



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Identification of health damage caused by Medicrime products in Europe

An exploratory study

RIVM report 040003001/2012

B. J. Venhuis et al.



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Identification of health damage caused by Medicrime products in Europe

An exploratory study

RIVM Report 040003001/2012

Colophon

© RIVM 2013

Parts of this publication may be reproduced, provided acknowledgement is given to the 'National Institute for Public Health and the Environment', along with the title and year of publication.

B. J. Venhuis, RIVM
R. Mosimann, Swissmedic
L. Scammell, MHRA
D. Digiorgio, AIFA
R. van Cauwenberghe, FAGG
M.G.A.M. Moester, IGZ
M. Arieli, Inspectorate IL
S. Walser, EDQM

Contact:
Bastiaan J. Venhuis
Health Protection Centre
bastiaan.venhuis@rivm.nl

This investigation has been performed by order and for the account of VWS-GMT, within the framework of V/370008/12.

This study was supported by the EDQM (Council of Europe) project and 2011-2012 contracts with RIVM in the framework of the activities of the Committee of experts on minimising public health risks posed by counterfeiting of medical products and similar crimes of the EDQM (Council of Europe), coordinated by the Dutch delegation (RIVM) of the Committee of Experts (Rapporteur).

Abstract

Identification of health damage caused by Medicrime products in Europe

In Europe, the use of falsified medical products (Medicrime products) is increasing. The unreliable quality of these products is expected to cause health damage. The nature and extent of this damage is difficult to determine because the expected symptoms are not sufficiently specific to be recognized in everyday practice. It is also unclear to health care professionals where and how they can report their suspicions about usage. This is shown in an exploratory study by RIVM.

Medicrime products are rarely found at (family) doctors and official pharmacies. However, consumers receive these products when they purchase medical products from unreliable suppliers, mainly over the internet. Through this source they are increasingly exposed to Medicrime products.

This study assesses Medicrime products that are seized throughout Europe and the associated health complaints expected. Six categories of Medicrime products are seized most: erectile dysfunction agents, psychoactive drugs (such as stimulants, and designer drugs), drugs (especially steroids), slimming agents, strong painkillers and medicines for heart disease. These categories represent about 40 per cent of the seized Medicrime products. The remaining 60 per cent comprises a large variety of drugs, including anti-cancer agents, antibiotics, and anti-retroviral drugs. Even though these are seized in smaller numbers, the health threat is not to be underestimated due to their nature. With respect to epidemics and the development of resistance, it is undesirable that unreliable anti-infective medicines are used.

It is recommended to raise awareness among physicians of the phenomenon of Medicrime products through, for example publications in medical journals. It is also recommended to create an information exchange platform on suspect products and complaints. Finally, it is important to devise a simple registration procedure for suspected medical products to set, for example, by adding a tick-box to the international adverse events reporting form by WHO. The recommendations have been incorporated into a pilot study in several European countries that is currently being tested.

Keywords:

Medicrime; health damage; harm; counterfeit medicines; falsified medicines; fake medicines

Rapport in het kort

De aantoonbaarheid van gezondheidsschade veroorzaakt door vervalste medische producten in Europa

In Europa neemt het gebruik van vervalste medische producten (Medicrime-producten) toe. De dubieuze kwaliteit van deze producten veroorzaakt naar verwachting gezondheidsschade. De aard en omvang ervan is echter moeilijk te bepalen, omdat de te verwachten klachten onvoldoende specifiek zijn om op te vallen in de alledaagse praktijk. Ook is het voor medici niet duidelijk waar en hoe zij hun vermoedens over gebruik kunnen rapporteren. Dit blijkt uit verkennend onderzoek van het RIVM.

Medicrime-producten worden zelden aangetroffen bij (huis)artsen en officiële apotheken. Consumenten krijgen ze juist door zelf medische producten te kopen bij onbetrouwbare leveranciers, voornamelijk via internet. Via deze 'bron' stellen zij zichzelf steeds vaker bloot aan Medicrime-producten.

Voor het onderzoek is op Europese schaal bekeken welke Medicrime-producten in beslag zijn genomen en welke klachten daarvan te verwachten zijn. De volgende zes categorieën Medicrime-producten worden het meest in beslag genomen: erectiemiddelen, psychoactieve drugs (zoals pepmiddelen en designer drugs), doping (vooral anabolen), afslankmiddelen, sterke pijnstillers, en geneesmiddelen voor hart- en vaatziekten. Deze categorieën vormen ongeveer 40 procent van de Medicrime-producten. De overige 60 procent wordt gevormd door een grote variatie aan geneesmiddelen, waaronder middelen tegen kanker, antibiotica, en hiv-remmers. Ook al worden deze middelen in geringere mate aangetroffen, vanwege de aard ervan moet de bedreiging voor de gezondheid niet worden onderschat. Met het oog op epidemieën en resistentievorming is het ongewenst dat onbetrouwbare anti-infectieuze middelen worden gebruikt.

Aanbevolen wordt om de bewustwording bij artsen van het verschijnsel Medicrime-producten te vergroten, bijvoorbeeld via publicaties in medische tijdschriften. Verder wordt aanbevolen om een informatiesysteem op te zetten over verdachte producten en klachten. Ten slotte is het van belang een eenvoudige registratiewijze van verdachte medisch producten in te richten, bijvoorbeeld door deze mogelijkheid toe te voegen aan het internationale rapportageformulier van de WHO voor bijwerkingen. De aanbevelingen zijn verwerkt in pilot studie, die momenteel in diverse Europese landen wordt uitgevoerd.

