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# EDITORIAL
# The evolution of the illegal market of falsified medicines and the experience of the Italian OMCL: from control to research

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Health risks due to low-quality or falsified drugs are a major concern for regulatory pharmaceutical authorities throughout the world.

Falsification of medicines is not limited to developing Countries, but is a global health problem [1, 2], mainly due to the increasing medicines sale through illegal markets (including gyms, sexy-shops, ethno-shops and illegal Internet pharmacies). To prevent the trade of falsified medicinal products through the legal supply chain, the EU Authorities developed specific legislative instruments, in particular the European Directive 2011/62/UE. The Directive also regulates the market of legal medicines through Internet by indicating the obligations of legal on-line pharmacies, for instance the obligation of exhibiting a "common logo" in each page of the web-site devoted to medicines sale [3].

The Community Directive is incorporated into the Italian Legislative Decree No. 17, February 19, 2014 which prohibits the sale at a distance of under-prescription medicinal products. Concurrently, a National Anti-Falsification task-force involving the Italian Medicines Agency (AIFA), the Italian National Institute of Health (Istituto Superiore di Sanità, ISS), the Ministry of Health, the Police Force "Carabinieri NAS", and the Customs and Monopolies Agency was established; the National task-force also benefits from the cooperation of other involved Ministries and from the support of the Italian Patent and Trademark Office of the Ministry of Economic Development [4].

In Italy, the first case of falsified medicines from the illegal market was analyzed by the Official Medicines Control Laboratory (OMCL) of the ISS in 2005. At the beginning the seized samples were mainly anabolic steroids and medicines for the treatment of erectile dysfunctions [5-7] but, successively, the illegal market modified its characteristics and evolved into "medicines in disguise", i.e. dietary supplements, cosmetics, medical devices and other products for health, fraudulently added with undeclared pharmaceutical active substances. In particular, the problem regards dietary supplements adulterated with synthetic drugs which increase their physiological effects. In most cases, adulteration regards sexual performance enhancers, body-building or athletic performance enhancers, nootropics and weight-loss supplements [8, 9]. Among the adulterants we found registered pharmaceutical substances but also drugs withdrawn from the market (as the anorectic sibutramine in plant food supplements) and even new chemicals of unknown toxicity. A very recent review [10] lists 80 new chemicals mimicking approved phosphodiesterase-5 inhibitors – PDE5-i (sildenafil, vardenafil, tadalafil) detected in illegally marketed sexual performance enhancers. Most of them are chemical products reported in Patents, but never approved for pharmaceutical use, while others are entirely new chemical entities; in both cases they show only minor differences in respect to an original patented molecule (analogues). The use of analogues as adulterants is a strategy adopted by many illegal laboratories, as the modified structures could deceive some analytical tests of the official laboratories of control.

New chemical substances are a great risk for consumers, as physiological effects, side effects and toxicity are unpredictable and outcomes can be very serious; cases of lethal consequences have even been reported [10].

Tracking new molecules constitutes a major challenge for OMCLs, whose activity cannot be limited to the identification of known chemicals in the illegal samples (usually by means of reference standards or spectral databases), but must be extended to the identification and structural characterization of unexpected chemical entities. In this regard, Mass (MS) and Nuclear Magnetic Resonance (NMR) spectrometry are first choice techniques to achieve a task which is not always straightforward (e.g. reference [10] mentions an example of disagreement between official laboratories about the formula of an adulterant). Chemical synthesis of the hypothesized compound, with the aim of obtaining a

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reference material, can sometimes be decisive for the structural elucidation of the adulterant.

In this scenario, it is fundamental to develop research activities to deal with the evolving challenges of the illegal market. The identification of MS and NMR diagnostic spectral features of a family of compounds is useful for the characterization of chemical analogues in suspicious samples. An example of this activity is the reported contribution of the Italian OMCL [11].

In short, fifteen analogues of PDE5-i, belonging to the sildenafil, acetildenafil and thio-sildenafil families, were synthesized and their high-resolution MS/MS and NMR spectra were compared. The study allowed to identify the fundamental spectral features of the three families of compounds. Mass spectra were obtained with an ESI source in positive targeted MS/MS mode with a Q-TOF instrument. MS data as the fragmentation patterns, the accurate mass and the relative intensities of fragments, are strongly related to the specific families and to the specific substituent within the family, becoming a predictive tool of the structure. NMR spectra gave a complete unambiguous characterization of each single analogue even in the case of isomers. It is also of importance the capability of NMR to perform quantification of molecules with no need of specific reference standards [12].

The diffusion of peptides employed for doping and cosmetics in the illegal market, is another main challenge concerning the European OMCLs [13]. These peptides can be substances unauthorized for use in humans, or still in investigational phase or authorized only for pathologies not corresponding to the suggested use in the illegal products advertisement.

In any case, it is important to highlight the constant risk for the consumer of falsified products: in the case of illegal/falsified medicines even if the active pharmaceutical ingredient is present in the correct dosage, unexpected impurities and residual solvents from the illegal manufacturing process and degradation products from uncontrolled storage conditions represent a serious danger for health. The risk is higher for medicines in disguise, because the consumer unawares takes a "bad medicine".

The Italian OMCL analyzed unlabeled vials seized by the Customs and identified different molecules: mannitol (an osmotic diuretic illegally used as a masking agent in doping), the hormone Somatropin, the Growth Hormone Releasing Peptide-2 (GHRP-2) used as a doping agent [14] and Melanotan II, a peptide which is illegally used as a skin tanning agent. In all cases, from the exact molecular formula obtained from high-resolution MS analysis it was possible to confirm the hypothesized structure by both MS/MS and NMR data; quantification and identification were performed without the support of any reference standard or database.

The cooperative application of various techniques based on different physicochemical principles, such as MS and NMR spectrometry, FT-IR spectroscopy and chromatography (GC and LC), is essential for successfully resolving many cases of falsified medicinal products, both medicines very well mimicking the branded product and the new molecules, often contained in unlabeled vials or in "medicines in disguise" [15]. The continuous updating on the new substances found in falsified medicines/dietary supplements and the knowledge of the trend of the illegal market are very important for the resolution of the different cases of falsification. For this purpose, particular attention should also be paid to the Grey Literature, Social Networks, and Body-builders forums to take information on illegal or off-label use of slimming agents, new analogues of PDE5-i and new drugs.

This contribution evidences that an OMCL is not only a laboratory where standard procedures are performed, but also a center where control and research activities are effectively joined to solve non-routine cases. In this context the presence of a chemical synthesis facility is an added value.

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