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IN THE COURT OF ARBITRATION FOR SPORT

IN THE MATTER OF FLOYD LANDIS,

CAS 2007/A/1394

FLOYD LANDIS V. UNITED STATES ANTI-DOPING AGENCY

BRIEF SUBMITTED BY FLOYD LANDIS

I.

INTRODUCTION

This appeal comes at a troubled time for professional cycling. Efforts to combat doping in cycling are being brought with unprecedented vigor. Appellant Floyd Landis fully supports these efforts and condemns the impact of doping on professional cycling. However, to wrongly strip a champion of his victory due to a flawed test result is much worse than to have an athlete cheat his way to victory. To ensure a fair process and to protect against the travesty of wrongfully convicting a person for an act he or she did not commit, the anti-doping system must strike an adequate balance between the need for accuracy and reliability of laboratory test results and fairness in sport. The rules of the Union Cycliste International ("UCI") and the rules of the International Standard for Laboratories ("ISL") and related technical documents have been developed to create this balance. But, any balance created by these rules is thrown off when the meaning of the rules are tortured to satisfy a pre-determined result. Simply put, to protect the integrity of the adjudicative process, the panel must not mold the ISL and other rules in attempt to avoid addressing evidentiary concerns; rather, the panel must apply the fair, clear, and common sense meaning of the rules to the facts as they are presented. When these rules are so applied, it is clear that the Labaratorie National de Depistage et du Dopage ("LNDD") committed so many critical rule violations and errors in rendering its alleged adverse analytical finding ("AAF") that the results are inaccurate, unreliable and offensive to proper scientific analysis.

This case is staked on the accuracy and reliability of the Gas Chromatography-Combustion-Isotope Ratio Mass Spectrometry test results ("GC/C/IRMS" or "IRMS") for

appellant's sample taken after Stage 17 (Sample 995474) of the 2006 Tour de France.[1] While the GC/C/IRMS is the test hailed as the gold standard for the detection of synthetic testosterone, it is also a complex test that must be performed with precision in order to obtain reliable and accurate results. LNDD's testing methods failed at every step of the way. These errors are not technical – they have resulted in inaccurate and unreliable test results that are an offense to proper laboratory procedure and accurate results. The failures of LNDD's testing procedure are readily apparent in its results. The positive GC/C/IRMS test results of LNDD are inconsistent with the known science and peer-reviewed articles detailing the breakdown of testosterone and its metabolites. This appeal will address each of these errors in detail, but the following is by way of introduction.

First, LNDD failed in a critical and basic step in GC/C/IRMS – ensuring that the test is being performed on testosterone and not something else. The GC/C/IRMS test uses instruments that (1) identify the metabolized compounds of testosterone and then (2) measure the isotopic value of each of those compounds. The body metabolizes testosterone into four different compounds -- Androsterone ("Andro"), Etiocholanolone ("Etio"), 5α-Androstanediol ("5 Alpha") and 5β-Androstanediol ("5 Beta"). These compounds are interchangeably described as "metabolites" or "analytes." The isotopic value is a calculation that identifies whether the source of the testosterone is synthetic or exogenous (pharmaceutical) or endogenous (from the body).

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[1] During the arbitration below, the United States Anti-Doping Agency ("USADA") recognized the many failures of the testing by the Labaratorie National de Depistage et du Dopage ("LNDD") in the screening test, known as the Testosterone-Epitestosterone ("T/E") test. Even the Arbitration Association of America's panel below found that the T/E test results were not accurate or reliable and violated the relevant International Standards for Laboratories ("ISL"). *See* Majority Award. The appeal summarizes the grievous errors committed by LNDD that resulted in the rejected test results at VII. The Results of the GC/MS Test are Flawed, *infra*.

The reason why the GC/C/IRMS measures the isotopic value of testosterone's metabolites as opposed to testosterone is that testosterone is metabolized quickly into its component compounds.

LNDD's own laboratory documentation proves that in this case, testosterone's metabolites were not properly identified, all in violation of the ISL. Because of this failure, it is impossible to know what compounds LNDD actually measured. Given the magnitude of the violation of the particular ISL in this case, it is unknown what LNDD was actually measuring.

