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Multidimensional regulatory approach in manufacturing, packaging and distribution – A key to prevent counterfeiting of medicines and medical devices

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ABSTRACT

The trade in pharmaceuticals is international in nature and counterfeiting of medicines and medical devices is major, organized, transnational crime and poses a significant public health risk. The presence of counterfeited pharmaceutical goods is more prevalent in countries with weak drug regulation control and enforcement. However, no single country in the world is immune to this problem. The countries drug regulatory authorities (DRAs) of different countries have a responsibility to vigorously combat this insidious criminal activity. Co-operation and information exchange between international DRAs is a vital component in the detection and prevention of these crimes, and in the protection of the public health. The WHO rapid regulatory alert system (RAS) is an excellent vehicle for combating the trade of counterfeit medicines.

Keywords: *Counterfeit Medicines, Regulatory Authorities, World Health Organization, Regulatory alert system.*

INTRODUCTION

A counterfeit medicine or medical device is a pharmaceutical product which is produced and sold with the intent to deceptively represent its origin, authenticity or effectiveness. A counterfeit drug may be one which does not contain active ingredients, contains an insufficient quantity of active ingredients, or contains entirely incorrect active ingredients (which may or may not be harmful), and which is typically sold with inaccurate, incorrect, or fake packaging. Counterfeit drugs are broadly defined as medicines that fall into these categories, fakes containing no active ingredient .(e.g., when a bag of lactose is sold as cocaine), different drug than prescribed, real drugs that are diluted with a diluents or spiked with a chemical enhancer, actual active ingredients differ from the purported active ingredients (e.g., when methamphetamine is sold as cocaine) [1].

World health organization (WHO) and its member states has efficiently defined the counterfeit drugs where the following definitions demonstrate that the nature of the problem of counterfeit drugs varies from country to country. In some countries the issue is more complex and there is no distinction between counterfeit and substandard drugs [2].

Available reports indicate that in developing countries a wide spectrum of types of counterfeit drugs, ranging from the precise copy of a genuine product to the extreme case of a drug product with none of the correct active ingredient exist. Consequently, counterfeit drug is defined broadly in order to cover drug products that have been copied or forged as well as certain substandard products, particularly those intentionally made to be substandard. The counterfeit pharmaceutical good and medical devices are defined as any drug product or medical device which is not what it purports to be, or any drug or drug product or medical device which is made to appear to be better or of greater therapeutic value than it really is, which is not labeled in the prescribed manner or which label or container or anything accompanying the drug and performance bears any statement, design which makes a false or misleading claim or any drug or drug product whose container is so made, formed or filled as to be misleading, or the drug product and medical device whose label and the user manual respectively does not bear adequate directions for use and such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health or unsafe dosage or methods or duration of use or any drug product which is not registered by the health agency in accordance with the provisions of the food, drugs and related products (registration, etc.) or the drug itself, or the container or labeling thereof or any part of such drug, container or labeling bearing without authorization the trademark, trade name, other identification mark, imprint or any likeness to that which is owned or registered in the bureau of patent, trademark, and technology transfer in the name of another natural or juridical person, a drug product refilled in containers by unauthorized persons if the legitimate labels or marks are used, an unregistered imported drug product, except drugs brought in the country for personal use as confirmed and justified by accompanying medical records [2, 3]. The United States federal food, drug and cosmetic act defines a counterfeit drug as, a drug which, or the containers or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor [4, 5].

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Factors Responsible for Counterfeiting Pharmaceutical Goods:

A variety of factors responsible by which medicines and medical devices attractive for counterfeiting are due to high value in relation to their bulk and the demand. Furthermore, for the counterfeiter, ingredient costs can be very low if cheap substitutes are used or if these are omitted altogether, as is often the case. Producing counterfeit drugs may not require building huge infrastructure or facilities. They can be produced in small cottage industries or in backyards or under the shade of a tree. There are also no overhead costs due to quality assurance or meeting good manufacturing practices (GMP) standards, since such standards are never implemented and gross margins are therefore very high [6-8].

