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## Microbiological quality of pharmaceutical products in Bangladesh: current research perspective

Rashed Noor\*, Nagma Zerin, Kamal Kanta Das

Department of Microbiology, Stamford University Bangladesh, 51 Siddeswari Road, Dhaka 1217, Bangladesh

## PEER REVIEW

## Peer reviewer

Dr. Sabina Mahmood, Cell Therapist,  
Okayama City, Japan.

Tel/Fax: +81-86-2444150

E-mail: [sabinazaheed@gmail.com](mailto:sabinazaheed@gmail.com)

## Comments

Quality assurance in any product particularly consumed by human beings such as medicinal products need to be attended to with great importance. In order to improve the quality of medicinal products it is first necessary to know the background information that gives a clear picture of the overall situation. I think this paper has met such standards where substantial knowledge is neatly presented and conveyed.

Details on Page 268

## ABSTRACT

Pharmaceutical industrialization in Bangladesh, both by multinational and local companies, has increased significantly in the last two decades. Most of the pharmaceutical products are found to be therapeutically competent to meet the demands of general population satisfactorily. However, complaints regarding the compromised quality of the products stored in markets are also reported very often. In order to ensure the overall drug user safety, the present review discussed the prime requirements for maintaining the desired microbiological quality of the commonly used pharmaceutical products in Bangladesh. Information relating to the prevalence of bacteria, fungi and the specific pathogens has been collected mostly from the recent researches conducted on an array of finished pharmaceutical medicaments. All data, achieved by means of traditional microbiological and biochemical analyses as described in the published papers cited in this review, have been further critically analyzed in context to the recommended microbial limits, user safety and the legislative aspects. Microbial contamination usually degrades the product quality as well as the product stability, which in turn creates treatment complications. Moreover, through microbial spoilage within the medicament, active drug constituents may be transformed to less potent or chemically inactive forms. Contamination by bacteria and fungi generally occur either from raw materials, manufacturing environment or at the storage stage which may hinder the consumer safety. This review article presented some valid evidences for microbial contamination in the pharmaceutical finished products in Bangladesh and discusses about possible remedies to improve the overall management of public health.

## KEYWORDS

Pharmaceutical microbiology, Product quality, Consumer safety, Public health

## 1. Introduction

The total quality management (TQM) of pharmaceutical products is known to start with the design of the production plant as per the criteria principally set by the good manufacturing practice (GMP) and the food and drug administration (FDA), which ends with the

final microbiological quality of the finished products meeting the specification criteria recommended by the associated regulatory bodies; *i.e.*, the European Pharmacopoeia (EP), the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP) [1-6]. The pharmaceutical quality management approach has been refined into the concept of hazard analysis of critical control points

\*Corresponding author: Rashed Noor, Ph.D., Post Doc. (Molecular Biology), Associate Professor & Chairman, Department of Microbiology, Stamford University Bangladesh, 51 Siddeswari Road, Dhaka-1217, Bangladesh.

Tel: +880 2 8355626, ext. 472

Fax: +880 2 9143531

E-mail: [noor.rashed@yahoo.com](mailto:noor.rashed@yahoo.com)

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(HACCP), which aims to improve the microbiological safety of the finished pharmaceutical products by developing rapid methods for the detection of contaminating microorganisms[1,7-9]. The *in vitro* studies revealed that a variety of microorganisms can metabolize a wide range of drugs as their substrates, which in turn result in the loss of the drug potency[1].

