Microbiological contamination in counterfeit and unapproved drugs

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Abstract

Background: Counterfeit and unapproved medicines are inherently dangerous and can cause patient injury due to ineffectiveness, chemical or biological contamination, or wrong dosage. Growth of the counterfeit medical market in developed countries is mainly attributable to life-style drugs, which are used in the treatment of non-life-threatening and non-painful conditions, such as slimming pills, cosmetic-related pharmaceuticals, and drugs for sexual enhancement. One of the main tasks of health authorities is to identify the exact active pharmaceutical ingredients (APIs) in confiscated drugs, because wrong API compounds, wrong concentrations, and/or the presence of chemical contaminants are the main risks associated with counterfeit medicines. Serious danger may also arise from microbiological contamination. We therefore performed a market surveillance study focused on the microbial burden in counterfeit and unapproved medicines.

Methods: Counterfeit and unapproved medicines confiscated in Canada and Austria and controls from the legal market were examined for microbial contaminations according to the US and European pharmacopoeia guidelines. The microbiological load of illegal and legitimate samples was statistically compared with the Wilcoxon rank-sum test.

Results: Microbial cultivable contaminations in counterfeit and unapproved phosphodiesterase type 5 inhibitors were significantly higher than in products from the legal medicines market (p < 0.0001). Contamination levels exceeding the USP and EP limits were seen in 23% of the tested illegal samples in Canada. Additionally, microbiological contaminations above the pharmacopoeial limits were detected in an anabolic steroid and an herbal medicinal product in Austria (6% of illegal products tested).

Conclusions: Our results show that counterfeit and unapproved pharmaceuticals are not manufactured under the same hygienic conditions as legitimate products. The microbiological contamination of illegal medicinal products often exceeds USP and EP limits, representing a potential threat to consumer health.
Unapproved medicines are drugs sold or imported without having been granted a marketing authorisation by health authorities [8]. Unapproved drugs are often marketed as being similar to, or a foreign version of, an approved drug. Such medicines may indeed comply with the quality standards in their country of origin, but because they are not imported or sold through the legal supply chain, their origin often remains unclear and their compliance with the quality standards of the target country cannot be verified [9,10].

Consumers are generally unaware of the dangers associated with the use of counterfeit and unapproved lifestyle drugs. Next to treatments for erectile dysfunction, appearance-enhancing medications such as slimming pills or anabolic steroids are in high demand. While non-treatment with these drugs does not lead to detrimental health effects, their use can result in dangerous adverse effects caused by overdosed content or contaminations [6]. Additionally, consumers of life-style drugs often bypass the healthcare system, so that underlying diseases, such as coronary artery disease, obesity, or anorexia, cannot be detected and pharmacodynamic or pharmacokinetic interactions with other drugs or substances cannot be identified and prevented [5].

Security and encryption experts are continuously working to devise new methods to protect originator drugs from being counterfeited. Thus, secret colour compositions and packaging materials as well as holograms interpretable only with laser readers have been developed to prevent counterfeits from entering the legal supply chain [11]. Yet, counterfeit drugs in developed countries are mainly detected on the illegal pharmaceutical market. Consumers buy medications via the internet to save money or time or because they are too embarrassed about their health problems to seek professional help [5]. The WHO estimates that 50% of medicines bought from online pharmacies that do not list their physical address are counterfeits [12].

The pharmacological content of counterfeit medicines has been examined by both authorities and manufacturers of original products [5]. For example, with PDE5 inhibitors being a main target for counterfeiting, they have been extensively studied [13,14]. A serious incident with counterfeit PDE5 inhibitors occurred in Singapore in 2008, when 4 people died due to hypoglycaemia caused by counterfeits contaminated with glyburide [15].

Microbial contamination and infection are known to be serious risks associated with illegal drug use, the legal use of pharmaceuticals distributed under poor hygienic conditions, and counterfeit medicines for parenteral administration [16–18]. For example, according to a recently published report from Shanghai, China, intravitreal injection of counterfeit bevacizumab contaminated with endotoxin caused acute intraocular inflammation in a series of 80 patients, 21 of whom had to undergo vitrectomy as a result [19]. Whereas parenteral pharmaceuticals must be sterile, non-sterile products may be administered to regions of the human body that are rich in microbial flora and have physical or immunological barriers to infection [20]. However, the US and European pharmacopoeia state that even in non-sterile preparations, the presence of certain microorganisms “may have the potential to reduce or even inactivate the therapeutic activity of the product and has a potential to adversely affect the health of the patient. Manufacturers therefore have to ensure a low bioburden of finished dosage forms by implementing current guidelines on Good Manufacturing Practice during the manufacture, storage and distribution of pharmaceutical preparations” [21,22]. Microbiological contamination levels above pharmacopoeial limits may lead to alterations and spoilage of active ingredients and cause adverse effects by infections or toxins.