A counterfeit drug has a better capacity to deceive, particularly if it is copied to make it look like the original product and if it comes from a supposedly legitimate source so that purchasers are unlikely to be suspicious. Moreover, the process by which patients get their drugs is different from that for other consumer goods that are doctors or health workers prescribe them. When patients choose their own drugs they may lack the specialized knowledge to detect whether the product they are buying is of good

quality let alone be able to detect whether the product is counterfeit [5, 9]. Other factors that encourage counterfeiting of medicines mentioned below are

Lack of political will and commitment: Drugs are unlike other consumer goods in that they are crucial to meeting the important objective of improving public health and so they should not be treated in the same way as other commodities. Their development, manufacture, import, subsequent handling within the distribution chain and use require specialized knowledge and skills. Consequently, they should conform to prescribed standards and their quality should be rigorously controlled. However, this would require strong government will and commitment to establish and operate a strong national drug regulatory authority [6, 10].

Lack of appropriate drug legislation: Legislation and regulations form the basis for drug regulation. Where legislation and regulations do not exist for proper control of medicines, the otherwise criminal activity of counterfeiting of medicines is not treated as a crime. Currently, only a few of the WHO member states have enacted special national legislation addressing the issue of counterfeit drugs. Moreover, sanctions imposed on counterfeiters are in most cases no deterrent. The absence of deterrent legislation encourages counterfeiters since there is no fear of being apprehended and prosecuted [6, 11].

Absence of or weak drug regulation: Drugs need to be safe, effective and of good quality in order to produce the desired effect. Ensuring these properties requires the creation of a competent national drug regulatory authority with the necessary human and other resources to control the manufacture, importation, distribution and sale of medicines. At present, out of the 191 WHO member states about 20% are known to have well developed drug regulation. Of the remaining member states, about 50% implement drug regulation at varying levels of development and operational capacity. The remaining 30% either have no drug regulation in place or a very limited capacity that hardly functions. Inadequate, ineffective or weak drug regulatory control could promote unregulated importation, manufacture and distribution of drugs, leading to the proliferation of counterfeit drugs in the national market [2, 3, 6].

Inadequate resources for drug regulation activities and absence of training of national drug regulatory authorities' personnel may also manifest itself as inefficiency and incompetence of national drug regulatory authorities. The consequence of this will be infiltration of counterfeit medicines into national distribution channels [12].

Weak enforcement and penal sanctions: Enacting deterrent anti-counterfeiting legislation alone will not solve the problem. It needs to be enforced, where existing laws are not enforced crime is perpetuated as criminals are not afraid of being arrested and prosecuted. Lenient punishments for offences tend to encourage criminal activities such as medicines counterfeiting, particularly when the penalties for counterfeiting non-medicinal products are more severe. Moreover, disregarding trademark rights may encourage large scale counterfeiting of drugs [9].

Corruption and conflict of interest: The efficiency of personnel is adversely affected by corruption and conflict of interest resulting in laws not being enforced and criminals not being arrested, prosecuted and convicted for their crimes. Governments need to develop strategies to reduce corruption. One approach could be to empower public interest and consumer groups to participate in drug regulation and to make regulatory authorities accountable and their decisions transparent [13].

Demand exceeding supply: In situations where demand for medicines exceeds supply, criminally minded people tend to profit out of crime by manufacturing and distributing counterfeit medicines as a substitute for genuine medicines. Also, consumers who use medicines inappropriately generate demand for such medicines, the sources of which may be counterfeit. For example, the misuse of creams containing steroids for skin bleaching and of body building medicines has generated a market for counterfeit steroid containing medicines. Often these medicines are distributed through unauthorized channels or illicit markets [14, 15].

High prices of medicines: When prices of medicines are high and price differentials between identical products exist there is a greater incentive to supply cheap counterfeit medicines. People engage in the trade of counterfeit medicines because the cost of manufacture of counterfeit medicines is minimal and the profits to be made are significant [13].