Pharmaceutical industry is considered to be one of the most developed sectors of Bangladesh after the garment industry, which contributes significantly to the progress of the country's economy. After the promulgation of Drug Control Ordinance-1982, the development of pharmaceuticals industry accelerated[10]. Especially in the last two decades the pharmaceutical industry in Bangladesh has expanded rapidly[10,11]. Currently around 230 pharmaceutical companies are operating in Bangladesh with the approximate total market size of BDT 76500 million per year[12]. Only 3% of the drugs are imported and the remaining 97% are produced in the local manufacturing sites[13-16]. It is indeed a great success that Bangladesh is capable of meeting most of the demands of its pharmaceutical products domestically. However, complaints regarding these products occur frequently which has not been reported publicly. Moreover, being a developing country with poor economy, majority of the people in Bangladesh cannot always afford appropriate medical treatment when disease complications arise[17-21]. The onset of an array of diseases is also very much frequent on account of highly dense population, malnutrition, insufficient treatment of industrial effluents, lack of awareness on personal hygiene, relatively lower number of health professionals, defective medication strategies, and above all, due to the emerging problems of ineffectiveness of a number of drugs[22-26].

While it is certain that the pharmaceutical companies are maintaining the records of manufacturing and distribution as well as the compliance departments to facilitate recalling any batch of the product from sale or supply stream in case of loss of quality, however, the sustainability of the quality of medicines is publicly obscure. Several small scale laboratory based research evidently revealed microbial contamination in various pharmaceutical finished products[24-30]. Degraded quality of pharmaceutical products can cause various infections and in drastic cases can seriously harm internal organs. This can result in severe consumer dissatisfaction, which can ultimately lead to undesirable financial loss in the pharmaceutical sector. To draw national attention to this gradually worsening situation and to generate concern in all levels of the society, this review discussed the basic requirements for achieving the desired quality of a pharmaceutical product as well as the quality status of commonly used pharmaceutical products in Bangladesh. Challenges faced by the pharmaceutical industries have also been included to aid in the rationale of the discussion and some feasible recommendations have been provided to address the mentioned issues.

## 2. Microorganisms gaining access into the pharmaceutical products

Even though all the stages of pharmaceutical product manufacturing are governed by the code of the regulatory