Urine is a dirty matrix – a waste matrix that contains many different compounds aside from testosterone. As a result, in order to test compounds in urine – like testosterone's metabolites – those compounds must be separated from all other compounds in the urine with precision. Once separated, they must be identified. The process of identification is made complicated by the particular way the GC/C/IRMS testing process works. At LNDD, it actually consists of the use of two separate instruments, a Gas Chromatography-Mass Spectrometer ("GC/MS") and a GC/C/IRMS. The GC/MS instrument identifies the compounds. The GC/C/IRMS instrument measures the isotopic value, or delta-delta value of those compounds. The GC/MS can not measure isotopic value. The GC/C/IRMS can not identify the compounds. The only common factor between the two tests is that the same compounds should elute at the same time as each other ("retention time") or elute at the same time as each other relative to an injected internal standard ("relative retention time"). In order to "match up" the two test results, a comparison must be made of the "retention time" or "relative retention time" between the two tests – that is how the technician knows that what substance is being measured for isotopic value. WADA TD20034IDCR requires that this occur within a specific and narrow time frame. In actuality, the relative retention time ranged between five and six times the permissible

percentage allowed by the ISL – a 500% to 600% error rate. A closer examination of LNDD's procedures demonstrates clearly why the retention time and relative retention time were so far off – a combination of running the two different instruments under different conditions and different equipment has made it impossible to compare retention times or relative retention times. Again, this is not a "technical" failure that does not impact the test results. Given the ISL violation, if LNDD can not show that it measured testosterone's compounds instead of some other compound, its test results are worse than unreliable, they are a farce.

Second, the failure to properly identify testosterone is just one of many, interrelated errors, all of which are either caused by or are necessitated by each other. The reasons for the failure in identification directly stem from LNDD's incompetence and lack of familiarity with proper GC/C/IRMS technique. LNDD demonstrated its incompetence in every other critical area related to GC/C/IRMS testing. These areas included the failure or absence of quality controls, which render other critical components of the chromatographic and laboratory technique unreliable. This incompetence is related to the poor chromatography produced by the LNDD technicians while operating the GC/C/IRMS instrument, which makes the final delta-delta values completely unreliable. This competence is demonstrated by LNDD's failure to maintain its GC/C/IRMS instrument within its linearity specifications and numerous other instances or examples of situations where LNDD's technicians simply failed to understand the errors they were making or the importance of those errors.

All of these examples of incompetence relate to the improper calculation of the delta-delta value in this case – the calculation that results in the adverse analytic finding in this case. More specifically, the delta-delta value is calculation of the ratio of the carbon 13 ("^{13}C") to carbon 12 ("^{12}C") ratio, as compared to an endogenous reference compound ("ERC"). Pursuant

to LNDD's own internal guidelines, this delta-delta value, if it exceeds -3.0 for any one testosterone metabolite, will establish a positive finding for synthetic testosterone. In greater detail, these examples of incompetence are as follows:

- LNDD failed its own quality control. LNDD injected a substance with a known isotopic value into appellant's samples so as to be able to determine whether its GC/C/IRMS instrument could properly measure its isotopic value. This substance, 5 Alpha AC, also called an internal standard, was measured outside of its target isotopic value in many of the sample fractions. This means, simply, that LNDD's GC/C/IRMS instrument failed to measure isotopic value of a known substance within the known parameters – that it simply was not accurate. This is strong evidence that LNDD could not measure other targets isotopes – including appellant's sample – with any accuracy.

- LNDD had no positive control. A positive control involves the running of a sample of the same matrix as the unknown sample (a urine sample in this case) that is known to contain the metabolites of synthetic testosterone. A positive control thus allows a laboratory the ability to test its own ability to properly measure isotopic value to a target value. However, in this case, LNDD's so called "positive control," Mix Cal Acetate, did not contain three of the four target analytes: 5 Alpha, Pdiol and Andro. Without these three key target analytes, there are no assurances that the IRMS instrument can accurately measure these substances. Accordingly, the target analytes that established the alleged positive finding are not in the so-called positive control. In combination with the failure of its quality control, LNDD created a situation whereby it could not test whether it was correctly measuring isotopic value for a known compound while being completely ignorant of knowing whether it could measure the target compounds with any precision at all.