Trefwoorden:

Medicrime, gezondheidsschade, namaakgeneesmiddelen, vervalste geneesmiddelen; neppureesmiddelen

Contents

Summary—6

1 Introduction—10

2 Methods—12

2.1 Definitions—12

2.1.1 Medicrime products—12

2.1.2 Health damage—12

2.2 General approach—12

2.3 Literature study—13

2.4 Confiscated Medicrime products—13

2.5 Expert meeting—14

3 Results and Discussion—15

3.1 Literature study—15

3.2 Confiscated Medicrime products—16

3.2.1 Therapeutic categories—16

3.2.2 Quantities—16

3.2.3 Destination—18

3.2.4 Regional differences—18

3.2.5 End users—18

3.3 Expert meeting—18

3.3.1 Symptoms—18

3.3.2 Anamnesis—19

3.3.3 Reporting—19

3.3.4 Conclusion of the expert meeting—20

3.3.5 Anamnesis formula for clinical use—20

4 Conclusions and recommendations—21

References—22

Appendix 1 Anamnesis formula—24

Summary

Despite solid national health systems, European countries are increasingly under threat of falsified and counterfeit medicines (Medicrime products). Although contamination of the legal supply chain in Europe seems limited to rare instances, Medicrime products are plentiful outside of the national health systems and through websites that trade them illegally. Though health and enforcement authorities go to great length in trying to prevent contamination of the legal supply chain, millions of people in Europe choose to purchase medicines from unreliable sources. These people have a high chance of receiving unreliable medication. Considering the type of products seized by customs around Europe, health damage is highly probable.

This report describes the initial steps towards a final goal of developing approaches, models and tools for recording and interpreting signals of health damage due to Medicrime products in Europe.

Objectives

The first objective of this report is to develop a validated appropriate protocol to identify, evaluate and report signals of health damage due to Medicrime products in Europe. The approach should be sufficiently flexible for use in different regions that share root causes and consequences of counterfeited medical products and similar crimes.

The second objective is to implement this protocol and thus widely improve the detection of signals of health damage caused by Medicrime pharmaceuticals and devices in Europe.

The third objective is to encourage health-care professionals to consider Medicrime pharmaceuticals and devices a possible cause of health damage and report these incidents according to the provided protocol. This should improve the level and quality of detection, verification and reporting, early treatment and prevention of health damage to patients.

Methods

Scientific literature was reviewed on cases and on how these were recognized. The participating countries were requested to provide information on the Medicrime products on their national legal and black markets, on how these products were manipulated, on the user group susceptible to health damage, and on the dimensions of the problem. This information was used in an expert meeting with specialist (medical) doctors in the Netherlands. The aim of this meeting was to provide insight into the leading symptoms of the expected health damage, persons susceptible to health damage, reporting points for health complaints, and the prerequisites for conducting a multinational pilot study. Using all the assembled information, a practical protocol (anamnesis form) was developed for identifying health damage in the countries that would participate in a future pilot study.

Results for the literature review

Since 1970, very few articles have been published in scientific literature on incidents related to Medicrime pharmaceuticals in developed countries. Most cases of health damage were connected to incidents involving counterfeit

gentamycin, toxic slimming drugs in foods, counterfeit heparin, and contaminated ED drugs. The common denominator among the actual cases was that patients would present themselves to the hospital with unspecific symptoms, unaware of the probable cause, or reluctant to be frank about the cause. Cases were more likely to be recognized when specific symptoms occur in multiple individuals in a small area (outbreak) or when the severity of a single case required extensive effort.

Results for the compilation of confiscated Medicrime products

The submitted data showed that six therapeutic categories were confiscated most often (Table S1). Among these are the so-called lifestyle medicines, such as erectile dysfunction drugs and weight loss drugs. However, overall the therapeutic categories ranged from lifestyle medicines to medicines used for treating life-threatening conditions. No specific information was available on the end users.

Table S1. The six therapeutic categories confiscated most frequently.

1. Erectile dysfunction drugs
 2. Psychoactive drugs
 3. Doping substances
 4. Weight loss drugs
 5. Analgesics
 6. Cardiovascular drugs
-

Data on confiscations were also available for Operation Pangea III, which was carried out in 44 countries worldwide in 2010. These data also showed the six prevalent therapeutic categories. In terms of quantities (e.g. of tablets or capsules), the Pangea III data showed that the prevalent therapeutic categories accounted for only 40% of the total. How this would translate to European countries only could not be derived from the data. Nevertheless, it showed that our focus should not be limited to only the prevalent therapeutic categories.

Results of the expert meeting

The medical specialists recommended to raise awareness among clinicians through publishing cases in medical journals. Furthermore, it was recommended to construct a searchable database of suspect product names, their details, and specific clinical symptoms for consultation by health-care professionals. The database should be fitted with a regularly updated watch list.

It was generally acknowledged that hospitals are not forensic institutes and that suspect cases need to be centrally reviewed in order to obtain perspective. The above-mentioned database could provide a suitable platform. Pharmacovigilance was considered the logical entity for receiving reports. It was recommended to add a tick-box to the international adverse events reporting form for 'suspect medical product'.

Prompted by the advice of the medical specialists, a protocol was developed in the form of a preliminary anamnesis form supported by an up-to-date watch list

of Medicrime products with chemical analytical data, associated clinical symptoms (ATC4-5 level) and selected anamnestic questions. The anamnesis form consisted of two parts: 1) exploratory (non-blaming) questions to be answered by the patient, and 2) an evaluation form to be filled out by the health-care professional. The supporting material was derived from the OMCL database of suspect products.

Recommendations

Health authorities should actively approach the medical community to raise awareness among health-care professionals.

Health authorities should provide a platform for clinicians to search and share information on suspect products, the associated symptoms, and unexplained suspect cases.

Health authorities are advised to accommodate Pharmacovigilance as the natural authority for reporting health damage caused by Medicrime products.

Reporting should be facilitated by a multi-country effort by having a tick-box added to the international adverse events reporting form for 'suspect medical product'.

Carry out a pilot study with a selected group of enthusiastic health-care professionals using the developed protocol. International studies based on standardised terminology and harmonised working methods are encouraged, such as the projected pilot-study by the Committee of Experts CD-P-PH/CMED, coordinated by the EDQM (Council of Europe).