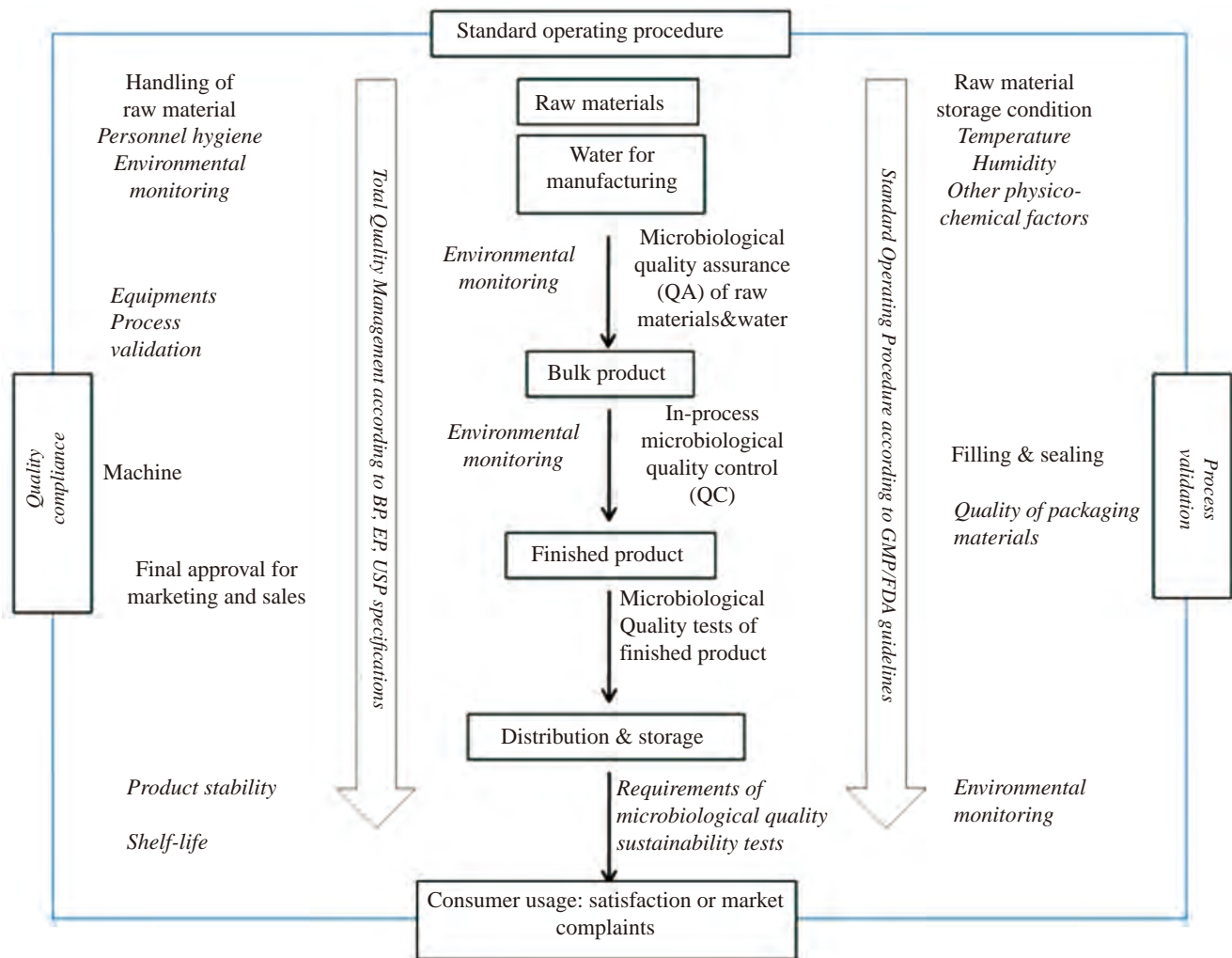
bodies; microbial access into the production stream with a final dissemination into the markets is not unlikely[1,4-7,31-35]. From the health point of view, common hazardous microorganisms in the pharmaceutical products and premises may include *Escherichia coli* (*E. coli*), *Salmonella* spp., *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*), *Burkholderia* spp., *Alcaligenes* spp., *Flavobacterium* spp., *Chromobacter* spp., *Serratia* spp., *Bacillus subtilis*, *Bacillus megaterium*, *Enterobacter aerogenes* and *Enterobacter cloacae*, *Proteus* spp., *Streptococcus faecalis*, *Clostridium* spp. and the opportunistic bacterial pathogens[1,34-37]. Such contaminant microorganism possess the trait of adapting with least nutritional requirements and are capable of multiplying within both bulk and finished products[38].

The contaminants may evolve from the raw materials, manufacturing machines, production atmosphere, from the persons conducting the process or from the container into which it is finally filled and sealed[1]. Poor-quality raw materials not only deteriorate the quality and shelf-life of the final product but also may impart to the overall microbiological contamination within the manufacturing plant[1,39]. Environmental parameters including temperature, relative humidity, differential air pressures, air turbulence and the status of high efficiency particulate air filters may also have a significant impact on the microbial access into the pharmaceutical products and premises[40,41]. Additionally, the inappropriate maintenance of hygiene during manufacturing, packaging, distribution and storage has also been reported to result in drug deterioration[1-4,42-44].

