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Analysis of pharmaceutical products and dietary supplements seized from the black market among bodybuilders

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Abstract:

Substandard/counterfeit drugs are a growing global problem. According to the World Health Organisation, counterfeit medicines are medicines that are mislabelled deliberately and fraudulently regarding their identity and/or source. In high income countries, drugs seized are mainly represented by performance and image enhancing drugs (PIEDs). The aim of this study was to present the qualitative and quantitative results of toxicological analyses of pharmaceutical and dietary supplements seized from the black market among bodybuilders in France.

All dietary supplements and pharmaceuticals seized from the black market and addressed to the laboratory for a qualitative and quantitative analysis between January 2016 and December 2019 were included in the study. A screening was carried out by gas chromatography-mass spectrometry and liquid chromatography-high resolution mass spectrometry. Identified compounds were quantified by liquid chromatography-tandem mass spectrometry.

One hundred and ten products were seized and submitted to the laboratory for identification of active compounds and quantification: 75 pharmaceuticals and 35 dietary supplements. This included 39 oily and 3 aqueous solutions for intramuscular injection, 34 tablets, 13 capsules, 14 powders, 4 liquids and 3 lyophilizates. Among the pharmaceuticals, 25/75 (33%) were substandard (dosage not on the acceptable range defined for original products), 24/75 (32%) were counterfeit (qualitative formulation does not match the label) and 14/75 (19%) were original (qualitative formulation and levels of active ingredients fully matches the declared formulation). The analysis of the 12 remaining products revealed a correct qualitative content for 11/75 (15%), but quantitation could not be carried out because of the lack of reference standards at the time of the analysis. Fifty-four pharmaceuticals contained anabolic-androgenic steroids (AAS). Four out of 54 (7.4%) AAS were found as original, 8/54 (15%) could not be quantified (one with wrong active ingredient), corresponding to 43/54 (80%) AAS being non-original. In contrast, only 1/35 dietary supplement (3%) was adulterated, with a doping substance (1,3-dimethylbutylamine, DMBA).

This work allows to show that France is not spared by the trafficking of PIEDs. The use of counterfeit drugs in mainstream population is an underestimated public health issue.

Key words: Anabolic Androgenic Steroids; Performance Enhancing Drugs; Doping; Toxicology; Forensics

1. Introduction

Counterfeit drugs are considered by the World Health Organization (WHO) as those which are substandard and falsified, and either fail to meet quality standards or are deliberately manufactured to imitate a legitimate product [1]. They may contain no active ingredient, a wrong active ingredient, the **true** active ingredient associated with other active substances or an incorrect amount of the correct active ingredient. These products can lead to a panel of life-threatening adverse events up to deaths due to therapeutic inefficacy or toxicity [2–4]. Counterfeit drugs affect mainly low income countries with a 10% risk of experiencing this problem, whereas this risk fall to 1% in high income countries [1,5].

As part of the fight against drug trafficking, Interpol organized in 2018 an operation (Pangea) mobilizing police, customs and health regulatory authorities from 116 countries targeting the illicit online sale of medicines and medical products [6]. This operation resulted in 859 arrests worldwide and the seizure of potentially dangerous pharmaceuticals worth more than USD 14 millions. Focusing on delivery services manipulated by organized criminal networks, the operation saw 3,671 web links closed down, including websites, social media pages, and online marketplaces. Almost one million packages were inspected during the week of action (9 – 16 October), with 500 tons of illicit pharmaceuticals seized worldwide. These figures allow us to appreciate the extent of the black market for drugs in the world.