Glossary

EDQM	European Directorate for the Quality of Medicines and Health-care. A body of the Council of Europe.
Committee of Experts CD-P-PH/CMED	An EDQM expert group on falsified and counterfeit medicines.
Council of Europe	The Council of Europe is an international organization promoting co-operation between all countries of Europe in the areas of legal standards, human rights, democratic development, the rule of law and cultural co-operation. It was founded in 1949, has 47 member states with some 800 million citizens, and is an entirely separate body from the European Union (EU), which has only 27 member states. The best known bodies of the Council of Europe are the European Court of Human Rights, which enforces the European Convention on Human Rights, and the European Pharmacopoeia Commission, which sets the quality standards for pharmaceutical products in Europe.
Medicrime Convention	The Council of Europe drafted a convention which constitutes a binding international instrument in the criminal law field on counterfeiting of medical products and similar crimes involving threats to public health.
OMCL	Official Medicines Control Laboratory.

1 Introduction

The last thing on a patient's mind should be whether to trust their medication. Therefore, one of the key assets of a national health system is that it ensures a legal supply chain of reliable medicines. Large parts of the world that lack such a system are plagued by counterfeit and other criminally manipulated medical products ('Medicrime products') that threaten people's lives and well-being. Unfortunately, Medicrime has reached such dimensions that European countries are also affected.

Despite solid national health systems, European countries are increasingly under threat of Medicrime products. Contamination of the legal supply chain in Europe seems limited to rare instances, but Medicrime products are plentiful outside of the national health systems and are available through websites trading illegally. While health and enforcement authorities go to great lengths in preventing contamination of the legal supply chain, millions of people in Europe choose to purchase medicines from unreliable sources. These people have a high chance of receiving unreliable medication. Considering the type of products seized by customs around Europe, health damage is highly probable.

This development is a health threat to European citizens and it undermines the confidence in national health systems. However, as only very few actual cases have been reported, there is uncertainty about the proportion of the threat. As underreporting of adverse events is already an issue for authorised medicinal products, this is expected to be even worse for medical products obtained from outside of the official system. Obviously, that is precisely where counterfeit or otherwise criminally manipulated products are expected most.

Criminally manipulated medicines are unreliable when it comes to their effects and are typically used without a doctor's consent. Therefore, compared to legitimate medical products, Medicrime products pose an inherently higher threat for causing harm. Users may particularly be harmed by unintended effects through adverse events and quality defects. Nevertheless, their intended effects may also cause harm as self-treating patients may be contraindicated and will miss any required follow-ups. Thus, both the intended and unintended effects of Medicrime products contribute to the health threat.

Harm caused by Medicrime products will only be noticed in cases when health complaints (including death) lead to an interaction with a health-care professional. As this will normally concern only the serious cases, that proportion of harm is defined as 'health damage'. Recognising cases of health damage depends on the user taking deliberate action and on how well-prepared a health-care professional is to deal with cases of health damage caused by Medicrime products. The role of health-care professionals is vital as they interact with users. To find signals of health damage they need to be provided with adequate tools to recognize and report suspect cases.

Recognising and reporting signals of health damage are essential for preventing and minimising the health threat posed by Medicrime products. Health-care professionals, as well as users, should be encouraged to report health complaints due to a suspect Medicrime product to Pharmacovigilance or a poisons information centre. These data should be centrally compiled and interpreted on a European level.

Objectives of this exploratory study

This report describes the initial steps towards a final goal of developing approaches, models and tools for recording and interpreting signals of health damage due to counterfeiting medicines and similar crimes in Europe.

The first objective of this report is to develop a validated appropriate protocol to identify, evaluate and report signals of health damage due to Medicrime products in Europe, through piloting in selected countries represented at the Committee of Experts CD-P-PH/CMED. The approach should be sufficiently flexible for use in different regions that share root causes and consequences of counterfeited medical products and similar crimes.

The second objective is to implement this protocol and thus widely improve the detection of signals of health damage caused by Medicrime pharmaceuticals and devices in Europe.

The third objective is to encourage health-care professionals to consider Medicrime pharmaceuticals and devices a possible cause of health damage and report these incidents according to the provided protocol. This should improve the level and quality of detection, verification and reporting, early treatment and prevention of health damage to patients.

This exploratory study supports the protection of public health from Medicrime products and similar crimes through national and international legislation. The Council of Europe's Committee of Ministers adopted the Council of Europe Convention on counterfeiting of medicines and similar crimes involving threats to public health (Medicrime Convention, Dec. 2010) and opened it for signature by states in October 2011. This is the first binding international legal instrument on criminalising the manipulation of medical products involving threats to public health.

In 2011, EU Directive 2011/62 amending EU Directive 2001/83 on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of counterfeit and falsified medicinal products, entered into force in the 27 EU Member States.

2 Methods

2.1 Definitions

2.1.1 *Medicrime products*

For the purpose of this study and within the working mandate of the Committee of Experts CD-P-PH/CMED, the Medicrime products are understood as covered by the terms '*counterfeiting of medical products and similar crimes*', in line with the Council of Europe Medicrime Convention*:

Without intellectual property rights connotation, a '*counterfeit*' medical product means a *false* representation as regards identity, history, and source. (Article 4 j Council of Europe Medicrime convention). This definition is compatible with current legislation of the European Union and other states.

Similar crimes involving threats to public health (Article 8 Council of Europe Medicrime convention) comprise (with criminal intent) the manufacturing, the keeping in stock for supply, importing, exporting, supplying, offering to supply or placing on the market of:

- I. medicinal products without authorisation where such authorisation is required under national law of the party; or
- II. medical devices without being in compliance with the conformity requirements, where such conformity is required under the national law of the party;
- III. the commercial use of original documents outside their intended use within the legal medical product supply chain, as specified by the national law of the party.

An example of a similar crime is a medicinal product sold without the authorisation of a competent drug regulatory authority for treating a disease and/or with unlabelled pharmacologically active ingredients. This study includes products that contain an experimental drug and medicinal products disguised as food supplements or functional foods.

2.1.2 *Health damage*

Health damage is defined as death of, or damage to the physical or mental health of the patient/consumer (Article 12, Council of Europe Medicrime Convention). For the purpose of this study, only health damage is considered that resulted in seeking medical assistance or death, which was recognized as such by a health-care professional based on patients' health complaints, statements, on apparently unexplained health findings, or on a medical condition known to be associated specifically to a Medicrime product.

2.2 General approach

For setting up projects to find health damage caused by Medicrime products it was considered useful to review scientific literature on cases and how these were recognized.