The acceptance criteria of pharmaceuticals should be strictly maintained according to the recommended specifications given by the BP, USP or EP. For instance, the total aerobic microbial count (TAMC) should be under  $10^3$  CFU/g and the total yeast mold count (TYMC) should not exceed  $10^2$  CFU/g within the finished products of oral non-aqueous preparations[45]. Likewise, the finished products of the oral aqueous preparation should not go over the limit of  $10^2$  CFU/mL for TAMC and 10 CFU/mL for TYMC. *E. coli* must be absent from both categories of oral preparations. For the preparations that are used through rectal route, the TAMC should not be more than  $10^3$  CFU/mL and for TYMC, it should not be more than  $10^2$  CFU/mL[34,35,45]. In case of some special oral preparations consisting of raw materials of natural origins, the acceptable microbial limit has been recommended to be  $10^4$  CFU/mL in case of TAMC and  $10^2$  CFU/mL for TYMC, and the products should be free from *Salmonella* spp., *E. coli*, *S. aureus*[45]. The microbial limit of herbal medicines might be up to  $10^5$  CFU/mL for TAMC and  $10^4$  CFU/mL for TYMC, and should not harbor *E. coli* (not more than  $10^2$  CFU/mL) or *Salmonella* spp.[46]. The microbial limit of  $10^2$  CFU/mL for TAMC and 10 CFU/mL for TYMC is commonly accepted for all non-sterile preparations with the complete absence of *S. aureus* and *P. aeruginosa*[45].

## 3. Quality assurance (QA) and microbiological quality control (QC) of pharmaceutical products

QA is known to encompass a system of management which consists of the entire procedures essential to ensure that a pharmaceutical product conforms consistently to a specified description of the recommended quality (Figure 1). Thus QA



**Figure 1:** Pharmaceutical quality control lay out.

The figure projected the total maintenance scheme of the microbiological quality standards of pharmaceutical products. To maintain this quality standards product formation should be observed from the early stage of raw materials processing to product packaging and marketing. Proper handling and the stringent maintenance of product specification as per BP, USP or EP guidelines may reduce the possibility to microbial contamination.

includes formulation design, research and development (R&D), GMP, QC and handling the market complaints[1,47,48]. The quality control of pharmaceutical products includes the estimation of microbiological burden in the production environment, machines, personnel, bulk materials, in-process checks, assessment of specific pathogens in the finished products before releasing to the market[40,42,49]. During production, the quality evaluation of the raw materials and water used in manufacturing is the first step of microbiological control (Figure 1). The in-process monitoring of a pharmaceutical product indicates whether the product quality has been maintained up to the recommended specifications during manufacturing and processing [4,34,35,45]. The finished product tests, based on microbiological, biochemical, serological and molecular techniques, demonstrate whether the release specifications have been met appropriately[5,6,50,51].

#### 4. Emergence of the drug-resistant bacteria: a challenge for the pharmaceutical industry

Industrial manufacturing of most antibiotics is mainly based on the large scale production of microorganisms which afterward convert

raw materials into antibiotics, the process is commonly referred to as fermentation which then undergoes the associated downstream cascades for the recovery of antibiotics[1,52]. Antibiotics have long been used as effective chemotherapeutic agents. However, in the last couple of years several of these drugs have been noticed to be less effective clinically as the pathogenic bacteria are gradually becoming resistant against them[17,24,53-61]. Such a situation has been one of the most drastic public health issues around the world, raising the possibility of leading to mass death from simple infections and treatment mediated complications. Along with a number of bacteria found to be resistant against commonly used antibiotics, the methicillin-resistant *S. aureus*, vancomycin-resistant *S. aureus*, coagulase-negative staphylococci, glycopeptides intermediate sensitive *S. aureus*, vancomycin-resistant *Enterococcus* species and penicillin-resistant *Streptococcus pneumoniae*, extended-spectrum  $\beta$ -lactamase producing bacteria and carbapenem-resistant bacteria are highly prominent[18,55-59]. Multidrug-resistant *P. aeruginosa*, *Stenotrophomonas maltophilia* and *Acinetobacter baumannii*, the acid-fast bacilli *Mycobacterium tuberculosis* and *Mycobacterium avium* complex have long been known to pose major health threats worldwide[1,19-20,55].

**Table 1**

Prevalence of pathogenic microorganisms in different local pharmaceutical finished products.

