General European OMCL Network
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Official Medicines Control Laboratories (OMCL)

Market Surveillance of Suspected Illegal Products (MSSIP)

MSSIP005: Illegal Products containing "non-INN" APIs

Summary Report

Scientific advisor: E. Deconinck (Sciensano – Research Institute and National Public Health Institute of Belgium)

Introduction

For the fifth Market Surveillance Study on Suspected Illegal Products (MSSIP005), the General European OMCL Network (GEON) decided to carry out a combined retrospective and prospective study on Suspected Illegal Products containing Active Pharmaceutical Ingredients (APIs) that are not described in the Anatomical Therapeutic Chemical (ATC) classification system – International Non-Proprietary Name (INN) list. Some of the described cases are not related to medicines by presentation and therefore normally fall out of the scope of market surveillance of medicines in Europe.

Scope of study

The participating OMCLs were asked to provide data on any product containing "non-INN" APIs tested in their laboratory between January 2017 and September 2019 and to report the presence and the identity of the API to the EDQM.

It was agreed that any product (medicines, herbal medicines, food supplements, cosmetics, medical devices, etc.) containing "non-INN" APIs (e.g. polypeptides, anabolics, slimming agents) would be in the scope of this study. In the context of this study, "Non-INN" APIs are all analogues of APIs which are part of the ATC-INN list (e.g. PDE-5 inhibitors or anabolic derivatives) as well as research chemicals which did not reach the final stage of development or had not yet been subjected to clinical trials (e.g. selective androgen receptor modulators (SARMs), growth hormone secretagogues).

Products containing APIs included in the ATC-INN list or products sold as street or party drugs were considered out of scope for this study, as well as products containing sibutramine. The latter molecule was excluded since it had been assessed as part of a previous study (MSSIP001).

Sixteen OMCLs volunteered to participate in this programme.

Selection of samples

Results for 1840 samples were reported, although 736 (40%) were excluded from the study for following reasons:

- The identified API is listed in the ATC-INN database. (718 cases)
- The identified API is a natural product, permitted in dietary supplements with no evidence that it has beneficial or toxic effects. (10 cases)
- The identified API is a party drug and the product was not presented as a medicine. (2 cases)
- The identified API is sibutramine, which was excluded from the study, since it was covered in a previous study (MSSIP001). (2 cases)
- The identified API is not in fact an API but a chemical contaminant, probably originating from non-GMP production. (4 cases)

Additional information about the selection of the samples:

Some molecules were excluded from the sample set because they were present in the ATC-INN database. Although several of these molecules are prohibited in some or even the majority of the participating countries, the decision to exclude them was necessary in order to follow one general policy and the fact that the focus of this study was on non-INN APIs, thus, on APIs for which very little or no toxicological and clinical data are available.

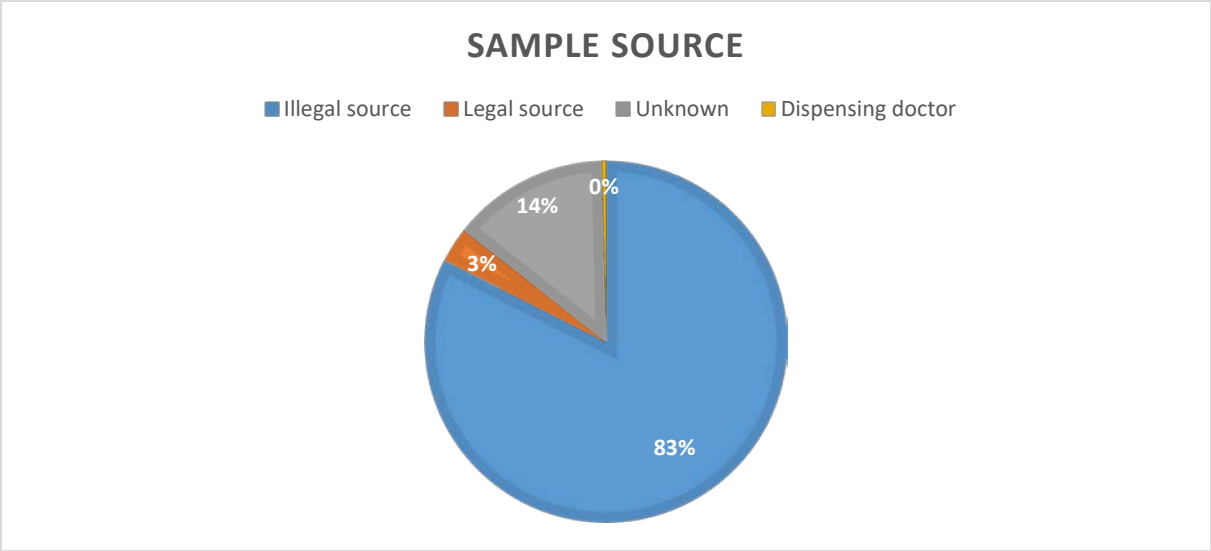
The samples containing methandrostenolone (= metandienone) were excluded from the sample set as the molecule is part of the ATC-INN database. Nevertheless, it is important to note that this molecule is no longer authorised in Europe and the USA, mainly due to side effects such as acne, estrogenic effects (fluid retention and breast enlargement) and liver damage. In total 189 of the samples tested contained methandrostenolone.