- LNDD's GC/C/IRMS instrument was not linear. Linearity is the ability of an IRMS instrument to accurately quantify the isotopic ratio of each testosterone metabolite and endogenous reference compound in different samples regardless of their concentration. LNDD failed to keep its instrument linear.

- LNDD produced extremely poor chromatograms in its GC/C/IRMS testing. Good chromatography is the key to reliable IRMS test results and is a requirement of the ISL. LNDD did not comply with the ISL because LLNDD failed to generate chromatograms that avoided interference in the detection of the prohibited substances or their metabolites and markers by components of the sample matrix. Matrix interference was common and clear in the critical chromatograms in this case. Matrix interference and poor chromatography can and will result in dramatic swings in isotopic values. Again, in combination with the poor identification techniques described earlier, LNDD created another completely scientifically intolerable situation. Because it could not identify target compounds using retention time or relative retention time, LNDD simply selected peaks based upon visual inspection. But here, poor chromatography resulted in peaks overlapping on top of peaks with poor separation. As detailed below, using visual inspection to identify compounds from GC/MS to GC/C/IRMS is impossible, but attempting to do so across chromatograms that have matrix interference makes the impossible simply, again, a farce.

- LNDD failed to comply with ISL 3.2 and WADA TD2003LCOC (Laboratory Internal Chain of Custody), which sets forth the requirements of internal chain of custody within a laboratory.

- LNDD did not comply with WADA TD2003LCOC and ISO 17025.4.3.3.3, which prohibit the cross-outs, interlineations and other changes made to the laboratory documents supporting the alleged AAF in this case.

- LNDD's incompetence is also obvious from its lack of familiarity with its own GC/C/IRMS instruments, whereby its staff mischaracterized technical features of the instrument and failed to prepare its GC/C/IRMS instruments for use following receipt by failing to detach packing devices that effect instrument accuracy.

Third, the many examples of incompetence described above forced LNDD technicians to breach their own internal guidelines and rules, to delete and alter data in violation of the ISL and to lie and produce fraudulent documents when confronted with these failures. Simply put, once LNDD committed to mistake, error and incompetence, it had to hide it. Examples of this misconduct includes:

- LNDD failed to run GC/C/IRMS runs in sequence, and instead stopped and restarted them to obtain desired results;

- LNDD violated several ISL provisions that require data entry and record keeping be retained for each analyzed sample when its technicians conducted manual processing. Manual processing is the process by which LNDD's technicians manually adjusted the start and end points of the peaks in the chromatograms and otherwise personally manipulated the GC/C/IRMS instrument with no record of that manipulation. This widespread use of manual processing in this case was necessitated by the poor chromatography in this case.

- LNDD technicians violated the ISL when they deleted relevant data that was obtained during the testing process. LNDD technicians deleted test results they found to be "incorrect" or that "did not correspond" to what they expected to find. In particular, LNDD

technicians deleted test results related to LNDD's quality control steps, including, but not limited to, results from the Mix Cal Acetate and blank urine runs. •

- Lastly, LNDD and USADA, as part of the litigation below, produced numerous false statements and at least one fraudulent document to conceal the errors and omissions described above.

The results of all of these ISL errors and breaches of laboratory protocol are evident in the GC/C/IRMS test results. LNDD's GC/C/IRMS results show a breakdown of testosterone that is inconsistent with both the peer-reviewed literature and the science of testosterone metabolism. In summary, the human body metabolizes testosterone into the four target istopes Androsterone ("Andro"), Etiocholanolone ("Etio"), 5α-Androstanediol ("5 Alpha") and 5β-Androstanediol ("5 Beta") in relatively equal quantities. More importantly, the ratio of ^{13}C to ^{12}C in testosterone should be reflected in these analytes. In other words, if the ^{13}C to ^{12}C ratio indicates that the testosterone was of synthetic origin, then the ^{13}C to ^{12}C ratio of the target analytes should similarly, and in approximately the proportion, show that same origin. Thus, when the delta-delta values of the target isotopes should be consistent with each other, and their values should rise and fall with each other.