Sample categories	Samples studied in laboratory	Total viable bacteria (TVB) (CFU/g)	Total fungal load (CFU/g)	Fecal coliform (CFU/g)	<i>E. coli</i>	<i>Bacillus</i> spp.	<i>Klebsiella</i> spp.	<i>Salmonella</i> & <i>Shigella</i> spp.	<i>Pseudomonas</i> spp.	<i>Staphylococcus</i> spp.
1	Antacid suspensions[24] (8)	10 <sup>5</sup> (8)	10 <sup>4</sup> (7) 10 <sup>5</sup> (1)	Not done	Absent (8)	Not done	Absent (8)	Absent (8)	Absent (8)	Present (8)
2	Pediatric drops [26] (20)	10 <sup>3</sup> (7) 10 <sup>4</sup> (12) 10 <sup>5</sup> (1)	Absent (19) 10 <sup>1</sup> (1)	Not done	Absent (19) Present (1)	Not done	Absent (14) Present (6)	Not done	Absent (16) Present (4)	Absent (9) Present (11)
3	Eye&ear ointment[27] (15)	10 <sup>1</sup> (1) 10 <sup>2</sup> (11) 10 <sup>4</sup> (3)	Absent (5) 10 <sup>1</sup> (4) 10 <sup>2</sup> (6)	Absent (15)	Present (2) Absent (13)	Present (8) Absent (7)	Present (5) Absent (10)	Absent (15)	Present (5) Absent (10)	Present (11) Absent (4)
4	Skin ointment[28] (15)	10 <sup>2</sup> (3) 10 <sup>3</sup> (6) 10 <sup>4</sup> (1) 10 <sup>5</sup> (5)	Absent (1) 10 <sup>1</sup> (12) 10 <sup>2</sup> (2)	Absent (15)	Present (1) Absent (14)	Not done	Present (10) Absent (5)	Not done	Present (9) Absent (6)	Present (12) Absent (3)
5	Skin creams[28] (15)	10 <sup>2</sup> (10) 10 <sup>3</sup> (3) 10 <sup>4</sup> (2)	10 <sup>1</sup> (15)	Absent (15)	Present (1) Absent (14)	Not done	Present (4) Absent (11)	Not done	Present (7) Absent (8)	Present (7) Absent (8)
6	Oral syrups[29] (26)	Absent (1) 10 <sup>1</sup> (15) 10 <sup>2</sup> (4) 10 <sup>3</sup> (6)	Absent (2) 10 <sup>1</sup> (17) 10 <sup>2</sup> (5) 10 <sup>3</sup> (2)	Not done	Absent (26)	Present (6) Absent (20)	Not done	Not done	Absent (26)	Present (24) Absent (2)
7	Oral suspensions[29] (14)	10 <sup>1</sup> (1) 10 <sup>2</sup> (13)	10 <sup>1</sup> (7) 10 <sup>2</sup> (6) 10 <sup>3</sup> (1)	Not done	Absent (14)	Present (4) Absent (10)	Not done	Not done	Absent (14)	Present (11) Absent (3)
8	Cosmetics samples[30] (20)	10 <sup>3</sup> (8) 10 <sup>4</sup> (5) 10 <sup>5</sup> (7)	Absent (2) 10 <sup>1</sup> (2) 10 <sup>2</sup> (15) 10 <sup>3</sup> (1)	Not done	Absent (20)	Present (11) Absent (9)	Present (13) Absent (7)	Not done	Present (14) Absent (6)	Present (19) Absent (1)

BP or USP Limit: Total viable bacteria <10<sup>2</sup> CFU/g; Total fungal load <10<sup>1</sup> CFU/g; Absence of specific pathogenic bacteria. Numbers of samples have been indicated in parentheses.

Bacterial resistance against the common antimicrobial agents can occur due to their chromosomal defects, natural mutation, plasmid or transposon exchange of plasmids carrying drug-resistance genes, and even due to the horizontal transfer of the genes translating into the drug-resistance traits[56]. As observed especially in the developing countries with less educated community as in Bangladesh, the inappropriate self-medication, random and excessive consumption of non-prescribed antibiotics, indiscriminate use of antibiotics in feeding of livestock are the major factors contributing to the heightening bacterial resistance[56,60,61].