In high income countries, drugs seized are mainly represented by performance and image enhancing drugs (PIEDs). These molecules are taken with the aim of improving athletic performance, body image and as a complement or even substitute for physical exercise. Focus and preoccupation on body image is increasingly common for both genders in recent decades [7]. Use of enhancement drug supplements is reportedly widespread among athletes at all ages and competitive levels [8]. Several analytical studies have been conducted on drugs and nutritional supplement seized on the black market [9–14]. The most common substances found are anabolic androgenic steroids (AAS). In France, only one testosterone ester (enanthate) is still marketed under medical prescription to treat hypogonadism. The multitude of websites selling PIEDs and the low cost offered have led to an explosion in their consumption among mainstream fitness groups or even among people who do not practice sport, and has contributed to an emergent public health issue. The use of such product poses a

health risk to consumers, who have reported harms such as infections at injecting sites when counterfeit or contaminated products are used [15]. Furthermore, chronic exposure to AAS is responsible for many complications: cardiovascular, endocrine, hepatic and behavioral [16].

To our knowledge, no study carried out on the analysis of pharmaceuticals products from the black market has been conducted in France. The aim of this study was to present the qualitative and whenever possible quantitative results of toxicological analyses of pharmaceutical and dietary supplements seized from the black market among bodybuilders in France.

2. Materials and Methods

2.1. Chemicals and reagents

Water, formic acid and methanol (MeOH) were MS grade and provided by Merck (Darmstadt, Germany). All other chemicals were analytical grade and provided by Sigma Aldrich (USA). 1,3-dimethylbutylamine, 4-chlorodehydromethyltestosterone (or turinabol), anastrozole, androstenedione, androstanolone (or dihydrotestosterone), boldenone, boldenone undecylenate, clenbuterol, dehydroepiandrosterone (DHEA), drostanolone propionate, epitestosterone, letrozole, lormetazepam, mesterolone, methandienone, methenolone enanthate, methoxsalen, methyltestosterone, nandrolone (19-nortestosterone), nandrolone decanoate, nandrolone phenylpropionate, nefopam, norandrostenedione, oxandrolone, sibutramine, sildenafil, stanozolol, tadalafil, tamoxifen, testosterone, testosterone-D₃, testosterone benzoate, testosterone cypionate, testosterone undecanoate, testosterone isocaproate, testosterone enanthate, testosterone propionate, testosterone phenylpropionate, testosterone decanoate, testosterone undecanoate, trenbolone enanthate and trenbolone acetate were supplied by Sigma Aldrich.

Methanolic solutions of each standard were prepared from pure powders at a concentration of 1 mg/mL and stored at -20°C. A working solution mixture, containing all the standards at a concentration of 1 µg/mL in methanol, was then prepared from the above-mentioned standard solutions and stored at -20°C. Internal standard solution containing testosterone-D₃ at a concentration of 1 µg/mL in methanol was prepared and stored at -20°C.

2.2. Samples

All dietary supplements and pharmaceuticals seized by the Justice in sport halls and addressed to the laboratory for a qualitative and quantitative analysis between January 2016 and December 2019 were included in the study. Samples were classified as original, counterfeit or substandard, according to the classification suggested by Neves et al. [11]:

Original:

- Qualitative formulation fully matches the one declared on the label
- Levels of active pharmaceuticals ingredients are between 80-130% of the declared formulation

Substandard:

- Qualitative formulation fully matches the one declared
- Levels of active ingredients detected are not **within** the acceptable range defined for original products

Counterfeit:

- Qualitative formulation does not match the label
- Fake packaging, or no indication of the active ingredient included

2.3. Sample preparation

Tablets and granules contained in the capsules were weighed and ground into a fine powder. **Ten milligrams of** powders were solubilized in MeOH to obtain a concentration of 1 mg/mL. The solutions were sonicated for 10 min and centrifuged for 10 min.

Regarding liquid samples, 50 to 100 μ L of aqueous solutions or 20 to 100 μ L of oil solutions were transferred to falcon tubes, and diluted into 10 mL with MeOH. Falcon tubes were vortexed and sonicated for 10 min. When dissolution was not achieved, a first 1/10 dilution in heptane was conducted and then a second 1/10 dilution in MeOH.