We here present the results from marketing surveillance studies performed by the Canadian and Austrian official control laboratories between 2008 and 2011 on microbiological contaminations in illegal medicines. Because microbial contamination is a well-known and already widely documented threat for sterile parenteral medicines and because counterfeit and unapproved drugs are frequently sold as solid dosage forms, the main focus of our studies was on solid life-style drugs.

Methods
All experiments were performed by Health Canada and by the AGES Austrian Medicines and Medical Devices Agency. Both organizations are responsible for market surveillance in their respective countries.

Canadian study design
Health Canada defines a counterfeit health product as one that is represented as, and likely to be mistaken for, an authentic product [23]. Analyses focused on randomly selected counterfeit and unapproved drugs for the treatment of erectile dysfunction from the illegal market. Twenty-one counterfeit and 31 unapproved PDE5 inhibitors were analysed for microbial contamination. As controls, samples of all available PDE5 inhibitors were obtained from the legal market (Viagra® 25, 50, 100 mg; Cialis® 2.5, 5, 10, 20 mg; Levitra® 5, 10, 20 mg) and analysed. All counterfeit and unapproved samples had been seized by the Royal Canadian Mounted Police or Border Integrity Officers between 2008 and 2010.

The drugs were tested for compliance with the US Pharmacopoeia. A total of five microbiological analyses were performed on the samples: total aerobic microbial count (TAMC), total yeast and mould count (TYMC), pathogens (Escherichia coli, Pseudomonas aeruginosa, Salmonella, and Staphylococcus aureus), and enumeration of enterobacteriae and anaerobic bacteria. All
analyses, including handling procedures, dilutions, and culture media, were conducted in accordance with the US Pharmacopoeia (USP), Chapters 61 and 62 [24,25], which are harmonized with the European Pharmacopoeia (EP). The assay for sildenafil citrate content was performed according to the corresponding USP monograph.

Austrian study design
According to the European Medicines Agency, counterfeit medicines are medicines that fail to comply with intellectual-property rights or infringe trademark law [26].

Seven counterfeit PDE5 inhibitors and 26 unapproved medicines (25 solid dosage forms and 1 herbal tea) from the illegal market were randomly selected and analysed for microbial contamination. Unapproved medicines consisted of suspected performance-enhancing drugs or slimming agents (Table 1). As a reference, PDE5 inhibitor products (Viagra® 50 mg; Cialis® 10 mg; Levitra® 10 mg) were obtained from the legal market and examined for microbial contaminations. The drugs had been seized by the Austrian police and the Austrian customs agency between 2008 and 2011. All samples were tested for EP compliance. As in the Canadian study, analyses for TAMC, TYMC, pathogens (Escherichia coli, Pseudomonas aeruginosa, Salmonella and Staphylococcus aureus), enterobacteriae, and anaerobic bacteria were performed as applicable. All analyses, including handling procedures, dilutions and culture media, were conducted in accordance with the EP, Chapters 2.6.12, 2.6.13, and 2.6.31 [27-29], which are harmonized with the USP. The assay for sildenafil citrate content was performed according to the corresponding EP monograph.

Acceptance criteria in the USP and EP
According to the USP and EP, the acceptance criteria for non-aqueous preparations for oral use are $10^3$ colony-forming units (CFU)/g in the TAMC test and $10^2$ CFU/g in the TYMC test. The acceptance criterion for herbal products with cold extraction is $10^5$ CFU/g in the TAMC test, $10^4$ in the TYMC test, and $10^4$ for bile-tolerant gram-negative bacteria.

According to the USP and EP, the acceptance criteria of $10^3$ CFU/g were interpreted as a maximum acceptable count of 2000 CFU/g. The acceptance criterion of $10^5$ CFU/g for herbal products with cold extraction was interpreted as a maximum acceptable count of 500 000 CFU/g.