Inefficient cooperation between stakeholders: Intersectoral cooperation between regulatory authorities, police, and customs services and the judiciary is essential for effective control of the national drug market and enforcement of drug legislation. When such cooperation is ineffective, counterfeiters can escape detection, arrest, and penal sanctions. Equally, the cooperation of the pharmaceutical industry, wholesalers, and retailers to report to the national drug regulatory authority cases of counterfeit drugs is necessary in combating counterfeit drugs. Where such cooperation is lacking the national drug authority may not be able to take measures against counterfeiters hence counterfeit medicines tend to flourish [16, 17].

Lack of regulation by exporting countries and within free trade zones: Pharmaceuticals made for export are not regulated by many exporting countries to the same standard as those produced for domestic use. In addition, pharmaceuticals are sometimes exported through free trade zones where drug control is lax and where repackaging and re-labeling take place. This kind of trade arrangement can provide better opportunities for counterfeiters to introduce illicit material into the distribution chain even when the system is highly regulated [2, 18, 19].

Trade through several intermediaries: Trade in pharmaceuticals rarely takes place between the manufacturing country and the importing country. Currently, it takes place through one or more intermediate countries or trading houses. Activities in trading houses may sometimes involve repackaging and re-labeling which may be carried out without any controls under conditions that do not comply with good manufacturing practices' requirements [2, 19].

Impact of Counterfeiting on Human Health:

In most cases, counterfeit drugs are not equivalent in safety, efficacy and quality to their genuine counterparts. Even if they are of the correct quality or contain the correct amount of active substance, their production and distribution are not within the control of the drug regulatory authority of the country concerned. This means that any associated defects and adverse reactions will not be easily recognized or monitored and, if needed, an effective product recall would not be possible [19-21].

So far counterfeit drugs that have been discovered have rarely been efficacious. In many cases they have been found to be without active ingredients, or with wrong ingredients or with incorrect quantities of active ingredients. The use of such drugs can prolong treatment periods as patients may not respond as quickly as they should and exacerbate conditions being treated. Treatment with ineffective counterfeit drugs such as antibiotics can lead to the emergence of resistant organisms and may have a deleterious effect on a wide section of the population. In extreme cases, counterfeit drugs may even cause death [16, 20, 22].

As a consequence of such damaging effects, counterfeit drugs may erode public confidence in health care systems, health care professionals, the suppliers and sellers of genuine drugs, the pharmaceutical industry and national DRAs. Incorrect labeling as to the source can also be detrimental to the reputation and financial standing of the original and/or current manufacturer whose name has been fraudulently used [16, 20, 22-24].

There is no simple solution or remedy that can be applied to eliminate counterfeit medicines nor can the problem be solved by an individual company or government. The problem has reached a global dimension and needs a global approach.

Identification of Counterfeit Medicines and Medical Devices:

Counterfeit medicines can be identified through chemical analysis done in a laboratory. However, there are some signs which indicate counterfeiting of medicine and medical devices as they may have a strange smell, taste, or color, lacking strength, poor quality packaging or packages with misspelled labels, comparative less cost, insufficient operating instructions, updation and calibration procedure [25-28].

Rise of Counterfeit Drugs:

Counterfeiting of drugs arises both in developed and developing countries, however, the true extent of the problem is not really known since no global study has been carried out. The

appearance of counterfeit medicines in international commerce was first mentioned as a problem at the WHO Conference in 1985. Both government authorities and manufacturers have been concerned with efforts aimed at preventing the problem, and WHO has received reports related to counterfeit drugs from some of its member states on a voluntary basis. According to this information, the problem is known to involve both developed and developing countries [29].

Between January 1999 and October 2000 alone, 46 confidential reports relating to such drugs were received by WHO from 20 countries. About 60% of these reports came from developing countries whereas the remaining 40% were reported by developed countries. Although, the reports received have not been validated and may not be useful for quantitative purposes, the information clearly shows that the problem exists. The data also reflects that only a few countries are willing to provide information about cases detected. The drugs counterfeited included antibiotics, hormones, analgesics, steroids, and antihistamines. These drugs form almost 60% of the products reported. In terms of types of counterfeits and their magnitude, a significant percentage of counterfeit products can be grouped into six categories, (a) 32.1% of products without active ingredients, (b) 20.2% with incorrect quantities of active ingredients, (c) 21.4% with wrong ingredients, (d) 15.6% with correct quantities of active ingredients but with fake packaging, (e) 1.0% are copies of an original product, and (f) 8.5% with high levels of impurities and contaminants [18, 22].