Fifty μ L of internal standard working solution were added to all samples prior to **gas chromatography-mass spectrometry** (GC-MS) and **liquid chromatography-high resolution mass spectrometry** (LC-HRMS) analysis. Identified compounds were then quantified by **liquid chromatography-tandem mass spectrometry** (LC-MS/MS) when a commercial

reference standard was available. Peptides and thyroid hormones were identified with [dedicated](#) analytical methods.

2.4. GC-MS analysis

[Samples were analyzed with a simple sample preparation procedure, and no derivatization step.](#) GC-MS analysis was carried out on a Focus GC equipped with a Triplus Duo autosampler and coupled with a DSQ II [single](#) quadrupole all supplied by Thermo Fisher (Les Ulis, France). Separation was performed using an UptiBond 5 (5% phenyl – 95 % dimethylpolysiloxane) column from Interchim (Montluçon, France) (dimensions: l = 30 m, I.D. = 0.25 mm, dF=0.25 µm) with helium as carrier gas at a constant flow of 1.2 mL.min⁻¹. Injection mode was splitless and injector temperature was maintained at 250°C. The GC conditions were as follows: column temperature began at 45°C, was held for 1 min, then increased to 115°C at a rate of 30°C/min, then held at 115°C for 2 min before increasing to 300 °C at a rate of 3°C/min and held 14 min. Total run duration was 56 min. Data acquisition was performed using the Xcalibur v2.1 software (Thermo Fisher, Les Ulis, France). The MS was operated in full scan with a mass range 30-560 *m/z*. Samples were not derivatized and data were processed with RIHunter software (Idecos, France) using three different MS library: N.I.S.T. 17 library, Maurer, Pflieger and Weber v3 and SWGDrug v3.6.

2.5. LC-HRMS analysis

Liquid chromatography was performed on a Thermo Ultimate 3000 (ThermoFisher, Les Ulis, France) pump and separation was carried out on a Hypersil GOLD column (100 x 2.1 mm x 1.9 µm, Thermo, USA) maintained at 40°C. The device was completed with a pre-column (Hypersil GOLD, 10 x 2.1 mm, 3 µm, Thermo, USA). Elution was achieved according to Fabresse et al. method [17], the mobile phase gradient being as follow: 60% A (water/methanol 90/10 with 0.1% formic acid) for 1 min, linear gradient to 100% B (methanol with 0.1% formic acid) in 7 min, held for 5.0 min. The column re-equilibration was performed with linear gradient to 60% A in 3.0 min, held for 3.0 min. The flow rate was set at 400 µL/min. The sample injection volume was 10 µL. Ionization was performed in positive ionization mode by heated electrospray ionization (HESI). Nitrogen (N2-45 nitrogen generator, VWR International, Fontenay sous bois, France) was employed as sheath and auxiliary gas. The source parameters were as follows: ion spray voltage: 3500 V; vaporizer

temperature: 150°C; sheath and auxiliary gas pressure: 45 and 10 arbitrary units, respectively; ion transfer tube temperature: 350°C.

Compounds were detected using an Orbitrap mass spectrometer (Q-Exactive, Thermo, USA). Data were acquired in data dependent acquisition mode according to a previously published method [18]. The masses of precursors and their related fragments ions were measured with a resolution of 70,000 and 17,500 FWHM at m/z 200, respectively, in the range 125-650 m/z . The mass isolation window was 1 m/z . The normalized collision energy (NCE) was set at 55%. Chromatographic data acquisition was performed using Xcalibur software (v.4.0, Thermo, USA). Raw data were processed with Compound Discoverer 2.0 software (Thermo, USA). Exact mass spectra identification was performed with the mzCloud™ data base (<https://www.mzcloud.org/>).