Information is needed on the kind of health damage to be expected for each country. For that, information will be assembled on the current Medicrime products on their legal and black markets, the criminal manipulations, the user

* See <http://www.coe.int/medicrime>.

group susceptible to health damage, and the dimensions of the problem. Medicrime products seized in the countries represented at the Committee of Experts CD-P-PH/CMED in the past 3 to 5 years were considered eligible.

To establish a practical approach for identifying leading symptoms of health damage caused by specific therapeutic classes, an expert meeting with specialist (medical) doctors was organised in the Netherlands. The aim of this meeting was to provide insight into the leading symptoms of the expected health damage, persons susceptible to health damage, reporting points for health complaints, and the prerequisites for conducting a multinational pilot study. Finally, it aimed to provide input for the development of a practical protocol (anamnesis form) for identifying health damage in the countries of a future pilot study.

2.3 Literature study

To assess the health impact of Medicrime pharmaceuticals in countries with a developed health system worldwide, we performed a systematic review of scientific literature between 1970 and 2011. The MEDLINE and EMBASE databases were searched for articles on counterfeit, falsified, and unauthorised products with medical claims, and adulterated food supplements in developed countries. Only articles reporting cases of death and hospital admissions were reviewed. Cases involving illicit drugs (narcotics) were not considered.

2.4 Confiscated Medicrime products

Members of the Committee of Experts CD-P-PH/CMED and collaborators were asked to approach their national single points of contact (SPOCs) within their health, police and customs authorities for obtaining the following information on Medicrime products confiscated in the last 3 to 5 years in- and outside of the legal supply chain using a standard reporting form:

1. *description of the product* (name, appearance, labelling) and *the nature of the criminal manipulation* (actual composition, modus operandi);
2. *circumstances of the seizure*. Confiscated Medicrime products do not necessarily reflect their true prevalence as seizure operations are not the result of random sampling. Operations targeted at specific types of Medicrime products were identified to limit the bias in prevalence;
3. *the quantity of the Medicrime products confiscated*. This should give an impression of the scale of the exposure and on whether a shipment was intended for personal use or for resale;
4. *destination*. Information on the destination of the confiscated product (e.g. private persons, a health or sports club, a beauty salon) was expected to enable identification of the susceptible population (characteristics of patients /consumers);
5. *any intelligence suggesting the possible (end) users* (health-care professional/patient/consumer) for predicting specific health damage and to narrow the possible entry ports for health complaints. Consumption mode, aim, and patterns need to be investigated separately.

Confiscated Medicrime products represent only a proportion of the quantities that reach the public. Therefore, the conclusions of this exploratory study

represent a minimal health damage scenario. Further, the types of confiscated medicinal products may not reflect the true prevalence of Medicrime products ('you find what you are searching for').

A separate pilot study is in progress, which aims at estimating the true exposure to Medicrime products. In that study, sewage loads for a model compound are correlated with the loads expected for the legitimate consumption.

Regional differences in consumption are expected to exist due to differences in societal factors, wealth, health-care system set-up and quality, medication traditions between the participating countries in middle-Europe (EU members), emerging democracies (non-EU members) and country in a conflict zone (Israel). When the submitted data suggests that such differences exist, it indicates that different regions may have specific health damage and specific requirements for their identification.

2.5 Expert meeting

On Jan 27th, 2012 a meeting was held with general practitioners and specialist (medical) doctors in the fields of neurology, emergency care, psychiatry, pathology, internal medicine, intensive care, ophthalmology, and a municipal coroner. During the preparation of the meeting, clinical pharmacologists had been consulted. The meeting was held to establish a suitable anamnestic approach including leading symptoms (triggers) of the health damage caused by Medicrime products and points of entry into the health-care system.

The therapeutic groups of the Medicrime products confiscated most often determined the choice of specialist (medical) doctors.

3 Results and Discussion

3.1 Literature study

Since 1970, 48 relevant articles were published in scientific literature reporting 73 separate incidents related to incidents that had occurred in *developed* countries. Actual cases were described in 8 articles, whereas 40 articles merely referred to the incidents in their introduction. Most reports were connected to five incidents involving Medicrime or adulterated herbal supplements. The major outbreaks and a series of isolated incidents are highlighted below.

1. In the 1990's falsified gentamicin sulphate (an antimicrobial) was imported into the US as bulk raw material.^{1,2} The substandard material was used to prepare authorised medicines. Because of the lack of strong signals of harm, it took several years before it was found out.
2. Between 2001-2002 more than 800 cases of liver damage were reported in Japan among people taking herbal slimming products.³⁻¹¹ The active ingredient was a designer drug inspired on the withdrawn slimming drug fenfluramine. This designer drug was particularly hepatotoxic, causing liver damage. Several people died or required a liver transplant.
3. In 2008 a large number of adverse events (including many deaths) were related to the use of heparin in the US.¹²⁻¹⁵ The subsequent inquiry showed that falsified bulk heparin had been imported for the production of authorised medicines. The raw material was adulterated with a heparin-like substance that did not show up in standard quality tests. By the time the adulterant was noticed, the falsified heparin had already reached patients in the US and in Europe.
4. In 2009, Singapore and Hong Kong witnessed an outbreak of hypoglycaemia caused by illicit erectile dysfunction (ED) drugs.¹⁶⁻¹⁸ The illicit medicines involved contained glibenclamide (an anti-diabetic) in addition to sildenafil (an ED drug). It is assumed that glibenclamide and sildenafil were accidentally mixed supposing they were both sildenafil. Over 200 elderly were admitted to the hospital and more than 10 people died. Although these products were probably not limited to Singapore and Hong Kong, only three small incidents were reported elsewhere (Australia).¹⁹⁻²¹
5. In the last couple of years, isolated incidents involving sibutramine and similar weight loss drugs are frequently reported.²²⁻²⁸ Sibutramine was withdrawn from the official market because its use was associated with cardiovascular events. There are several papers associating the use of sibutramine with psychosis.^{8,29-34} Nevertheless, these drugs were often found as an adulterant in food supplements, slimming coffee, and slimming tea. Several cases are described in Europe, involving users being admitted to hospitals with cardiovascular problems and psychological problems.

