Counterfeit protein drugs: how to discover and how to prevent?

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In developed countries, counterfeit protein drugs are mainly observed in illegal markets. However, counterfeits have made their way onto the shelves of hospital and community pharmacies. This article gives an overview of prominent cases and some advice on strategies for discovery and prevention.

Introduction

According to the WHO, a counterfeit medicine is “a medicine, which is deliberately and fraudulently mislabelled with respect to identity and/or source”. Although exact numbers are not available, it is reasonable to estimate that the prevalence of counterfeit medicines ranges from far less than 1% of sales in developed countries, to over 10% in developing countries [1].

Counterfeit and substandard drugs have long been recognised as being mainly a problem of developing countries with weak structures of drug regulatory systems and market control. However, during the last decade it has become evident that industrialised countries are also affected by the problem, mainly in illegal market scenarios, but also in the tightly controlled legal supply chain.

FDA counterfeit drug investigations have increased to over 20 per year since 2000, after averaging only five per year through the late 1990’s [2]. Recent cases of batch recalls in the UK have shown that the legitimate supply chain in European countries is also affected by the problem, mainly in illegal market scenarios, but also in the tightly controlled legal supply chain.

Protein drugs – an attractive target for counterfeiters

Due to their relatively simple production technology, solid dosage forms of so-called “lifestyle” drugs, such as PDE5-inhibitors (like Viagra (sildenafil)) and medicines for weight loss have traditionally been the main targets for counterfeiting. Because these types of medicines are often not covered by reimbursement in public healthcare systems, patients are tempted to look for prescription-free, cheap buys from often illegitimate sources, leading to a demand on the illegal market.

In spite of more complex production technologies, the inherently high price of protein drugs offers the chance of high profits and thus makes them attractive targets for counterfeiters. Criminals have become increasingly sophisticated in their ability to fake and package more complex injectable dosage forms such as lyophylisates. While the authentic protein drug products are often very difficult to fake as the following examples will show.

Counterfeit and substandard somatropin formulations in the illegal market

In addition to their legitimate use in their approved indication fields, some protein drugs such as somatropin and epoietin are illegally used for doping purposes, resulting in a high demand for these products on the black market. Somatropin is also used off-label as a lifestyle-drug against aging and obesity. Outside of the regular supply chain, preparations of doubtful origin with substantial lack of quality are frequently offered on the black market. In the last few years counterfeited, contaminated and low quality somatropin has been found, both in the European Union and in the United States. Laboratory analysis of seized products performed by Official Medicines Control Laboratories (OMCLs) demonstrated that instead of the expected recombinant human growth hormone some counterfeit products contained the pregnancy hormone HCG, growth hormone extracted from human pituitary glands, immuno-genic somatropin variants or somatropin from other species [5, 6]. Looking at the more than 50 proven cases of the transmission of the deadly Creutzfeldt-Jakob Disease by contaminated growth hormone preparations in the beginning of the 1980’s, people must be urgently warned not to use such substandard products from the illegal markets [7-10].
Counterfeit protein drugs in the legitimate supply chain

During the last decade, several cases have emerged in the US where counterfeit protein drugs have made their way onto the shelves of hospital or community pharmacies and into patients. This has led to several batch recalls. Health warnings have been issued by the FDA and manufacturers of the affected authentic products. Examples of protein drugs and their active pharmaceutical ingredient (APIs) affected by counterfeiting are Procrit [11] (epoietin alpha), Epogen [12] (epoietin alpha), Serostim [13] (somatropin), Nutropin [14] (somatropin) and Neupogen [15] (filgrastim). The counterfeit products contained either no active pharmaceutical ingredient, less than the declared amount of API, APIs other than those declared (e.g. steroids or insulin instead of somatropin) and in some cases were contaminated with bacteria and endotoxins. All counterfeit products led to serious health risks for patients. Most of the counterfeit products slipped into the regular supply chain by unscrupulous or careless secondary wholesalers who, willingly or unwillingly, bought from criminal sources.

How to discover?

As the printing and manufacturing capabilities of counterfeiters have become more sophisticated, counterfeit protein drugs are becoming increasingly difficult to discover. In the past, labelling of counterfeiters sometimes showed slightly different font types and different print quality than the authentic product. Thus it was possible to distinguish the counterfeit from the authentic product by visual comparison of primary and/or secondary packaging [13-15]. However, past cases have also shown that subtle differences in packaging or printing which could provide a hint to counterfeit products are often not noticed by end users or distributors. In addition, some counterfeiters are so good that simple visual comparison will not be sufficient to distinguish them from the authentic product. As pharmaceutical manufacturers have gradually introduced new overt and hidden security marks in their packaging design, there are now additional ways to identify counterfeits by analysis of the packaging. In the future, new track and trace and authentication technologies using 2D-matrix-codes and/or radio frequency identification devices may provide further options.

In addition, an extensive physicochemical and biochemical analysis of the finished dosage form, covering parameters like identity, content and purity of the API, composition of excipients and microbiological quality is usually required to characterise and to evaluate a suspect counterfeit in terms of health risks. Due to the complexity of therapeutic proteins usually a combination of sophisticated protein analytical technologies has to be used for analysis.

In cases of a lack of therapeutic effects or unexplainable adverse reactions the hospital pharmacist should consider the possibility of a counterfeit drug being the root cause and seek further evidence. The competent authorities [16] should be contacted using established rapid alert pathways for product defects. It is also advisable to secure sufficient material for subsequent laboratory testing. Competent authorities can then initiate independent testing of suspect counterfeits to be performed by Official Medicines Control Laboratories [17].

In addition to the investigation of suspect samples, risk based, routine market surveillance testing performed by OMCLs in the European countries provides an independent means of identifying substandard or counterfeit protein drugs. In many countries OMCL sampling procedures have now been optimised to cover the complete supply chain of pharmaceuticals in a risk based approach.

All counterfeit products led to serious health risks for patients. Don’t buy from suspicious sources!

How to prevent?

The risk of counterfeit medicines entering the legitimate supply chain can be reduced by some fairly simple means [18]. Medicines should only be bought from qualified suppliers with appropriate wholesaler licences. Don’t buy from suspicious sources! If a product is offered at an unusually cheap price, treat with extra caution. Look for signs of a removed or switched product label. Look for altered expiry dates. Look for subtle changes in

Pharmaceutical companies, industry organisations, the European Commission, EU Heads of Medicines Agencies Working Groups, the Council of Europe and WHO, as well as the national authorities of the European Countries and other stakeholders are currently undertaking massive efforts in developing and improving anti-counterfeit strategies.

Conclusion

In the industrialised European countries counterfeit drugs in the legitimate supply chain have been extremely rare. However, recent events have shown that the threat is real and that even tightly regulated pharmaceutical supply chains are not impenebrable. Hospital pharmacists can best contribute to discover and combat counterfeits by keeping a high level of awareness of the problem and by notifying suspect cases to the competent authorities.

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References