2.6. LC-MS/MS

Quantification was achieved using the same equipment (LC system, chromatographic column) and conditions as those described in the section 2.5. for LC-HRMS. Compounds were then detected with a triple quadrupole TSQ Quantiva mass spectrometer (Thermo, USA) using multiple reaction monitoring (MRM). Argon (Messer, Puteaux, France) was used as a collision gas with a pressure set at 1.5 mTor, Q1 and Q3 resolutions were set at 0.7 FWHM and cycle time 1 s. **Identified analytes were confirmed and quantified by using the corresponding reference standard solutions and product ion scan experiments. The method was validated for quantitation by LC-MS/MS in the range 10-1000 ng/mL according to EMA guidelines [19].**

2.7. Peptide and thyroid hormone analysis

CJC-1295 was analyzed by LC-HRMS according to a previously published method [20]. Human chorionic gonadotrophin (HCG) was quantified on a Siemens™ dimension EXL (Siemens, Munich, Germany) automated system by enzyme-linked immunosorbent assay (ELISA) using an antibody specific for HCG. Dilutions are carried out automatically according to the concentration obtained. The analytical range is from 1 to 1000 international units per liter (IU/L). Triiodothyronine assay was performed on a fully automated ADVIA Centaur CP analyzer (Siemens Healthcare Diagnostics, Munich, Germany). The TSH3-UL assay is based upon a two-site sandwich principle.

3. Results and discussion

During the study period, a total of 110 products were seized [by justice in sport halls](#) and submitted to the laboratory for identification of active compounds and quantification: 35 dietary supplements and 75 pharmaceuticals. The pharmaceuticals included 39 oily and 3 aqueous solutions for intramuscular injection, 30 tablets or capsules and 3 lyophilizates. Dietary products were 17 tablets or capsules, 14 powders and 4 oral liquids.

All the results are detailed in “supplemental table 1”.

All oil based injectables contained AAS esters (n=39). This result was consistent with previous published results [11,12,21]. Steroid esters are widely used by bodybuilders, since they allow a slow release of steroids from the injection site for periods of up to 4 weeks. Two substances should not be found among injectable products: stanozolol and methandrostenolone since they are 17-alpha-methyld steroids, and designed to be taken orally since they did not have a first-pass hepatic effect. However, since they present hepatotoxicity, parenteral form could limit this side effect, but required a daily injection rather than a daily oral intake, which seems more restrictive. Thus, one out of the 6 methandrostenolone-containing products and 2 out of the 4 containing-stanozolol products analyzed in the present study were injectable forms. The two products containing stanozolol were aqueous solution for injection. A third aqueous solution for injection contained nefopam, an analgesic, probably used to reduce pain during or after exercise. Interestingly, this substance did not belong to the WADA list of prohibited substances [22].

Pharmaceutical tablets and capsules (n=30) contained 17-alpha-alkylated steroids (n=12), other AAS like boldenone and DHEA both associated with oxandrolone (n=1), non-steroid anabolic agent like clenbuterol (n=3), anti-estrogens (anastrozole, n=1, letrozole, n=2, tamoxifen, n=1), anxiolytic (lormetazepam, n=2), photosensitizer (methoxsalen, n=1), amphetamine related (sibutramine, n=1), phosphodiesterase-5 enzyme inhibitors (PDE5i, sildenafil, n=1, tadalafil, n=2) and thyroid hormone (triiodothyronine, n=1). No substance was detected in two tablets: clenbuterol 0.02 mg named [Кленбутерол®](#) (clenbuterol) sold [originally](#) by Софарма (Sofarma) and mesterolone 25 mg named Proviron® sold [originally](#) by Bayer.