Approach to Prevent Counterfeiting Pharmaceutical Goods:

At a national level, each country should develop appropriate medicines policy options, legislation, and enforcement strategies in view of its own situation and availability of institutional framework, professional and financial resources. The policies should aim at involving the Government, its agencies, the pharmaceutical industry, drug importers and distributors, the pharmaceutical profession, governmental organizations, public interest groups and consumer groups, in efforts to prevent the supply of counterfeit medicines. Measures are often effective when carried out by all concerned working together [30].

More specifically, governments of each country should show political will/commitment for evolving and implementing programs for combating counterfeit medicines. Political will and commitment should be demonstrated by enacting new drug laws or updating existing drug laws for prohibiting counterfeit medicines, establishing institutions for the regulation of medicines and clearly setting out in the drug laws, the power, duties and responsibilities of the institution(s), training of personnel, including enforcement officers, for national drug control, making available necessary financial and other resources, ensuring that the drug laws are enforced, and fostering international cooperation in the control of pharmaceuticals and entering into bilateral and multilateral agreements with other governments and with international organizations such as WHO, interpol and the world customs organization (WCO) [23].

The judicial procedures and policies should reflect the seriousness of the problem and the offence. Courts should speedily dispose of cases involving counterfeit medicines and impose appropriately severe penalties on convicted offenders. In addition, courts should order the confiscation/forfeiture and destruction of counterfeit medicines [24].

Combating counterfeiting of medicines is a shared responsibility to which all interested parties have to contribute. Non-governmental organizations or community based organizations such as consumer associations should be informed about the problem of counterfeiting and the possible presence of counterfeit drugs in the national distribution chain. They should be provided with information and methods for detection so that they are able to report cases to the national drug regulatory agencies [23].

The general public should be encouraged to become involved in the fight against drug counterfeiting. Education and information campaigns directed at the general public should be established and the public should be advised to buy medicines from legitimate sources rather than from peddlers and hawkers or from market places and streets. Consumers should also be encouraged and advised to report to their prescribers or physicians any lack of improvement in their health status in spite of the treatment or any adverse reactions experienced [25, 31].

More privatization and liberalization of the world economy, more extensive opening of borders to trade and increased promotion and sale of drugs through the internet are going to lead to increased circulation of counterfeit drugs in national and international markets. This means greater cooperation between countries at subregional, regional and international levels will be needed to combat counterfeit drugs in the future. Cooperation should include developing common strategies, timely exchange of information and harmonization of measures to prevent the spread of counterfeit drugs. Cooperation would improve if all countries adopt a common definition of counterfeit drugs. At a global level, a more effective response to the threat of counterfeit drugs could be the development of an international convention to control trade in counterfeit and substandard drugs [25, 31].

Utilization of technological advancement to prevent counterfeiting:

Technology plays a pivotal role in preventing counterfeiting of medicines and medical devices, the RAS serves as a quick warning mechanism and facilitates the exchange of information among different countries and areas in an efficient manner through certain measures to strengthen legislation, regulatory oversight, improve collaboration among governmental entities to work together to combat counterfeiters effectively, to develop a communication strategy, implementation of new technologies, to ensure effective reporting of counterfeit drugs to the agency, adoption of secured business practices, to develop strategies to deter and detect counterfeit drugs globally, education of consumers and health professionals about the risks of counterfeit drugs and how to protect against these risks [25, 26].