In this case, LNDD has declared a positive finding for exogenous testosterone using its GC/C/IRMS test when the delta-delta values were grossly inconsistent with each other. For example, in the B Sample, the 5β-Adiol - 5β-Pdiol value was -2.65‰. The 5α-Adiol - 5β-Pdiol was -6.39‰. The Etiocholanolone – 11-Ketoetio was -2.02‰. The Androsterone – 11-Ketoetio was -3.51‰ (failing to account for measurement of error, which if accounted for, would have meant this was less negative than the -3.0 positivity criteria). The IRMS test results for Sample B show a difference of -3.74 per mil between the 5 Alpha – Pdiol and the 5 Beta – Pdiol value.

Id. These differences are inconsistent with the known metabolism of testosterone – the difference in the delta-delta values is simply too great. Similar inconsistent results appear in LNDD's GC/C/IRMS test results for the testing of other stages from the 2006 Tour de France that LNDD tested in preparation for trial. These other test results had no positive findings in the T/E tests, but nonetheless, LNDD managed to find positive findings for the same samples for the GC/C/IRMS test results. Moreover, the test results were inconsistent with known science because only one testosterone metabolite of four tested outside of the -3.0 range in the B Sample, again which is inconsistent with the known science about the breakdown of testosterone. Other laboratories, such as the U.S. Olympic laboratory have required that at least two metabolites test outside of the -3.0 limit.

From a technical and legal standpoint, this case is about science, and the rules of the ISL and the UCI. Appellant will prove, as he did below, critical scientific errors that directly dispute the accuracy and reliability of LNDD's test results. However, more fundamentally, this case is one of conscience and of the integrity of a adjudicative system. To allow these myriad errors to stand is to validate gross laboratory errors and unreliable results, all with the effect of stripping a champion of his title and destroying a reputation and career. This would be a simple miscarriage of justice.

A. Statement Of Jurisdiction

On September 20, 2007, a three-arbitrator panel of the North American Court of Arbitration of Sport of the American Arbitration Association ("AAA") issued its decision in *USADA v. Floyd Landis*, Case No. AAA No. 30 190 00847 06 (the "Appealed Case"). The panel's decision consisted of a majority opinion finding that the alleged anti-doping rule violation had been established by a comfortable satisfaction (Brunet, P. and McLaren, R.) and a

contemporaneously filed dissenting opinion (Campbell, C.). On October 8 and 11, 2007, Mr. Landis filed his notice of intent to appeal. The Court of Arbitration for Sport ("CAS") has jurisdiction over this appeal pursuant to Arts. 280 and 242 of the UCI Cycling Regulations and R47 of the Code of Sports-related Arbitration ("CAS Code"). This brief is timely filed pursuant to R51 of the CAS Code.

B. Prayer For Relief

1. That the decision of the majority panel in *USADA v. Floyd Landis*, Case No. AAA No. 30 190 00847 06 be reversed;

2. That all allegations of any anti-doping rule violation, and related proceedings, against Appellant be dismissed with prejudice;

3. That Appellant be reinstated as the winner of the 2006 Tour de France and that (1) the classifications and records of the UCI and ASO reflect that Appellant is the winner of the 2006 Tour de France, (2) all UCI ProTour points and standing shall be restored to Appellant and (3) he shall be entitled to collect, retain and receive all other prizes and premiums associated with winning the 2006 Tour de France;

4. That any suspicion, restriction, or prohibition on Appellant's ability to race in any UCI, Olympic, or other associated organization be immediately voided and/or removed;

5. That Appellee shall bear all costs of the arbitration and all the legal fees and costs of Appellant in bringing this appeal; and

6. Such further relief as this Panel may deem necessary to effect the relief sought above.

C. Standard of Review

CAS Art. R57 provides that this is a *de novo* hearing, and that CAS shall review all of the facts and the law. As such, neither the Panel nor the parties are constrained in any way by the evidence that was previously presented; to the contrary, the Panel is entitled to consider new evidence. See H v. FIM (CAS 2000/A/281).

D. The Record From The Appealed Case, Its Previously Filed Exhibits And Testimony

Appellant respectfully requests that the entire record from the Appealed Case be made part of the record in this case. The record includes:

1. The pretrial motions, responses and briefs of the Parties, inclusive of exhibits to those filings;

2. The Interim Awards and Procedural Orders, and accompanying dissents;

3. All briefing filed in conjunction with the arbitration hearing held on May 14 – 23, 2007;

4. Appellant's trial exhibits;

5. Appellee's trial exhibits;

6. The DVD of the hearing;

7. Appellant's Proposed Findings of Fact; and

8. The Final Award and accompanying dissent.

II.