17-alpha-alkylated steroids, clenbuterol and DHEA are common substances reported to be abused by athletes [23] since they are administered orally. Boldenone does not belong to AAS designed to be taken orally, because it presents a weak bioavailability. Boldenone is

normally a veterinary pharmaceutical marketed as a prodrug (boldenone undecylenate, Equipoise[®]) [24]. Tamoxifen is a Selective Estrogen Receptor Modulator (SERMs). Letrozole and anastrozole are aromatase inhibitors, blocking the transformation of testosterone into estrogen. The athletes could illicitly use SERMs or aromatase inhibitors to increase endogenous testosterone levels, with the aim to by-pass the specific testing regimens for known synthetic androgens including exogenous testosterone, and to balance the feminizing adverse effects of an extensive abuse of AAS [25,26]. Methoxsalen is a pharmaceutical drug marketed under the brand name Meladinine[®], prescribed in several skin diseases (psoriasis, vitiligo, and dermatitis). It is a photosensitizing agent probably used for tanning by bodybuilders, however it provides a high risk of skin burns. PDE5i are usually used by bodybuilders in order to compensate the erectile dysfunction caused by long term use of AAS [26].

CJC-1295 (n=1) and HCG (n=2) were identified in the 3 lyophilisates. CJC-1295 is an analog of growth hormone releasing hormone (GHRH), developed by ConjuChem Biotechnology Inc. (Montreal, Canada) and in its original form, it utilizes a novel bioconjugation technology referred to as Drug Affinity Construct (DAC[™]). A maleimidopropionamide derivative of lysine at the C-terminus allows this compound to bind covalently to albumin in vivo thereby significantly extending its half-life [28]. However, the substance identified in this study is lacking the DAC[™] feature, and should therefore have a shortened half-life [20]. HCG is used in male athletes to stimulate testosterone production and normalize suppressed testosterone concentrations due to prolonged use of anabolic steroids. [29,30]. Analysis of the two samples described as HCG revealed the presence of the hormone at the concentrations indicated on the label.

Among the 75 pharmaceuticals, 25/75 (33%) were substandard, 24/75 (32%) were counterfeit and 14/75 were original (19%). For the remaining 12 products, 11/75 (15%) revealed a correct qualitative content, but quantitation could not be carried out because we did not have the standard at the time of the analysis. The last one had the true active ingredient (4-chlorodehydromethyltestosterone) but was associated with methandrostenolone (not mentioned on the label). According to the qualitative composition of the samples, 51/75 (68%) were accurately labelled, showing the interest in quantification of the compounds in these kinds of studies.

Fifty-four pharmaceuticals were anabolic agents (72%), 22/54 (41%) were counterfeit, 20/54 (37%) were substandard, 8/54 (15%) were not quantified (7/54 were qualitatively

accurately labelled) and solely 4/54 (7%) were original. In most cases, steroid esters were substituted by another steroid ester (e.g. boldenone undecylenate by nandrolone decanoate or drostanolone propionate by testosterone enanthate). Similarly, a steroid ester could be replaced by another ester (e.g. testosterone cypionate substituted by testosterone propionate) (Figure 1).

Several qualitative and quantitative studies have been realized on doping substances seized from the black market, and are summarized in Table 1. The proportion of products accurately labelled varies between 13% and 58.9%. These observations are in accordance with the results of our study, which showed a high-rate of non-original products (at least 25/75 of pharmaceuticals, 66%), and an even higher rate among AAS (at least 80%) seized from the black market among bodybuilders in France. As suggested by Coomber et al., adulteration does occur with substances that mimic or enhance the drug being supplied [31]. These adulterations do not seem to follow a rule, they are probably related to the good availability and low cost of one product rather than another at a given time [21].

Only 1/35 dietary supplement (3%) was adulterated with a doping substance (capsule containing 1,3-dimethylbutylamine, DMBA) in a product named “Thermo Shock” sold by Sci Labs Nutrition. DMBA is an analogue of dimethylamylamine. DMBA has been found in a number of dietary supplements labelled as sport supplements, weight loss supplements, and supplements that claim to enhance brain function [31,32]. The rate of adulterated dietary supplements is very low in comparison with previous studies showing rates over 50 % [11,34–36]. This could reflect an improvement in the quality of the products. However, we cannot exclude the presence of new doping substances absent from the mass spectral libraries used in this study, although this was unlikely given the use of LC-HRMS and on-line libraries.