Statistical analysis
Due to the skewed distribution of microbiological burden, the non-parametric Wilcoxon rank-sum test, applying the normal approximation, was used to test for differences between medicines in the degree of microbiological contamination. In addition, Fisher’s exact test was used to compare contamination after dichotomization, both with respect to no/any microbiological burden as well as with respect to the acceptance limit of $< 2000$ CFU/g versus $> 2000$ CFU/g as defined according to the USP and EP. All statistical tests are presented with two-sided significance levels. The Wilcoxon rank-sum test comparing microbiological contamination of legal versus illegal medicines in Austria 

### Table 1 Microbiological contamination in counterfeit and unapproved drugs in the Austrian study

| Product                        | TAMC (CFU/g) | TYMC (CFU/g) | Pathogens               |
|-------------------------------|-------------|--------------|-------------------------|
| **Approved PDE5 inhibitors**  |             |              |                         |
| Sildenafil 50 mg              | < 5         | < 5          | nd                      |
| Tadalafil 10 mg               | < 5         | < 5          | nd                      |
| Vardenafil 10 mg              | < 5         | < 5          | nd                      |
| **Counterfeit PDE5 inhibitors** |             |              |                         |
| Sildenafil 100 mg #1           | < 5         | < 5          | nd                      |
| Sildenafil 100 mg #2           | < 5         | 10           | negative                |
| Sildenafil 100 mg #3           | < 5         | < 5          | nd                      |
| Sildenafil 100 mg #4           | < 5         | < 5          | nd                      |
| Sildenafil 100 mg #5           | < 5         | < 5          | nd                      |
| Sildenafil 100 mg #6           | 170         | < 5          | negative                |
| Tadalafil 80 mg #7             | < 5         | < 5          | nd                      |
| **Other unapproved products** |             |              |                         |
| Zinc gluconate #8              | < 5         | < 5          | nd                      |
| Nicotinic acid #9              | < 5         | < 5          | nd                      |
| Methandienone #10              | 80          | < 5          | negative                |
| Methandienone #11              | 11 000      | < 5          | negative                |
| Mephedrone HCl #12             | n/a         | n/a          | n/a                     |
| Butylone HCl #13               | n/a         | n/a          | n/a                     |
| Methandienone #14              | 80          | 60           | negative                |
| Stanozolol #15                 | 100         | < 5          | negative                |
| Stanozolol #16                 | 110         | < 5          | negative                |
| Clebuterol 0.02 mg #17         | < 5         | < 5          | nd                      |
| Sibutramine, phenolphtalein #18| 20          | 40           | negative                |
| Sildenafil 100 mg #19           | < 5         | < 5          | nd                      |
| 4-Methyllethcathinone #20      | < 5         | < 5          | nd                      |
| 4-Methycathinone/Coffein #21   | < 5         | < 5          | n/a                     |
| 4-Methyllethcathinone/Coffein #22| < 5       | < 5          | n/a                     |
| 4-Methyllethcathinone/Coffein #23| < 5       | < 5          | nd                      |
| 3-Fluoromethcathinone/ Lidocaine/Coffein #24| <5         | <5          | nd                      |
| Coffein/Acetylsalicylic acid #25| < 5         | < 5          | nd                      |
| Slimming herb #26 (herbal product) | 720 000 4 000  >10^6 bile-tolerant gram-negative bacteria |

TAMC: Total aerobic microbial count; TYMC: Total yeast and mould count; nd: Not determined; n/a: Not applicable (interfering substance prevented successful completion of the test).
Results

Only counterfeit and unapproved PDE inhibitors showed increased contamination

Not a single CFU was detected in the approved PDE5 inhibitor products obtained through the legal pharmaceutical supply chain—neither in the Canadian nor in the Austrian study. Thus, although the USP and EP allow an upper limit of $10^3$ CFU/g, no cultivable microbial contaminations were detected for these pharmaceuticals produced under controlled GMP conditions (Figure 1).

In the Canadian study, 12 of the 31 unapproved PDE5 inhibitor samples (39%) were contaminated with more than $10^3$ CFU/g (Figure 1). Taking counterfeit and unapproved drugs together, 12 of the 52 samples (23%) were contaminated with more than $10^3$ CFU/g. 36 samples (69%) showed increased levels of microbial contamination that were within the acceptable limits, and only 4 of the 52 illegal products (8%) showed excellent results with no cultivable contamination.