STATEMENT OF FACTS

This case involves the single issue of whether Floyd Landis violated an anti-doping rule based on the testing of Sample 995474 provided after Stage 17 of the 2006 Tour de France.[2] The Adverse Analytical Finding on Sample 995474 rested on the results from two testing methods: the GC/MS test[3] and the GC/C/IRMS test.

A. The Testing Of Sample 995474

The 2006 Tour de France (the "Tour") began on July 1, 2006, and ended on July 23, 2006. On July 23, 2006, Mr. Landis was declared the winner of the 2006 Tour, having won the general classification by 57 seconds.

On July 20, 2006, immediately after Stage 17, Mr. Landis provided a urine sample, Sample 995474, to the Union Cycliste International ("UCI"). Ex. 41, USADA0447. As set forth more fully below, this was one of eight samples Mr. Landis provided during the Tour. Sample 995474 was tested at the Labaratorie National de Depistage et du Dopage ("LNDD").

On July 25, 2006, after receiving allegedly positive test results on both the GC/MS and IRMS tests on the A Sample from Sample 995474, LNDD notified the Conseil de Prevention et du Lutte Contre le Dopage ("CPLD") and the UCI that the A Sample from Sample 995474 displayed an Adverse Analytical Finding ("AAF"). *See* Ex. 24, USADA0188-0199.

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[2] There will be references to testing completed on other Samples provided by Floyd Landis during the 2006 Tour; however, as will described below, these tests cannot provide the basis for any anti-doping rule violation and were performed by Appellee several months after the 2006 Tour as a means of gaining further evidence to be used during the arbitration.

[3] WADA rules require that a GC/MS test for testosterone, also known as the Testosterone/Epitestosterone test or "T/E" be corroborated by other testing method in order to establish an Adverse Analytic finding. *See* Exhibit 49, WADA0011-0021.

On July 27, 2006, USADA notified Mr. Landis of the AAF and commenced prosecution of the Appealed Case. *See* Exs. GDC00001-00003. In its communication to Mr. Landis, USADA indicated that he could either request testing of the B Sample of Sample 995474 or accept the AAF from the A Sample. Mr. Landis refused to accept the AAF and elected to have the B Sample tested. *See* Exs. GDC00004-00005.

Between August 3 and 5, 2006, LNDD tested the B Sample from Sample 995474. Ex. 25, USADA0365-0366.

The GC/MS and IRMS tests performed on the B Sample of Sample 995474 resulted in the alleged AAF at issue here. *See id.*

On August 5, 2006, the UCI notified Mr. Landis, USADA, the Agence Française de Lutte Contre le Dopage ("AFLD") and the media of its findings. *See* Ex. GDC00006.

On September 11, 2006, Mr. Landis filed pleadings before USADA's Anti-Doping Review Board to have this case dismissed. *See* Exs. GDC00007-00022. On September 18, 2006, the Anti-Doping Review Board rejected Mr. Landis's petition and the Appealed Case began. *See* Ex. GDC00023.

B. The Retesting Procedure

During the course of the 2006 Tour, Mr. Landis provided seven urine samples in addition to Sample 995474. Mr. Landis provided those samples at the conclusion of the following stages: Stage 2 (Sample 995642 on July 3), Stage 9 (Sample 994203 on July 11), Stage 11 (Sample 994277 on July 13), Stage 12 (Sample 994276 on July 14), Stage 15 (Sample 994075 on July 18), Stage 19 (Sample 994080 on July 22), and Stage 20 (Sample 994171 on July 23). *See* Ex. 41, USADA0412, 0419, 0426, 0433, 0440, 0447, 0458, 0465.

Each of these seven other samples was tested at LNDD. *See* Ex. 41, USADA0415, 0422, 0429, 0436, 0443, 0461, 0468. All of the A Samples from these other samples resulted in a negative finding on the GC/MS test and, thus, were not reported as an AAF. Accordingly, during the Tour: (1) Mr. Landis was not notified of any issue related to an anti-doping rule violation based on these other samples and (2) no further testing of the B Samples from these other samples was conducted.