#### 4.1. R&D commencement and the associated prospect of pharmaceutical industries in Bangladesh

In order to combat the health problem due to the emergence of drug-resistance bacteria, new molecules of drugs need to be generated through the commencement of appropriate R&D strategies. Currently the pharmaceutical industries around the world are focusing on designing and developing new drugs and targeted drug delivery systems for better treatment of existing and newly emerging diseases[62,63]. In the United States, the biopharmaceutical research companies invested approximately 48.5 billion USD in new R&D and the FDA approved 44 new medicines in 2012[64]. In Bangladesh the R&D stage of pharmaceutical industry is in its infancy. However, research performed by some of the top pharmaceutical companies in Bangladesh is of significance. For instance, one of the leading local pharmaceutical companies in Bangladesh is presently working on vaccine development[65]. This is also to be mentioned that Bangladesh is exporting a range of pharmaceutical products to other

countries like Vietnam, Singapore, Myanmar, Bhutan, Nepal, Sri Lanka, Pakistan, Yemen, Oman, Thailand, and some countries of Central Asia and Africa. The country is also expanding its market in the European countries as well[10]. The export in 2003 was approximately 17 million USD, which increased to 30 million USD by the year 2009 (Figure 2). It is highly expected by various industry analysts and experts that this rising trend will continue in the upcoming years as well.



**Figure 2.** Trend of export of pharmaceutical products in Bangladesh.

The trend of export of pharmaceutical products (in Million USD) in Bangladesh has been observed to increase with time. The quantity of export items was around 17 million USD in the year of 2003 but this increased to 30 million USD within six years[10].

#### 4.2. Current state of quality of pharmaceutical products in Bangladesh: in vitro analysis

Unsatisfactory microbial presence has been detected in oral liquid drugs, creams and ointments acquired from the local stores of

Dhaka in Bangladesh (Table 1). For example, Antacid liquid drugs were determined to be highly contaminated with *Staphylococcus* spp.[24]. *S. aureus* was also identified in both cough syrup and multivitamin syrup[25]. Pediatric oral liquid drugs were contaminated with *Staphylococcus* spp., *Klebsiella* spp., *Pseudomonas* spp. and *E. coli*[26]. The eye and ear ointments were found to be contaminated by the bacterial pathogens including *Staphylococcus* spp., *Bacillus* spp., *E. coli* and *Klebsiella* spp.[27]. Topical products (creams and ointments) were found to be contaminated with the bacterial load exceeding the USP and BP limit ( $<10^2$  CFU/g) in 50% cases. Prevalence of *Staphylococcus* spp. and *Pseudomonas* spp. was noticed within these samples[28]. All oral syrup and suspension samples were contaminated with bacteria and fungi, where 23.7% of syrup and 92.8% of suspension samples were exceeded the USP or BP microbial limit[29]. Besides, the cosmetic samples studied were also found to be populated with an array of bacteria and fungi[30]. As discussed in some aspects earlier, the origin or sources of such microbial contamination in the finished samples studied might be due to the uncontrolled microbial and particle rich manufacturing premise, insufficient in-process quality control within the bulk products, lack of aseptic handling during filling and sealing or even in the packaging belt, and finally due to the inappropriate storage condition during distribution and sales.

#### 4.3. Recommendations

Despite the fact that the microbial analysis of pharmaceutical products in various research laboratories has been done on a small scale, it is still a valid indicator of the quality problem of the pharmaceutical products commonly available in Bangladesh. Hence, it is highly imperative to take preventive steps and necessary actions to mitigate the current concerns. Below are some of the recommendations that can be applied feasibly.

Firstly, collaborative technical and research efforts by the universities and research organizations in Bangladesh can increase the quantity of the assessed pharmaceutical products prominently. Analysis of higher number of products by higher number of researchers/professionals can be performed within a short period. This will not only enhance the amount of evidence regarding the quality of the products, but also will provide incentive on a national level to encourage this kind of study in future.