It was the same situation for 16 samples containing phenolphthalein. They were excluded as the molecule is part of the ATC-INN database. Phenolphthalein has been used for over a century as a laxative but is no longer marketed due to the carcinogenicity of the molecule.

Concerning testosterone, all its esters are included in the INN list, thus 98 samples containing testosterone esters were also excluded from the sample set.

Origin of tested samples

The majority of the samples were obtained from the illegal supply chain. For about 14% of the samples included in this study, participants could not confirm whether they were obtained from a legal or illegal source.



Overall, the origin of the tested samples was reported as follows:

Targeted police/customs operation	**816**
Unknown	146
Other	78
Commercial shop	24
Postal office	10
Suspect's house	7
Wholesaler	6
Internet	5
Retail pharmacy	5
Industry	3
Race course	2
Body search	1
Prison	1

The vast majority of samples (75%) came from customs and police operations, which is considered logical since these are all illegal products.

Providers of tested samples

The providers of the test samples were reported as follows:

Law enforcement	**870**
Inspectorate	**119**
Customs	**105**
Patient	5
OMCL	2
Unknown	2
Industry	1

This gives more or less the same result as the figures about sample origin. The majority originated from police or other law enforcement investigations and the samples coming from law enforcement, customs and inspectorates together constitute 98.7% of the complete sample set.

Product types of tested samples

The following main product types were reported:

Illegal medicine	**763**
Other	184
Food supplement	98
Unknown	53
Cosmetic	3
Substance	3

Based on these results, we can conclude that the majority of the products containing “non-INN” APIs are sold or presented as medicines. In this case, the patient is aware of taking a medicine, although they probably do not know that for the product in question no toxicological/clinical data are available. Furthermore, 98 samples (9%) were sold as food supplements. In the latter case the patients are not aware that they are consuming a product containing a non-approved pharmaceutical ingredient, which may result in side effects that cannot immediately be related to the product either by the patient or by health professionals.

Dosage form of tested samples

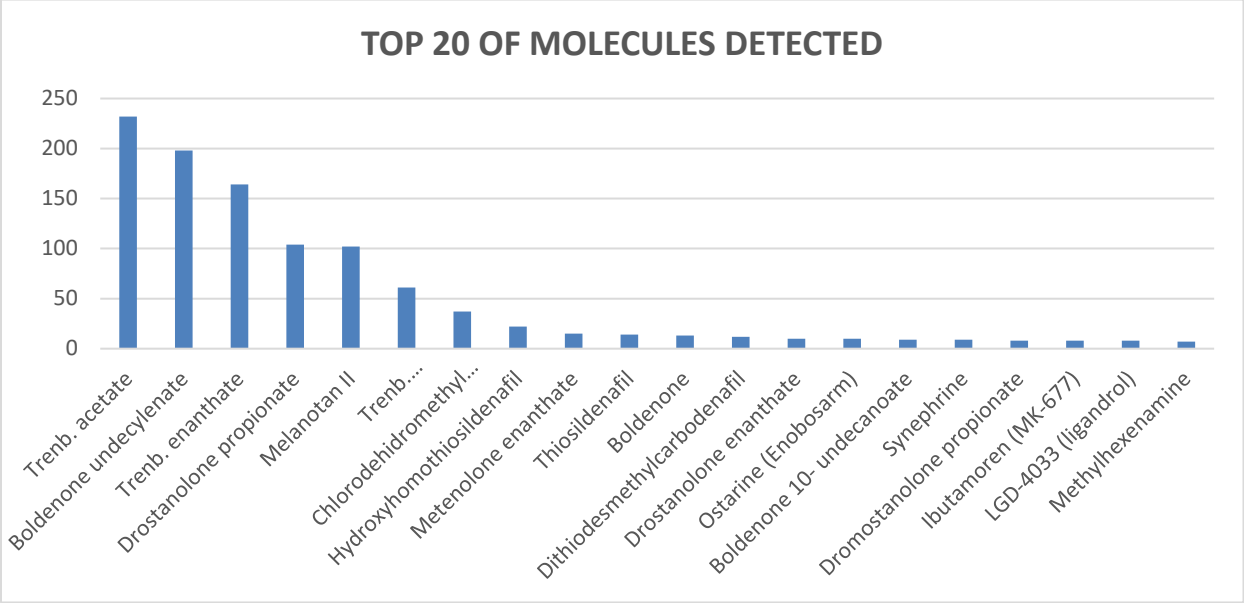
The following dosage forms were reported:

Solution	**709**
Powder	154
Capsules	127
Tablets	108
Lyophilisates	2
Suspension	3
Cream	1

From the table and the figure above, it can be seen that the majority of samples are solutions. This is due to the large number of anabolics present in the data set, which are often applied as solutions for injection. With the exception of the dosage form “powder” which is often related to “powder for injection”, the other pharmaceutical forms reflect the distribution of dosage forms for non-anabolic molecules.