RAS is effective in introducing and implementing the latest techniques involved in tracing and combating counterfeiting of medicines and can be shared between developed and developing countries. There are several technologies that may prove helpful in combating this problem are RFID (Radio frequency identification), mass serialization, e-pedigree method, raman spectroscopy, energy dispersive x-ray diffraction (EDXRD) and x-ray diffraction (XRD). Comparison of the diffraction pattern obtained from the original against the counterfeit, Surface Analysis of products, Cold chain management for proper transportation of sensitive pharmaceutical materials, antidiversion, unit of use packaging, tamper evident packaging, **a**uthentication technologies for pharmaceuticals, and nuclear magnetic resonance (NMR) Screening [32]. The pictorial respresentation of techniques strictly required to prevent the counterfeiting of medicines and medical devices is addressed in Figure-1.

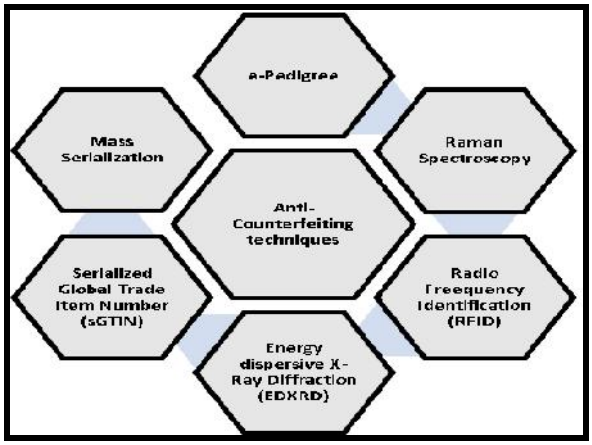

Fig. 1: The techniques proved to be efficient in preventing the counterfeiting of medicines and medical devices. E-Pedigree, Raman spectroscopy, RFID, EDXRD, sGTIN and mass serialization techniques must be globally implemented to the registered manufacturing, packaging and storage facilities of pharmaceutical goods

Thus, an approach proposed to prevent counterfeiting of medicines and medical devices is triangle approach which is based on three key parameters that are (1) strict regulation to distribute medicines and medical devices, (2) Implementation of strict legislation and requirements of novel techniques in manufacturing and packaging pharmaceutical goods with unique identification markings and (3) to initiate and publicize the awareness program to assess the medical goods to judge the authenticity of medicine and medical device [2, 6]. Pictorial presentation of this triangle approach to prevent counterfeiting is addressed in Figure-2.

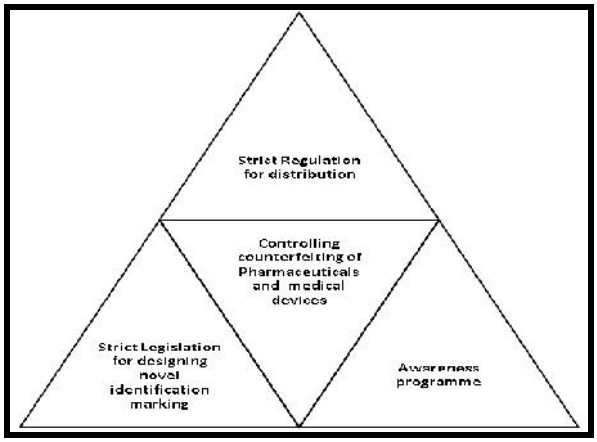

Fig. 2: A triangle approach to prevent counterfeiting of medicines and medical devices are based on three key parameters which needs to be reworked logically that are, regulation of distribution of pharmaceutical goods, legislation to implement novel identification markings to prevent fraudulence and to publicize the awareness program to assess the authenticity of medicines and medical devices [32].

At present counterfeiters are able to copy most of the techniques used in anti-counterfeiting of medicines and medical devices. Pharmaceutical segment is one of the major sector where counterfeiting is a significant problem. However, recent developments in nanotechnology have proved potential improvement in the field of anti-counterfeiting but its implementation requires the development of new policies.

Nanotechnology strengthens the barrier against counterfeiting:

Nanotechnology based development of non-reproducible features offer a significant move forward in preventing duplicity of intellectual properties and products. The implementation of these novel techniques will significantly improve the health, safety and quality of human life [33].