In the Austrian study, none of the 7 counterfeit PDE5 inhibitor samples tested showed a microbial contamination above the EP limit. Contamination with colony-forming microorganisms within EP limits was found in 2 of the 7 samples (29%, Table 1).

Statistical analysis of increased microbiological burden in counterfeit and unapproved PDE5 inhibitors in Canada

Wilcoxon rank-sum and Fisher’s exact tests were performed to test for statistical significance of observed differences between legal and illegal (counterfeit and unapproved) PDE5 inhibitors in Canada. In the Wilcoxon rank-sum test, the degree of microbiological contamination (CFU/g) in illegal medicines was significantly higher than in the legal products ($p < 0.0001$, two-sided). The Fisher’s exact test demonstrated that the number of contaminated illegal samples ($> 0$ CFU/g; as opposed to no contamination at all) was statistically significantly higher than in legal samples ($p < 0.0001$, two-sided). Overall, therefore, both the number of cultivable contaminations (Wilcoxon rank-sum test) and the number of contaminated samples ($> 0$ CFU/g; Fisher’s exact test) were significantly higher among illegal PDE5 inhibitors.

Comparison for non-compliance with the pharmacopoeia limits ($> 2000$ CFU/g) did not show a statistically significant difference between illegal and legal medicines, but a clear trend was observed ($p = 0.1864$, two-sided Fisher’s exact test). Unapproved medicines showed a clear statistically significant increase of non-compliance when compared to the counterfeit products ($p < 0.0001$, two-sided Fisher’s exact test).

Due to the limited number of PDE5 inhibitors from Austria, statistical analysis was only performed for the Canadian market.

Bacillus contaminations were frequent in counterfeit and unapproved PDE5 inhibitors

The identified species are summarized in Table 2. None of the pathogens specifically defined in the pharmacopeiae were detected. Amongst others, mainly contaminations with *Bacillus* ssp. were observed. Identified *Bacillus* species included *B. firmus*, *B. lentus*, *B. megaterium*, *B. pumilus*, *B. polymyxa*, *B. subtillis/amy-lo liquefaciens/atrophaeus*, *B. licheniformis*, *B. cereus/thuringensis/mycoides*, *B. pumilus*, *B. coagulans*, *B. fusiformis*, *B. circulans*, and *B. glucanolyticus*.
Inconsistent doses of active pharmaceutical ingredients in counterfeit PDE5 inhibitors

Although this was not the main focus of our study, we also examined the content of active ingredients in the counterfeit samples (Additional file 1). Of all 26 counterfeits tested, 24 (92%) did not contain the labelled amount of PDE5 inhibitor (acceptance criterion ± 10% of the labelled amount). In 21 samples (81%), a reduced content of the active ingredient was detected, whereas 3 samples (12%) were about 2-fold over-dosed. Interestingly, 14 of the 26 samples (54%) also contained trace amounts of a second PDE5 inhibitor.

Microbiological contamination in other product classes tested

When examining the 25 non-PDE5-inhibitor unapproved medicines with solid dosage forms from the Austrian
market, one product containing methandienone was contaminated with $1.1 \times 10^4$ CFU/g in the TAMC test, thus exceeding the EP limit of $10^5$ CFU/g. Of the 25 unapproved medicines, one (4%) did not comply with EP standards and an additional 7 (28%) showed a microbial load higher than that seen in the legal products manufactured under defined GMP conditions.

**Increased microbiological burden in an unapproved herbal product**

One unapproved herbal medicinal product was tested in Austria. The product contained brown-coloured dried plant tissue and was contaminated with 720,000 CFU/g in the TAMC test (Table 1), exceeding the acceptance criterion of $10^7$ CFU/g (maximum of 500,000 counts). Besides, the sample also exceeded the EP limit of $10^4$ CFU/g of bile-tolerant gram-negative bacteria. *Klebsiella pneumonia* was identified as the prevalent bile-tolerant species.

**Discussion**

The microbiological content in non-sterile products has to be controlled to a level consistent with patient safety [20]. Microbial enumeration tests are required to demonstrate production under acceptable hygienic conditions. Whenever pharmacopoeial limits are exceeded, the microbiological quality of manufacturing was not sufficiently controlled and adverse effects on product and patient safety cannot be excluded. Additionally, according to the US and European pharmacopoeiae, the significance of recovered microorganisms must be evaluated and the absence of specific pathogens demonstrated depending on the route of administration [21,22]. Microbiological contaminations may be introduced by the raw material, through the manufacturing process, or during packaging and transport, and risk-based control points should be incorporated into the manufacturing process [20].