The common denominator among the actual cases was that patients would present themselves to the hospital with unspecific symptoms, unaware of the probable cause, or reluctant to be frank about the cause. Cases were more likely to be recognized when specific symptoms occur in multiple individuals in a small area (outbreak) or when the severity of a single case required extensive effort. Literature also underscores the potential consequences of falsified raw material entering the official production system.

3.2 Confiscated Medicrime products

The Members of the Committee of Experts CD-P-PH/CMED from Belgium, Italy, Switzerland, the United Kingdom, and an expert from Israel provided information. In addition to the national data, information was received on Operation Pangea III (2010). Pangea is an annual operation by customs agencies which focusses on monitoring imports of medicines. The Pangea III was carried out in 44 countries worldwide and the available data was used to investigate differences in regional distribution.

Most reports provided general information on the confiscated Medicrime medicines. Little information was received on the nature of the criminal manipulation, therapeutic claims, dosage strength, or possible user groups. The UK and Switzerland also provided substantial data on seized Medicrime devices. Because of the enormous diversity in Medicrime devices it was decided to first build experience on identifying health damage caused by Medicrime pharmaceuticals.

3.2.1 *Therapeutic categories*

The submitted data showed that, in terms of packages, six therapeutic categories were confiscated most often by the participating countries (Table 1). Among these are the so-called lifestyle medicines, such as erectile dysfunction drugs and weight loss drugs. However, overall the therapeutic categories ranged from lifestyle medicines to medicines used for treating life-threatening conditions. Food supplements that had been adulterated with pharmaceuticals were classified according to the therapeutic class of the pharmaceutical.

For Pangea III, the label claim for adulterated food supplements and the actual composition were largely not reported. As a result a seventh prevalent therapeutic category is observed ('Adulteration'). However, according to the participating countries in this study, this category largely reflects the six therapeutic categories.

Table 1. The six therapeutic categories confiscated most frequently.

-
1. Erectile dysfunction drugs
 2. Psychoactive drugs
 3. Doping substances
 4. Weight loss drugs
 5. Analgesics
 6. Cardiovascular drugs
-

3.2.2 *Quantities*

The data received for Pangea III showed that the six therapeutic categories described in Table 1 were reported by 25-50% of the 44 countries. In terms of dose units it showed that vast majority of the 6 therapeutic categories (75-90%) were confiscated by 34% of the participating countries. About 800.000 dose units were confiscated for these six therapeutic categories on a total of 2.000.000 confiscated dose units.

Because the Pangea III data was often not supported by analytical verification of the labelled composition (such as carried out by the OMCL network of the EDQM), this dataset does not permit assessing health risks.

The Pangea III dataset shows the following:

1. The vast numbers of confiscated dose units underscore that Medicrime is a health threat. The number of confiscated dose units represents a fraction of what is on the market.
2. Regional differences are found in the confiscated therapeutic categories. This may reflect not only operational differences, but also differences in demand due to health-care systems and societal factors.
3. The six therapeutic categories that were confiscated most often represent only about 40% of the total dose units confiscated. These therapeutic categories comprise *inter alia* the common lifestyle medicines (Figure 1).
4. The sum of all minor therapeutic categories represents 60% of the confiscated dose units, comprising medicines for treating serious illnesses (Figure 1).

Consequently, a high diversity must exist among the 'other' therapeutic categories and they should not be ignored as a health threat both in terms of volume and in terms of types of medicine. How this applies to the situation in European countries, could not be derived from the available data.

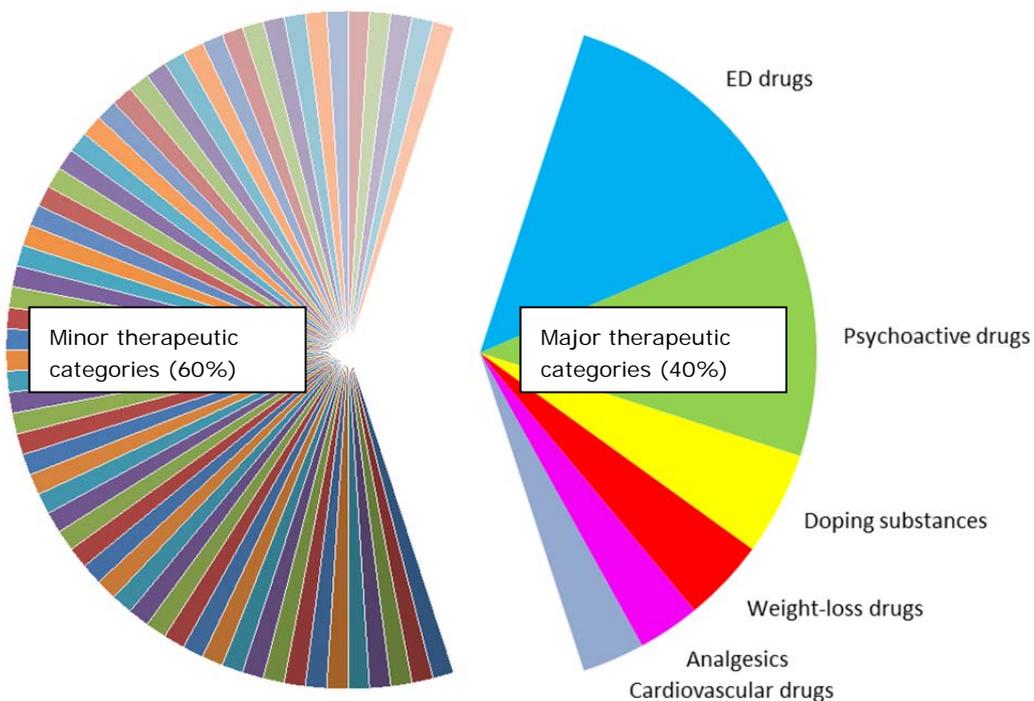


Figure 1. Impression of the amount of dose units confiscated for the therapeutic categories in Pangea III. Left: small quantities of myriads of minor therapeutic categories (60%). Right: the six major therapeutic categories (40%).