Holograms, tamper-evident closures, tags and markings and RFID labels are the most common anti-counterfeiting techniques but the limitation of these methods can be copied. Exploring the intrinsic nature of nanomaterials make items complex and unique which are utilizing in the development of new approach to prevent counterfeiting and to improve the existing techniques such as holography, laser surface identification, nano barcodes, quantum dots tags and nanocomposite tags [33].

Holograms: Holography, primarily show the manufacturers logo as an identification mark but can be easily copied. Addition of two-dimentional nanoscale gratings, photopolymers and luminescent nanoparticles can provide and additional security for holograms [34].

A Security Identification Code (SIC) is etched physically through the body of the nickel tag. The same SIC is repeated through the thousands of NanoTags contained in each personalised set or batch of NanoTag products, mixed with special proprietary adhesives or embedded into the body of plastics. Once the mixture of tags and adhesive/plastic becomes dry and solid, the NanoTags become fully resistant to water, most chemicals and environments. NanoTags are extremely robust, chemically resistant, able to withstand temperatures of over 1,000^{0}C without oxidising and with a melting point of 1,453^{0}C [34] (Figure-3).

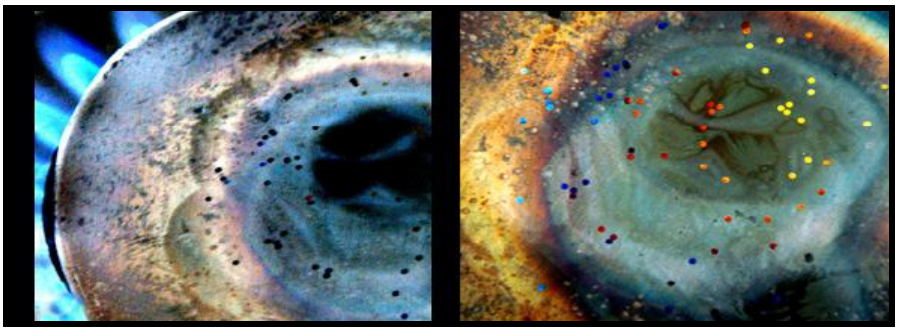

Fig. 3: Test of NanoTags heated up to 1,000^{0}C. Note the adhesive gradually burns out but the tags remain clean – adhered to the surface and retaining all information [34, 35].

Laser surface identification: A laser is used to examine the roughness of an object surface. The unique and complex features of surface roughness code can be identified by laser identification technique. The advantage of this technique is that the surface roughness at nanoscale cannot be replicated. Therefore, a high level of security can be attained to pharmaceutical products compared to holograms and watermarks [35, 36].

Nanobarcodes: The three dimensional polymer patterns on the order of tens of nanometres can be made on silicon substrates to provide 3D nanoscale data encryption key, similar to barcodes. The advantages over conventional barcode/marking are difficulty of detecting presence (covert marking) and duplication [35, 37].

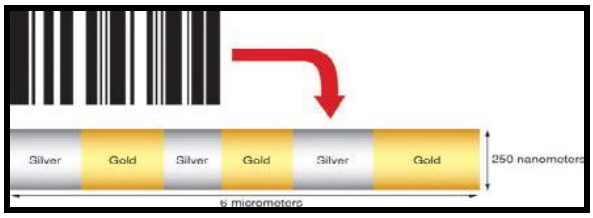

Fig. 4: Utilization of a nano barcode technique to enhance the protection of medicines and medical devices against counterfeiting [34].

Quantum dots tags: The metal nanoparticles produces unique electromagnetic spectra, also known as surface enhanced Raman scattering) while the semiconductor nanoparticles known as quantum dots which have different fluorescence based on size and chemical composition. Both can be exploited as an identification tool as it is difficult to reproduce due to its infinite combinations, covert security feature, non-toxicity and multifunctionality [33, 38].

Nanocomposite tags: It consist of a materials-based pattern (with magnetic and/or optical features) that forms part of a label, tag or embedded portion of an item. The nanometre sized magnetic and optical features are generated randomly during manufacturing, constituting a unique fingerprint that is read and stored in a central database. The result is a secure identity for an individual item that is prohibitively expensive and difficult to copy. Incorporating encapsulated and functionalized (e.g. thermochromic) nanoparticles in labels is another promising solution based on the use of nanocomposites [33].