Secondly, stringent regulatory actions should be employed by the Bangladesh government to ensure that the GMP and the TQM are being accurately maintained in all the local pharmaceutical industries of the country. Regular examination of the production environment of the industries should be performed by government personnel to improve the overall production quality. The pharmaceutical production and premises, especially of the newly designed pharmaceuticals must comply with the FDA requirement, which needs to be endorsed officially. Another important point is to ponder that despite a rigorous adherence to GMP and TQM during manufacturing and packaging procedures, it is not enough to warrant that a medicine will never fail under the austere abuses of real-life circumstances. An appropriate QA system must include the regular practice of monitoring the in-use performance and for responding to the consumer complaints.

Thirdly, microbial contamination of products is always possible even after following all the regulations, possibly due to the

microbiological imbalance in the production environment which may be un-noticed. Moreover, improper handling and storage of the products in the local stores may also attribute to the product quality degradation if there is no issue in the production level. In that case, the people in the stores responsible for handling and keeping the products should be properly trained and educated before being appointed for the respective duties and responsibilities. It should be made mandatory for the local store owners to ensure that the staff is adequately trained to maintain the optimum conditions of the stored products.

Finally, more internal and external funding should be provided to progress the R&D stages of the local pharmaceutical industries to develop novel and more effective drugs against the drug-resistant pathogenic microorganisms.

#### 5. Conclusion

According to laboratory investigations, even at a minor scale, a range of pharmaceutical products manufactured in Bangladesh has been found to be contaminated with pathogenic microorganisms, which accounts for high public health concern. If this issue is not addressed seriously and actively, the health complications will only deteriorate with time. It can ultimately lead to disease outbreaks on a national level, which will be hard to control if not prevented now. Thus, the local pharmaceutical industries need to be more careful and attentive about following the safety rules and standard regulations in all stages of manufacturing, packaging and distribution of the products. The local stores should maintain the appropriate conditions for the storage of the pharmaceutical products. Currently, lack of funding is one of the hindrances for progressive research activities in the pharmaceutical industries in Bangladesh. Thus, the government should take more initiatives to aid in this regard. In future, the researchers and professionals around the country should initiate joint research projects to study about the quality of the pharmaceutical products in more detail and also for raising awareness throughout the country.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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#### Comments

##### Background

Although most pharmaceutical products in Bangladesh therapeutically meet and satisfy the demands of the general population, the presence of some compromised products require further research to maintain the desired microbiological quality and ensure overall drug user safety.

##### Research frontiers

This paper emphasizes the need for awareness, research funds and government cooperation in preventing microbial contamination of pharmaceutical products from Bangladesh and to ensure the drug safety for the overall management of public health.

##### Related reports

The authors have researched their data well and presented related papers sequentially and as per their theme, such as research related to microbial contamination, inappropriate maintenance of hygiene, doses based on different routes of administration, quality assurance, etc.

### Innovations & breakthroughs

Suggestions for: (a) collaborative technical and research efforts by universities and research organizations in Bangladesh; (b) importance and need of stringent regulatory actions by the Bangladesh Government to ensure that the GMP and the TQM are ensured; (c) mandatory rules for local store owners to ensure that staff is adequately trained to maintain the optimum conditions of products; (d) need of more internal and external funding for progress the R&D in the Bangladesh pharmaceutical industry.

### Applications

This research provides a clear picture about the different deficiencies present in pharmaceutical products which hamper consumer needs. Awareness through information provided by this study will help to improve the quality of pharmaceutical products and contribute to the flourishing of the pharmaceutical industry further, in Bangladesh.

### Peer review

Quality assurance in any product particularly consumed by human beings such as medicinal products need to be attended to with great importance. In order to improve the quality of products it is first necessary to know the background information that gives a clear picture of the overall situation. I think this paper has met such standards where substantial knowledge is neatly presented and conveyed.

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