3.2.3 *Destination*

According to the information on Pangea III, postal shipments destined for Europe containing Medicrime pharmaceuticals contained 292 dose units on average. In addition, about 55% of these shipments contained more than 100 dose units. Because such quantities are regarded as shipments intended for commercial use, over half of the addressees do not concern the end user. There is no information on resale being domestic or international.

3.2.4 *Regional differences*

Considerable differences were observed between countries as regards the therapeutic categories of the confiscated medicinal products. This reflects both differences in national consumption and operational differences between the national enforcement agencies. Nevertheless, future studies need to take into account that health damage may differ from one country to another.

3.2.5 *End users*

No specific information was available on the possible user groups, so clearly more research should be done into this area.³⁵

3.3 **Expert meeting**

Most specialist (medical) doctors were not familiar with the issue of Medicrime pharmaceuticals and considered it of little importance for their daily practice. The results described in sections 3.1 and 3.2 were used to start the discussion on ways to develop an effective approach to identify health damage. The discussion dealt with three key areas: clinical symptoms, quality of anamnesis and reporting/references.

3.3.1 *Symptoms*

The participants agreed that the expected general clinical symptoms for the prevalent confiscated medicines were cardiovascular events, psychic/mental events, and drug ineffectiveness (Table 2). It was advised to draw up a detailed list of specific adverse effects for common Medicrime pharmaceuticals.

Table 2. General symptoms for the prevalent therapeutic categories.

ED drugs	Priapism, blood pressure changes, sudden hearing loss, visual disturbances
Psychoactive drugs	Hallucinations, suicidal tendencies
Doping substances	Mood swings, prostate cancer
Weight loss drugs	Palpitations, psychosis, suicidal tendencies
Analgesics	Sedation, drowsiness, orthostatic hypotension
Cardiovascular drugs	Palpitations, myocardial infarction

Four root causes of harm were identified (Table 3). The intended effects of an Medicrime medicine are harmful for a person unsuited for treatment (e.g. a healthy person, allergies present, drug-drug interactions). The unintended effects are harmful because there is something wrong with the product. Table 3 shows the general clinical symptoms associated with the root causes.

Table 3. Root causes of harm caused by Medicrime pharmaceuticals in Europe.

Root cause	Harm
User unsuited	Adverse reactions, intoxication, aggravating medical condition.
Overdose	Adverse reactions, intoxication.
Lack of efficacy	Aggravating medical condition.
Toxic effects	Depending on toxic ingredient.

It should be noted that health damage may become apparent through the adverse effects of interacting with prescribed medicines. Further, the effects of toxicity (e.g. impaired renal function) may be found out years after exposure, which makes it virtually impossible to trace back the cause.

3.3.2 *Anamnesis*

The medical specialists pointed out that the use of Medicrime pharmaceuticals did not play a role in anamnesis. Foul play would only be suspected in certain circumstances, such as a series of cases. Therefore, the medical specialists suggested a campaign to raise awareness among health-care professionals about the existence and the scale of this phenomenon. The audience was confident that victims generally would be forthcoming with information when addressed properly.

Deceptively mislabelled medicines and food supplements particularly hamper the identification of health damage. This specifically applies to products with unlabelled active ingredients (e.g. adulterated food supplements). The labelled ingredients on an adulterated food supplement may purposefully be designed to fool clinicians. Health-care professionals may either rule out the product as a probable cause or wrongfully attribute the symptoms to a labelled ingredient. For instance: transient palpitations after drinking instant slimming coffee would generally be ascribed to the labelled caffeine. Consequently, the possible presence of sibutramine would probably not be investigated.

3.3.3 *Reporting*

The medical specialists pointed out that there is a considerable stretch of deliberation between an initial suspicion of a drug-induced complaint and reporting to Pharmacovigilance. The preparedness to report suspect cases is inhibited by the required amount of paperwork and the desire to obtain some evidence first. In addition, when a victim responds to treatment well, the sense of urgency to investigate and report dwindles.

Further, Pharmacovigilance is perceived as an organization that records adverse events caused by legitimate medicines after normal use. Therefore, cases involving unlicensed medicines (e.g. adulterated foods) would probably not be reported. Suspect intoxications may be reported to the National Poisons Information Institute for obtaining treatment options. However, such inquiries were said to be in decline, as the local toxicology departments gradually take on that role.

3.3.4 *Conclusion of the expert meeting*

It was recommended to raise the awareness among clinicians through publishing cases in medical journals.

Pharmacovigilance was considered the logical entity for receiving reports. It was recommended to add a tick-box to the international adverse events reporting form for 'suspect medical product'.

It was recommended to construct a searchable database of suspect product names, their details, and specific clinical symptoms for consultation by health-care professionals. The database should be fitted with a regularly updated watch list.

It was generally acknowledged that hospitals are not forensic institutes and that suspect cases need to be centrally reviewed in order to obtain perspective. The above-mentioned database may provide a suitable platform.

3.3.5 *Anamnesis formula for clinical use*

Figure 1 suggests that the bulk of health damage is expected from highly-diverse therapeutic categories. Because this would generate small pockets of diverse health damage, it is likely to remain concealed under the current circumstances. Therefore, the key to the identification of health damage was to sift out patients susceptible to health damage by Medicrime from the general population.

It was considered very important to incite patients into self-reporting by clearly not criminalising them. In that context, the Council of Europe Convention on counterfeiting of medical products and similar crimes involving threats to public health (Medicrime Convention) provides a basis for harmonised terminology in this domain. Harmonisation is an indispensable prerequisite for obtaining valid information/data for identifying signals of health damage.

The Committee of Experts CD-P-PH/CMED developed a protocol in the form of a preliminary anamnesis form supported by an up-to-date watch list of Medicrime products with chemical analytical data, associated clinical symptoms (ATC4-5 level) and selected anamnestic questions. The anamnesis form consisted of two parts: 1) exploratory (non-blaming) questions to be answered by the patient, and 2) an evaluation form to be filled out by the health-care professional. The supporting material was derived from the OMCL database of suspect products.