The adoption of improved anti-counterfeiting techniques, would result in a dramatic reduction in financial costs associated, with purchase and use of counterfeited goods, fewer job losses due to unfair competition caused by counterfeiting, a significant rise in customer goodwill and confidence in products and services, a reduction in tax revenue losses to government, reduced costs to protect and enforce intellectual property rights [33]. The importance of implementing nanotechnology based methods to

prevent counterfeiting depends on the stage of the product where probability of copying is more. Stage of product life prone to counterfeiting needs potential implementation of anti-counterfeiting nanotech methods. Based on the requirement of nanotechnology to prevent counterfeiting, the technology readiness levels (TRL) were designed as mentioned in Figure-5.

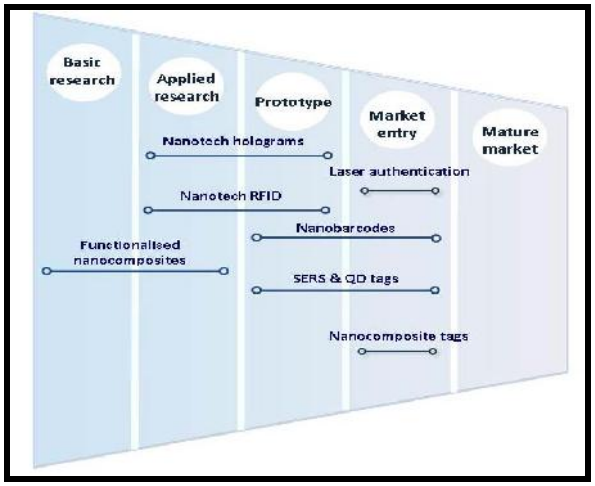

Fig. 5: TRL for a number of nanotechnology based methods as an anti-counterfeiting applications at different levels of pharmaceutical product life [33].

Challenges in implementing novel anti-counterfeiting techniques: As with any other technological development, anti-counterfeiting methods utilizing nanotechnologies should be developed in a responsible, sustainable way, and efforts are needed to let those in developing countries share the benefits. A number of international organizations have been established to work with government officials and industry groups across the globe to educate the public on the danger of counterfeit and measures to combat it. The database of seizure reports enabling everyone to see the details of recent anti-counterfeiting operations. It is potentially recommended that more actions should be undertaken to raise public awareness of the risks of illegal goods and counterfeits, and the availability of advanced anti-counterfeiting technologies [33].

CONCLUSION

Short term strategies are now designed to strengthening international cooperation in law enforcement efforts, identifying counterfeit products, using anti-counterfeiting technologies, and educating stakeholders and consumers. Global standards for packaging of pharmaceuticals and the use of anti-counterfeiting technologies are under process. Counterfeit drugs are a global challenge to all nations, and criminal counterfeiting operations are increasingly operating across national borders. FDA intends to work with the WHO, Interpol, and other international public health and law enforcement organizations to develop and implement worldwide strategies to combat counterfeit drugs. A long term strategies for next three years and beyond will be available to use e-Pedigree, adoption of model rules for state licensure and widespread international collaboration [39-41].

The WHO has developed guidelines for the development of measures to combat counterfeit drugs." These guidelines provide advice on measures that should be taken by the various stakeholders and interested parties to combat counterfeiting of medicines and medical devices which recommend important measures to follow at national and international levels [42, 43].

At national level governments must improve the availability and affordability of medicines, enact deterrent legislation prohibiting the manufacture, importation, exportation, distribution and sale of counterfeit medicines, establish or strengthen national medicines regulatory authority (NMRA) by clearly setting out its power, duties and responsibilities, provide the necessary human, financial and other resources to the NMRA, train NMRA personnel, including enforcement officers in the detection and investigation of counterfeit drugs, foster cooperation between NMRA and other national law enforcement agencies such as police, customs, and the judiciary, ensure that personnel working in national medicine regulation and those involved in the detection and investigation of counterfeit medicines sign conflict of interest forms, ensure that the medicine legislation is enforced, ensure that courts speedily dispose of cases involving counterfeit medicines and that sentences passed by the judiciary reflect the seriousness of the problem and the offence, ensure that counterfeit medicines are confiscated and destroyed [2, 3, 13, 14, 44, 45].

