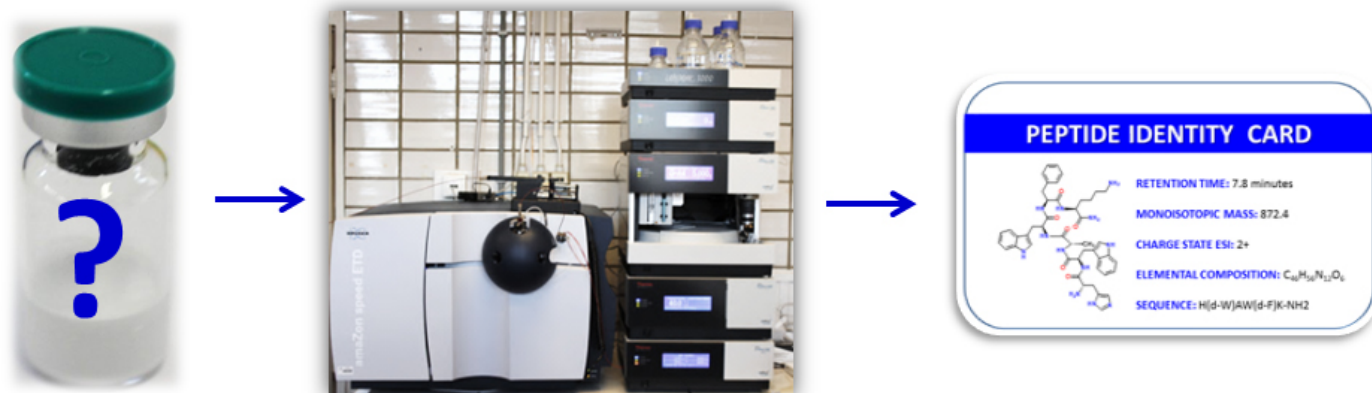


Mass spec: a powerful weapon in the battle against illegal polypeptide drugs



The occurrence of illegal medicines is a well-established global problem and concerns mostly small molecules (Molecular weight below 900 Da), including sildenafil (active pharmaceutical ingredient of Viagra[®] and Cialis[®]) and analogues, anti-biotics, HIV medication, anti-malaria products, anabolic hormones and slimming products. The growing threat of these products is mainly due to the extension of the internet, where about 50% of the medicines sold through internet sites disclosing their identity is estimated to be counterfeit. However, due to the advances in genomics, recombinant expression technologies and peptide synthesis, there is an increased development of polypeptide (= chain of amino acids) therapeutics. Unfortunately the uprising of these kinds of active pharmaceutical ingredients also goes hand in hand with an increase in the number incidents with counterfeited and illegal biopharmaceuticals, including polypeptides that are still under pre-clinical and clinical development. The Belgian Federal Agency for Medicines and Health Products (FAMHP) and customs are striving, together with their global counterparts, to curtail the trafficking and distributions of these substances. Reports originating from Germany, UK, Denmark, Norway, Italy, USA, Australia and Belgium show that potential doping peptides, putative anti-obesity drugs, skin tanning peptides and a putative anti-cancer polypeptide were identified in seized samples. The danger of these illegal polypeptides resides not only in the limited knowledge of their effects and/or side-effects (long and short term), but also in the fact that these polypeptide products are not produced under controlled environment and may therefore contain bacteria, viruses, heavy metals, etc. which could result in severe health issues.



Most of the samples analysed by the different controlling agencies contained lyophilised polypeptides with a molecular mass below 5 kDa (which roughly corresponds to a chain of 45 amino acid) and were upon reconstitution meant for injection purposes. It stands to reason that the battle against these counterfeit and illegal peptide drugs would benefit from a general screening method for the analysis of these polypeptides. To our knowledge, no such full scan screening method, incorporating 25 different peptides encountered or suspected to be used based on the many internet forums, in the different European countries, was reported and validated at the time. In Vanhee et al., 2015 we present such general full scan screening method (not assuming anything about the content that should be present) employing liquid chromatography followed by tandem mass spectrometry (LC-MS/MS) for the identification of counterfeit and illegal injectable peptide preparations. Unfortunately the European and/or United States Pharmacopeia, the holy manuscript for quality control of pharmacological preparations, does not provide any guidelines for a positive identification of these substances. Therefore we applied, for the identification of these peptides, the proposed minimum of five identification points (IP) as was recommended in the past for sports drug (doping) testing applications. Furthermore, we also showed that we could accurately quantify a subset of 10 different peptides representing the peptides identified in our real-life samples and having different retention times, molecular weights and chemical and biological properties by means of ultra high performance liquid chromatography with diode array detection (UHPLC-DAD). The quantification of these peptides is very important for criminal incidents hence the presence of small traces or amounts above 100 µg can affect the outcome of a court case. Furthermore our findings could also be incorporated in a guideline for the correct identification of illegal biopharmaceuticals within the EDQM network (European directorate for the quality control of medicines). Additionally our findings are also added to the Know-X database, a tool which helps data exchange between the other European controlling agencies and their battle against illegal medicine.

Publication

[Analysis of illegal peptide biopharmaceuticals frequently encountered by controlling agencies.](#)

Vanhee C, Janvier S, Desmedt B, Moens G, Deconinck E, De Beer JO, Courselle P
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