Our data, derived from independent studies performed in two different pharmaceutical markets, confirm that counterfeit and unapproved medicines are not manufactured under the same hygienic condition as genuine products. The Canadian and Austrian studies presented both showed that none of the PDE5 inhibitors from the legitimate supply were contaminated with 1.1 × 10⁴ CFU/g in the TAMC test, thus exceeding the acceptance criterion of 10⁵ CFU/g (maximum of 500,000 counts). Besides, the sample also exceeded the EP limit of 10⁴ CFU/g of bile-tolerant gram-negative bacteria. *Klebsiella pneumonia* was identified as the prevalent bile-tolerant species.

Klebsiella pneumoniae was identified in an unapproved herbal medicinal tea, with the included package leaflet recommending extraction with cold water. This method of extraction may not be expected to reduce viable contaminations. *K. pneumoniae* is a gram-negative bacterium that can cause bacterial pneumonia and hospital-acquired urinary tract and wound infections [33]. *K. pneumoniae* mainly attacks immunocompromised patients and individuals with underlying diseases, such as diabetes mellitus [33]. The examined infusion failed to comply with the EP limits for bile-tolerant gram-negative bacteria and for total bacterial counts (TAMC). Although the concentrations of *K. pneumoniae* detected in this product are unlikely to lead to clinical infection in healthy humans [34], a potential threat cannot be excluded, especially when storage conditions are not monitored and further bacterial growth might occur.

Two potential threats arise from microbiological contaminations in pharmaceutical products. First, certain microorganisms may alter the quality of the active ingredients and even lead to spoilage of the product. Second, microbiological contaminations may directly cause adverse effects by producing toxins or causing infections. Product alterations are less likely in solid PDE5 inhibitors but may occur in...
herbal products. In general, the threats from microbiological contaminations are higher for herbal products and products with a moisture content that supports bacterial survival and growth than for solid dosage forms. Accordingly, a recent study found high levels of bacterial contaminations in counterfeit toothpaste [35], and an outbreak of Salmonella montevideo has been associated with a dietary herbal food supplement [36]. Herbal products show higher levels and limits of contamination because of the raw materials they contain and the mild production methods used. In contrast, PDE5 inhibitors are less likely to be contaminated with bacteria due to the synthesis process of the active substances, the chemicals used, and the low moisture content. Even in synthesised medicines, however, contaminations by excipients or cutting agents and human manipulation during manufacture and transport pose a risk when hygienic production conditions are not guaranteed. In recent years, several cases of injectional anthrax most likely caused by contaminated heroin have been described in Europe [37]. Suggested routes of contaminations included animal-derived sources, such as bone meal or animal hides [38]. Although this is clearly a worst-case scenario associated with injectional administration of an illicit drug, it illustrates that the lack of controls during manufacturing and/or transport of pharmaceutical active substances can lead to contamination with severe pathogens. Interestingly, despite good evidence for the cause of infection, neither B. anthracis nor its genome was detected in any of the heroin samples tested [37]. The production of illegal drugs and illegal pharmaceuticals might differ, but for both, in the absence of strictly quality-controlled hygienic production conditions, even testing for specific pathogens may not be sufficient to detect serious contaminations.

Conclusions
Based on our studies, it may be assumed that various groups of illegal medications contain increased levels of microbial contaminations. Our results demonstrate that illegal pharmaceuticals are produced under less hygienic conditions than legitimate products manufactured under controlled and defined GMP conditions. To gain broader insights into the microbiological burden in counterfeit drugs, we recommend the risk-based inclusion of microbiological quality studies in the surveillance of the illegal pharmaceutical market.

Additional file

Additional file 1: PDE5 Inhibitor content in counterfeit drugs from Canada and Austria. Inconsistent doses of active pharmaceutical ingredients were detected in counterfeit PDE5 inhibitors.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
All authors read and approved the final manuscript. DP collected and analysed the data and drafted the article. YLT and CT analysed the results, drafted the study report by Health Canada, and critically revised the article. JB and XS planned and designed the Canadian study part, analysed the Canadian results, and critically reviewed the article. AH, HS, GB, and AM planned and designed the Austrian part of the study and analysed the data. BG performed the experiments and analysed the results. CG performed the statistical analyses of the results and critically revised the article.

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