The NMRAs must ensure that all medicine manufacturing, importation, exportation and distribution activities are carried out in premises approved by the NMRA, and that individuals and companies engaged have licence to operate such activities, inspect medicine establishments regularly to ensure that they comply with national medicine regulatory requirements, ensure that all medicines are assessed and authorized before they are introduced to the market, define the ports of entry for medicines and starting materials used for the manufacture of pharmaceutical products, control importation of finished pharmaceutical products and starting materials by issuing import permits and inspecting consignments at points of entry as necessary, inspect the informal market to prevent any illegal trade in medicines, monitor the quality of medicines on the market to detect and prevent any substandard and counterfeit medicines from reaching the public, work closely with national law enforcement agencies such as the policy and custom officers, inform the public about the problem of counterfeit medicines and educate and advise them to buy medicines from NMRA authorized sources rather than from peddlers and hawkers or from market places and streets, encourage and advise consumers to report to their prescribers or physicians any lack of improvement in their health status in spite of the treatment or any adverse reactions experienced, foster bilateral and multilateral agreements with other countries, in particular with countries sharing common borders to prevent cross border trade and smuggling, seek international cooperation with organizations such as WHO, Interpol, the WCO [3, 20, 31, 46].

At personal level, the consumers should buy medicines only from licensed pharmacies and medicine outlets,be suspicious of heavily discounted medicines, do not buy from peddlers or market places, insist to get receipts when buying medicines, check packaging carefully if it is properly sealed, check if the packaging indicates the batch number, manufacturing date, expiry date, and the manufacturer's name, report to your health worker or doctors any lack of improvement after taking a medicine.

At international level, counterfeiting of medicines is now a global issue affecting all countries. Therefore in order to combat the problem effectively, there should timely exchange of information on counterfeit medicines between, medicine regulatory authorities, pharmaceutical manufacturers, national law enforcement officers, international organizations such WHO, Interpol, WCO, there should be more cooperation between all interested parties to develop harmonized measures to prevent the spread of counterfeit medicines globally, cooperation would improve if all countries adopt a common definition of counterfeit medicines, a global mechanism similar to the one used to control narcotic drugs should be created to control trade in counterfeit medicines. Counterfeit drugs not only affect the sick and innocent consumers but also the general public and deserve more attention [15, 16, 47].

Assessing national medicines regulatory systems, NMRAs are responsible for the regulation and control of medical products such as medicines, vaccines, blood products and medical devices. They contribute to promoting and protecting public health by ensuring that medicines are of the required quality, safety and efficacy, health professionals and patients have the necessary information to enable them to use medicines rationally, medicines are appropriately manufactured, stored, distributed and dispensed, illegal manufacturing and trade are detected and adequately sanctioned, promotion and adverting is fair, balanced and aimed at rational drug use, fair access to drugs as well as medical devices is not hindered by unjustified regulatory work [12, 17, 48].

Intensification of international commerce and increasing technological complexity of manufacturing and product specifications have created additional challenges for national regulatory authorities and manufacturers, particularly to those of developing countries. This requires that national regulatory capacity is regularly assessed, areas of weakness are identified and appropriate, necessary measures are taken. Assessments are conducted using a standardized WHO data collection tool for the review of drug regulatory Systems [3, 46, 49].

Review an existing legal framework, regulations and control activities with regard to medicinal products and medical devices in order to assess the national regulatory capacity against a

set of predefined parameters aim at strengthening national regulatory and control capacity through an assessment of the situation. In addition, identification of specific needs, areas and activities for WHO's and other international regulatory authorities technical input are essential and the provision of appropriate technical support and training is an efficient approach to control the counterfeiting of medicines and medical devices globally [6, 11, 50].

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