A pilot study will need to evaluate the utility of the anamnesis form, supporting material, and reporting tools. An outline of the anamnesis form is presented in Appendix 1. Although the tool developed in this exploratory study was based on information on Medicrime pharmaceuticals only, the projected pilot study will attempt to cover Medicrime pharmaceuticals and Medicrime devices. Pending their evaluation in the pilot study, the preliminary forms and supporting material remain confidential.

4 Conclusions and recommendations

Scientific literature worldwide shows very few publications on health damage caused by Medicrime pharmaceuticals in developed countries. The prerequisites for being recognized were outbreaks of serious unexplained medical conditions.

The submitted data on Medicrime pharmaceuticals indicates that European authorities primarily confiscate six therapeutic categories; ED drugs, psychoactive drugs, doping substances, weight loss drugs, analgesics, and cardiovascular drugs. Nevertheless, the Pangea III data indicates that the less prevalent therapeutic categories should not be ruled out as a health threat in terms of volume and type of medicine.

Because of the operational differences between agencies and the possibility of international resale, the differences in confiscated therapeutic categories cannot be ascribed to differences in consumption alone.

The health damage caused by Medicrime products is concealed by their deceptive presentation, the variability in quality defects, and the diversity in Medicrime products. Accurate data on the exposure (types of medical products, criminal manipulation, and prevalence on the legal/illegal markets) is lacking.

Only part of the harm incurred by Medicrime products will result in a health complaint to a health-care professional or in abnormal clinical test results. This subsection of harm needs to be recognized amidst a bulk of similar complaints caused by prescribed legit medicines, ageing and disease. Finding health damage relies on the awareness among health-care professionals, the availability and sharing of information, the quality of anamnesis, and facilitating a simple reporting procedure.

The current Pharmacovigilance systems seem not yet adapted to deal with Medicrime products. Therefore it is essential to increase the awareness of health-care professionals and provide them with specific tools and data.

The particularly vulnerable population will consist of those that are unsuited for treatment. Overall, there is insufficient information for pinpointing specific user groups.

The following is recommended:

Health authorities should actively approach the medical community to raise awareness among health-care professionals.

Health authorities should provide a platform for clinicians to search and share information on suspect products, the associated symptoms, and unexplained suspect cases.

Health authorities are advised to accommodate Pharmacovigilance as the natural authority for reporting health damage caused by Medicrime products.

Reporting should be facilitated by a multi-country effort by having a tick-box added to the international adverse events reporting form for 'suspect medical product'.

Use the developed protocol to carry out a pilot study with a selected group of enthusiastic health-care professionals. International studies based on standardised terminology and harmonised working methods are encouraged, such as the projected pilot study by the Committee of Experts CD-P-PH/CMED, coordinated by the EDQM (Council of Europe).

References

1. Kelesidis, T.; Kelesidis, I.; Rafailidis, P.I.; Falagas, M.E., 'Counterfeit or substandard antimicrobial drugs: A review of the scientific evidence', *Journal of Antimicrobial Chemotherapy* 60 (2007), 214-236.
2. Akunyili, D.N.; Nnani, I.P.C., 'Risk of medicines: Counterfeit drugs', *International Journal of Risk and Safety in Medicine* 16 (2004), 181-190.
3. Kawaguchi, T.; Harada, M.; Arimatsu, H.; Nagata, S.; Koga, Y.; Kuwahara, R. et al., 'Severe hepatotoxicity associated with a N-nitrosufenfluramine-containing weight-loss supplement: report of three cases', *J Gastroenterol Hepatol* 19 (2004), 349-50.
4. Lau, G.; Lo, D.S.; Yao, Y.J.; Leong, H.T.; Chan, C.L.; Chu, S.S., 'A fatal case of hepatic failure possibly induced by nitrosufenfluramine: a case report', *Med Sci Law* 44 (2004), 252-63.
5. Nakadai, A.; Inagaki, H.; Minami, M.; Takahashi, H.; Namme, R.; Ohsawa, M.; Ikegami, S., '[Determination of the optical purity of N-nitrosufenfluramine found in the Chinese slimming diet]', *Yakugaku Zasshi* 123 (2003), 805-809.
6. Tang, M.H.Y.; Chen, S.P.L.; Ng, S.W.; Chan, A.Y.W.; Mak, T.W.L., 'Case series on a diversity of illicit weight-reducing agents: From the well known to the unexpected', *British Journal of Clinical Pharmacology* 71 (2011), 250-253.
7. Wu, M.; Wang, J.; Wang, S.; Lu, J.; Zhang, Y.; Liu, X.; Zhang, H., 'Identifying N-nitrosufenfluramine in a nutrition supplement', *J Chromatogr Sci* 43 (2005), 7-10.
8. Yuen, Y.P.; Lai, C.K.; Poon, W.T.; Ng, S.W.; Chan, A.Y.; Mak, T.W., 'Adulteration of over-the-counter slimming products with pharmaceutical analogue--an emerging threat', *Hong Kong Med J* 13 (2007), 216-20.
9. Adachi, M.; Saito, H.; Kobayashi, H.; Horie, Y.; Kato, S.; Yoshioka, M.; Ishii, H., 'Hepatic injury in 12 patients taking the herbal weight loss AIDS Chaso or Onshido', *Ann Intern Med* 139 (2003), 488-92.
10. Kawata, K.; Takehira, Y.; Kobayashi, Y.; Kitagawa, M.; Yamada, M.; Hanajima, K. et al., 'Three cases of liver injury caused by Sennomotokounou, a Chinese dietary supplement for weight loss', *Intern Med* 42 (2003), 1188-92.
11. Lai, V.; Smith, A.; Thorburn, D.; Raman, V.S., 'Severe hepatic injury and adulterated Chinese medicines [8]', *British Medical Journal* 332 (2006), 304-305.
12. Guerrini, M.; Beccati, D.; Shriver, Z.; Naggi, A.; Viswanathan, K.; Bisio, A. et al., 'Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events', *Nature Biotechnology* 26 (2008), 669-675.
13. Guerrini, M.; Shriver, Z.; Bisio, A.; Naggi, A.; Casu, B.; Sasisekharan, R.; Torri, G., 'The tainted heparin story: An update', *Thrombosis and Haemostasis* 102 (2009), 907-911.
14. Kishimoto, T.K.; Viswanathan, K.; Ganguly, T.; Elankumaran, S.; Smith, S.; Pelzer, K. et al., 'Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System', *N Engl J Med* (2008).
15. Ramacciotti, E.; Wahi, R.; Messmore, H.L., 'Contaminated heparin preparations, severe adverse events and the contact system', *Clin Appl Thromb Hemost* 14 (2008), 489-91.