Most of these products are bought on the internet, and come from South East Asian countries. Fourteen products analyzed in this study were sold by the Pacific Pharmaceutical Company LTD. Malay Tiger. The French Medicines Safety Agency (ANSM) launched an alert [37] in February 2019 regarding two products analyzed in our study (Stanox-10[®] and Clenox[®]) recalling the health risks associated with exposure to these products after the death of an athlete identified by a forensic toxicologist laboratory [38]. The label of the two products mentioned stanozolol 10 mg for Stanox-10[®] and clenbuterol 0.04 mg for Clenox[®]. The forensic laboratory found a dosage of 11.5 mg and 0.073 mg, respectively, while the

ANSM laboratory found 0.6 mg and 0.22 mg on other batches, respectively. In our study, these two compounds contained 6.5 mg and 0.05 mg, respectively, with the same concentration claimed by the label, showing the very important variation of the concentration in the same products over time. Despite this alert, the website remains functional where users can freely continue to buy these products. This underlines the difficulty of the authorities in tracking the trafficking of PIEDs.

4. Conclusion

This study shed light on the issue related to the trafficking of anabolic products in France. The majority of the products analyzed were counterfeit or substandard. Two products were devoid of active substances. The low quality of these products associated with invasive modes of administration (injection) exposes users to risks of acute and chronic toxicity. Regarding food supplements, only one sample was adulterated with DMBA, this proportion is clearly lower than those reported in previous studies. This may reflect an improvement in the quality of the marketed products. Few studies have been carried out on anabolic steroids in France, this work allows to show that France is not spared by the trafficking of PIEDs. The use of DCs in mainstream population is an underestimated public health.

Author statement

All authors have participated to this study and to the writing of this manuscript.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Figure 1. Photography of sample n°55, theoretical content, experimental content and LC-HRMS extracted ion chromatograms of testosterone cypionate ($m/z=413.3050$) and testosterone propionate ($m/z=345.2424$) (ND: not detected).

Supplemental Table 1. Trade name, product type, company, galenic, theoretical content, theoretical amount, pharmacological class, experimental content, experimental amount, classification (NQ: not quantified).

References	Country, Study period, Number of products analyzed	Results
Tircova et al. [37]	Czech Republic and Slovakia, October 2017 to January 2018, N=358	58.9% contained the declared active substances at the declared concentrations, 15.9% no active substances, 16.8% underconcentrated, 4.5% contained pharmaceutical substance different of the label, 3.6% over concentrated
Weber et al. [21]	Switzerland, January 1st 2013 to December 31st 2014, N=1,190	AAS (n=889): <ul style="list-style-type: none"> - 41% accurately labelled - 23% adulterated - 31% substituted - 6% inert Peptide hormones, growth factor-related substances and mimetics (n=146): <ul style="list-style-type: none"> - 66% accurately labelled - 0% adulterated - 5% substituted - 30% inert Hormone and metabolic modulators (n=113): <ul style="list-style-type: none"> - 88% accurately labelled - 4% adulterated - 3% substituted 5% inert
Krug et al. [12]	Germany, 2010 – 2013, N=337	AAS (n=288): <ul style="list-style-type: none"> - 45% accurately labelled - 55% not labelled Others doping and non-doping agents (n=56): <ul style="list-style-type: none"> - 38% accurately labelled - 62% not labelled
Coopman et al. [10]	Belgium, 2012, N=74	33.8% contained other or did not contained the labeled active ingredients -
Pellegrini et al. [38]	Italy, 2012, N=15	13% accurately labelled 53% contained other substances 20% underconcentrated 13% did not contained any substance
Neves et al. [11]	Brazil, 2011-2016, N=328	42.1% counterfeit 11% substandard
Shapira et al. [39]	Israel, 2018, N=113	38.9% had labels misrepresenting content 18% contained other substances

Hullstein et al. [13]	Norway, 2011-2014, N=296	20% did not contained any substances
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Table 1. Published analytical studies carried out on seizures of doping products.