent with the calls from various researchers to provide a standard protocol, that is aligned to research and standard protocols, when assessing the risk of nanoparticles that can be more rigourously replicated. It touched on the inclusion of regulatory requirements to ensure environmental and occupational care.

This paper touched on some of the oversight that is required to understand the responsibilities of research departments and manufacturers when dealing with the development of nano-enabled drugs.

An understanding of these stages will inform the critical discussions that need to be prioritized to militate practice at various stages of product development according to the probability and severity of the threat.

6. Conclusion

The nuances of each step and their integration has been proposed. It demonstrated a coordinated and structured approach to product development that included all key-role players, facilities, and considerations to tap into the immense benefits of nanotechnology for the progress of mankind. An alignment of practice to these figures could reduce rework and cycle-time, offer opportunities and understanding of automation to reduce and remove human interaction to improve safety, improve process capability and facilitate continuous improvement.

It is envisaged that this will provide the conformity, consistency and uniformity of practice that will be required for nano-enabled products to evolve to more reliable stages of manufacture and commercialization while able to withstand legal scrutiny.

Recommendations

From the preceding discourse it is reasonable to propose that a strong multidisciplinary team is required for future product engagement and development.

Moreover, governments globally have established scientific councils and agencies to facilitate niche area development arising from various nano-enabled projects to facilitate and support entrepreneurship and industries' in innovation to anticipate nanotechnologies full potential for socio-economic upliftment (National Planning Commission, 2015) and should thus be widely advertised and utilized.

Acknowledgments

We acknowledge the University of Valladolid and Prof L Nieto for the opportunity to conduct this research.

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