Editorial

Anti-doping testing: a moving target?

Giuseppe Lippi[1], **Camilla Mattiuzzi**[2]

[1]Section of Clinical Biochemistry, University of Verona, Verona, Italy; [2]Service of Clinical Governance, Provincial Agency for Sanitary Services, Trento, Italy

Correspondence to: Prof. Giuseppe Lippi. Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, Verona 37100, Italy. Email: giuseppe.lippi@univr.it.

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On July 2, 2018, the Union Cycliste Internationale (UCI) has confirmed that the four-time Tour de France winner Christopher Froome has been cleared by the allegation of possible doping, notified on a urine sample collected during the Tour of Spain 2017, since the positivity of this specimen was no longer considered an adverse analytical finding (AAF) by the World Anti-Doping Agency (WADA) (1). More specifically, a urine sample collected in September 2017 was originally found to contain a concentration of the beta-2 agonist salbutamol (i.e., a conventional anti-asthmatic drug, which also carries anabolic activities) (2) which was nearly twice as higher than the maximum allowable concentration of 1,000 ng/mL, as currently defined by WADA in its 2018 "Prohibited List" (3). The famous British road cyclist, along with his experts, lawyers and World Tour cycling team, were ultimately capable to demonstrate that this AAF finding was actually compatible with a physiological range of biological variation occurring after inhaling a therapeutic dose of the anti-asthmatic drug, for which Christopher Froome had already provided a valid therapeutic use exemption (TUE) motivated by a long-lasting history of severe asthma. Once corrected for dehydration, the urine concentration of salbutamol was found to be only 19% higher than the WADA decision limit, and hence still comprised within the limit of analytical imprecision of the assay (1). Notably, the validity of the WADA threshold has also been recently disputed by Heuberger *et al.*, who showed that up to 15% of healthy subjects may actually exceed this cut-off after inhaling salbutamol at therapeutic dosage (4). Albeit further discussion as to whether this important pronouncement may be reasonable or justified is outside the scope of this article, some important concerns need to be addressed.

The first and foremost consideration regards the long time usually taken by the competent sport Federations to reach a definitive verdict once an AAF has been notified, since this aspect may have a substantial psychological impact on the alleged guilty subject and on the many other athletes against whom he/she will be competing. Clearly, racing with the sword of ineligibility hanging over the charged athlete may largely influence the results, since no one would be able to know in advance whether the final ranking will be revolutionized by subsequent sanctions. Another important aspect regards the confidentiality that shall be kept until a final verdict of guilt or acquittal can be issued. Against obvious evidence, confidentiality of AAF remains mostly theoretical, since the news typically reaches the public domain much earlier than the WADA, the sport Federations or the same athlete and his/her team can organize a suitable plan for communicating the AAF. The final issue regards the validity of the thresholds currently applied by the WADA in its current 2018 "Prohibited List" for substances such as salbutamol, other beta-2 agonists and ephedrine, for example (3). As for the this recent case, once the concept that these limits are not always valid but may be questioned, and thus even exceeded by some athletes as consequence of permitted drug usage according to individual physiology, metabolism or environmental conditions (i.e., heat, humidity, dehydration, physical effort), a notion which seems now in accordance with the modern concept of precision laboratory medicine (5), one may then argue that providing fixed cut-offs in the WADA "Prohibited List" may be no longer reasonable or advisable. It can be at least concluded that assessing the urine concentration of beta-2 agonists and other TUE drugs in a single urine specimen should not be regarded as a reliable measure of the total pharmacological amount assumed by the individual athlete.

Table 1 Current drawbacks of anti-doping testing

Pre-analytical issues (including biological variation and environmental conditions)
Exploitation of therapeutic use exemption
High expenditure
Long time to reach a final decision
Low confidentiality
Low test predictability
Suboptimal sensitivity for certain doping agents and methods
Long lag phase between introduction of new drugs and development of analytical methods
Gene doping
Poor involvement of laboratory professionals and laboratory medicine organizations

Two alternative solutions can be envisaged, the former entailing withdrawing these agents from the list of banned substances, the latter encompassing abolition of TUE and, thereby, of the relative analytical thresholds. Whenever a concentration of one or more of these substances can be measured, this will be no longer interpreted as AAF but rather as incontestable positivity.

Although we would all agree that anti-doping testing is probably unavoidable for safeguarding athletes' health and preserving fairness in competition (6), the current anti-doping strategy has many drawbacks other than the potential impact of preanalytical issues (thus including biological variation) on the fixed thresholds for drugs subjects to TUE (7,8), as briefly summarized in *Table 1*. Some of these limitations are probably unsurmountable (i.e., high cost, late development of tests for new doping agents and methods), whilst additional efforts should be envisaged to overcome other current caveats, which seem generally more amendable and relatively easier to address. Rethinking the whole anti-doping policy as a continuously moving target, dependent also on human biology rather than simply based on analytical findings, is perhaps the more suitable strategy to preserve sport integrity and safeguarding athletes' reputation in the foreseeable future.

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Footnote

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