16. Chan, T.Y.K., 'Outbreaks of severe hypoglycaemia due to illegal sexual enhancement products containing undeclared glibenclamide', *Pharmacoepidemiology and Drug Safety* 18 (2009), 1250-1251.
17. Low, M.Y.; Zeng, Y.; Li, L.; Ge, X.W.; Lee, R.; Bloodworth, B.C.; Koh, H.L., 'Safety and quality assessment of 175 illegal sexual enhancement products seized in red-light districts in Singapore', *Drug Saf* 32 (2009), 1141-6.
18. Poon, W.T.; Lam, Y.H.; Lee, H.H.; Ching, C.K.; Chan, W.T.; Chan, S.S. et al., 'Outbreak of hypoglycaemia: sexual enhancement products containing oral hypoglycaemic agent', *Hong Kong Med. J.* 15 (2009), 196-200.
19. Chaubey, S.K.; Sangla, K.S.; Suthaharan, E.N.; Tan, Y.M., 'Severe hypoglycaemia associated with ingesting counterfeit medication', *Med J Aust* 192 (2010), 716-7.
20. TGA 2012, <http://www.tga.gov.au/safety/alerts-medicine-ultra-men-120829.htm>.
21. TGA 2012, <http://www.tga.gov.au/safety/alerts-medicine-rock-hard-120829.htm>.
22. Blachut, D.; Siwinska-Ziolkowska, A.; Szukalski, B.; Wojtasiewicz, K.; Czarnocki, Z.; Kobylecka, A.; Bykas-Strekowska, M., 'Identification of N-desmethylsibutramine as a new ingredient in Chinese herbal dietary supplements', *Problems of Forensic Sciences* 70 (2007), 225-235.
23. Davies, B., 'Dangerous drugs online', *Australian Prescriber* 35 (2012), 32-35.
24. Muller, D.; Weinmann, W.; Hermanns-Clausen, M., 'Chinese slimming capsules containing sibutramine sold over the Internet: a case series', *Dtsch. Arztebl. Int.* 106 (2009), 218-22.
25. Binbay, T., '[Letter to the Editor: First-episode mania with psychotic features induced by over-the-counter diet aids containing sibutramine.]', *Turk Psikiyatri Derg* 21 (2010), 335-337.
26. Vidal, C.; Quandt, S., 'Identification of a sibutramine-metabolite in patient urine after intake of a "pure herbal" Chinese slimming product', *Ther Drug Monit* 28 (2006), 690-2.
27. Jung, J.; Hermanns-Clausen, M.; Weinmann, W., 'Anorectic sibutramine detected in a Chinese herbal drug for weight loss', *Forensic Sci. Int.* 161 (2006), 221-2.
28. Van Hunsel, F.; Van Grootheest, K., '[Adverse drug reactions of a slimming product contaminated with sibutramine]', *Ned Tijdschr Geneesk* 155 (2011), A3695.
29. Chen, S.P.; Tang, M.H.; Ng, S.W.; Poon, W.T.; Chan, A.Y.; Mak, T.W., 'Psychosis associated with usage of herbal slimming products adulterated with sibutramine: a case series', *Clin. Toxicol. (Phila.)* 48 (2010), 832-8.
30. Lee, J.; Teoh, T.; Lee, T.S., 'Catatonia and psychosis associated with sibutramine: a case report and pathophysiologic correlation', *J Psychosom Res* 64 (2008), 107-9.
31. Litvan, L.; Alcoverro-Fortuny, O., 'Sibutramine and psychosis', *J Clin Psychopharmacol* 27 (2007), 726-7.
32. Rosenbohm, A.; Bux, C.J.; Connemann, B.J., 'Psychosis with sibutramine', *J Clin Psychopharmacol* 27 (2007), 315-7.
33. Binkley, K.; Knowles, S.R., 'Sibutramine and panic attacks', *Am J Psychiatry* 159 (2002), 1793-4.
34. Taflinski, T.; Chojnacka, J., 'Sibutramine-associated psychotic episode', *Am J Psychiatry* 157 (2000), 2057-8.
35. Koenraadt, R. (2012), thesis, University of Utrecht.

Appendix 1 Anamnesis formula

Doctor-patient conversation

1. What symptoms made you seek medical help? (open question)
 - i. Most pressing?
 - ii. Other symptoms of ill health?
2. What diseases do you actually suffer from? (open question)
3. What medicines do you use? (open question)
 - i. Other products e.g. dietary supplements, vitamins, minerals, herbs?
4. Selected lifestyle questions (associated with the symptoms and medicine products the patient indicates as used)

Doctors' evaluation (confirmation/exclusion)

5. Is the main/other symptom associated reasonably to underlying disease (YES/NO)? (weighted score for reply)
6. Is the symptom (main/other) included in the list of leading symptoms based on OMCL Watch list and related list of expected symptoms (YES/NO)? (weighted score for reply)
7. Could the patient have come into contact with the medicine product in their counterfeit or illegal form?) → refer to **list of selected lifestyle questions** (weighted score for reply)
8. Have such symptoms been described in Pharmacovigilance or scientific literature or in other literature (YES/NO)? (weighted score for reply)

Sum of scores for reply: X
9. Referral for further medical exams to confirm/exclude suspicion of harm by counterfeit medical product: YES/NO
If YES: **result** of further medical exam: suspicion confirmed – YES/NO

AVAILABLE TO PARTICIPATING IN THE STUDY DOCTORS:

APPENDIX 1: WATCHLIST OF COUNTERFEIT OR CRIMINAL MEDICINES

APPENDIX 2: LEADING SYMPTOMS AND APPROPRIATE QUESTIONS