Detected molecules

In total 120 molecules not present in the INN database were identified. The graph below shows the top 20 molecules found in decreasing frequency of detection.



Legend: Trenb.= Trenbolone

From the figure, it can be seen that the top 4 molecules are the anabolics trenbolone acetate, boldenone undecylenate, trenbolone enanthate and drostanolone propionate. Fifth in the list is the research peptide Melanotan II, a product used mainly for tanning and as a sexual stimulant. Other molecules in the top 20 list are other anabolics as well as three structural analogues of sildenafil (PDE-5 inhibitors), a sympathomimetic agent (synephrine) and three selective androgen receptor modulators (SARMs; ostarine, MK-677 and LGD-4033).

This clearly shows that the "classic categories" of illegal medicines are well represented, even if only non-INN molecules are taken into account. However, the increasing popularity of the SARMs should not be underestimated. What is perhaps more interesting than the molecules themselves are the therapeutic categories detected. The following table shows the different therapeutic classes of detected molecules, together with the frequency with which they were encountered.

Therapeutic category	# identified
Anabolic	928
Research peptide (e.g. Melanotan II)	136
PDE-5 inhibitor	95
SARM	44
CNS drug	31
Nootropic	6
Natural product	6
Slimming agent	6
Prostaglandin	3
Insulin growth factor	2
Antioxidant	1
Industrial component with cell toxicity	1
Nonsteroidal antiandrogen	1
Pesticide	1

The table confirms that anabolics are the largest group identified in this study. After anabolics, the next three most common molecules are research peptides, PDE-5 inhibitors and SARMS. The PDE-5 inhibitors were predictable, although it appears that new categories such as research peptides and SARMS are becoming important in the context of illegal medicines and related products. Another trend is the increase in molecules of biological origin. From the 1104 reports

taken into account in this study, 133 were related to biological molecules. This is more than 10% and deserves more attention from the national authorities as well as the GEON.

The next categories in the list are the central nervous system (CNS) drugs that have also been found in other studies as an important target group for illegal trading, and the nootropics. Nootropics in illegal medicines are a recent phenomenon and apparently an increasing problem.

Conclusions and perspectives

Illegal medicines or adulterated products containing non-INN active substances are being sold and consumed. In total, 16 OMCLs reported 1104 cases over a period of less than two years. It is therefore reasonable to assume that far more products containing non-INN active substances are illegally circulating on the European market.

In all, 83% of the tested products were sampled from illegal sources, the majority of which were seized during targeted police or customs operations. Only 3% of the samples were taken from the legal market.

Furthermore, 68.7% of the tested samples were presented as medicines and could therefore be classified as illegal medicines. It is also important to note that 9% of the samples were presented as food supplements, meaning that the patient/consumer is not aware that they are taking a medicine and therefore adverse effects might not immediately be linked to the food supplement, either by the consumer or by health professionals. This represents a real danger to consumer health, in particular as these illegally added substances can interfere with other medicines or have consequences for the development or treatment of already manifested diseases.

When looking at the reported molecules around 74% could be categorised as anabolics. It seems that the problem of illegally traded anabolics is still significant, bearing in mind that only non-INN anabolics were taken into account in this study. Needless to say that the illegal trading of anabolics is even more important, since for this study testosterone and its esters were excluded as they are covered by the INN database.

Surprisingly, the second most encountered category in this study was research peptides at around 11%. These are peptides sold as research products claiming different effects and health benefits, but for which no clinical tests have been performed or for which clinical studies failed. As no toxicological and clinical data are available and these products are often for parenteral use, these products represent a potential increased health risk for the users.

Non-INN analogues of PDE-5 inhibitors were also detected, representing 7.6% of all cases.

In addition, an increasing trend in the use of illegal SARMs and nootropics was confirmed by this study. For these molecules, and in general for all molecules encountered in this study, there are no toxicological and clinical data available or they failed clinical trials. All products of this study can therefore be categorised as posing a high risk to users.

It should be stressed again that this study only takes into account non-INN molecules. There is also the problem of illegal medicines containing active ingredients that have been withdrawn from the market due to the risks they represent. The adulteration of food supplements with INN molecules was shown in the previous study MSSIP004. This study also shows that the adulteration of food supplements with medicines withdrawn from the market (e.g. phenolphthalein and yohimbine) is a supplementary issue that needs attention.

Therefore, continuous efforts are needed to control and screen illegal and suspect products for their composition. The results of this study should be used to raise awareness among the public and the policy-makers regarding the danger posed by these products and, in more general terms, to raise awareness and discourage the purchase of medicinal products or food supplements from suspicious websites that are not reputable or that conceal their physical identity.

Since in this study 138 cases (12%) concerned active ingredients of biological origin, a future MSSIP could focus on biologicals. Another topic for a future study could be illegal SARMs and/or nootropics which are apparently on the rise.