Solely in preparation for arbitration, Appellee requested that LNDD test the B Samples of these other samples using the IRMS method. Mr. Landis strenuously objected to LNDD performing the testing of these B Samples because the same methods and procedures that Mr. Landis was challenging would be used, and LNDD had a conflict of interest. Following extensive briefing, the Panel in the Appealed Case permitted LNDD to perform these tests. The IRMS testing of the B Samples from the other samples provided by Mr. Landis during the Tour was commenced by LNDD on April 16, 2007.

The specific results of the retesting are summarized at Exhibit GDC01363. However, in sum, LNDD found that some of the B Samples were allegedly positive for testosterone. Notwithstanding the fact that these samples were previously reported negative for testosterone, at the arbitration, USADA sought to admit these test results as "corroborating evidence" for the alleged AAF in Sample 995474.

C. The Reprocessing Of The Electronic Data Files

As noted above, the AAF for Sample 995474 was based on two different testing methods: the GC/MS and the IRMS. During the IRMS testing process, several data files are created, which are known as Electronic Data Files ("EDFs"). The EDFs contain raw data, which is data before any analysis and interpretation.

Appellant requested that the EDF's be reprocessed because the IRMS test on Sample 995474 was performed on an older instrument, did not have audit capabilities, and, critically, allowed the operator to manually adjust, without any record, two important factors that affect the test results – the background points[4] and the integration of the peaks.[5]

Pursuant generally to the Panel's discovery rulings and, specifically, Procedural Order No. 2, on April 26, 2007, the EDFs from the IRMS test of Sample 995474 were supposed to be extracted from the instrument that performed the IRMS test, the IsoPrime1. Representatives of both Mr. Landis (Dr. Simon Davis and Dr. Will Price) and of USADA (Dr. Larry Bowers and Dr. Jeanine Jumeau), as well as by the Panel's expert, Dr. Francesco Botrè, arrived to observe this extraction; however, they were told that: (1) the EDFs from the IsoPrime1 (the instrument used to test Sample 995474) had already been copied to an archive CD and (2) the original information on the IsoPrime1 hard-drive had been erased.[6] This process involved a third party subcontractor removing the hard disk from the instrument control computer, copying the data and re-formatting the hard disk. This operation was carried out the morning we arrived to obtain the data. Further it did not appear that this followed the normal pattern of backing up the data.

On May 4, 2007, Dr. Botrè and representatives for both USADA and Mr. Landis arrived at LNDD to reprocess, or in other words re-analyze and interpret, the EDFs. Pursuant to

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4 Background is the isotopic value read by the detector when no substance (e.g., peak) is present.

5 Peak integration is accomplished by defining the start and end points of each peak.

6 Also on April 26, 2007, the log files from the IsoPrime2 were copied onto a separate CD. These log files are a record of the testing procedures performed in conjunction with the retesting of the other samples taken from Mr. Landis during the Tour. The log files are Exhibits GDC01056-01075.

directions provided by Mr. Landis's representatives, LNDD technicians performed a series of operations on the EDFs.[7]

The first operation occurred at Dr. Botrè's direction. This operation involved LNDD's attempt to reproduce the original test results using the same processes used, and the same instrument (IsoPrime1), to determine those results. In attempting to reproduce the original test results, LNDD's IRMS technicians used a manual processing technique, which they said they used during the original processing of Sample 995474. Manual Processing includes both: (1) manual adjustments to the background, and (2) manual integration of peaks. Tr. of R. at 1763:1-10. However, despite 22 attempts to do so, LNDD technicians were unable to reproduce the original IRMS test results on the A and B Samples of Sample 995474. The chart showing the number of reprocessing attempts is Exhibit GDC01365. The chart showing the results of the reprocessing is Exhibit GDC01350.

In addition, three other sets of values were obtained using three distinct processes: (1) delta-delta values[8] were calculated using the automatic background subtraction embedded within the software program, (2) delta-delta values were calculated with the automatic background subtraction disabled and (3) delta-delta values were calculated using the Masslynx software

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[7] Because LNDD technicians did not know how to transfer data from the CD onto the computer operating the IsoPrime1, Dr. Davis performed this part of the procedure.

[8] The delta-delta value equals the delta value of the target compound minus the delta value of the endogenous reference compound. The delta-delta value is the value used to determine an AAF and is expressed as the "per mil" value. This will be further explanation below.

loaded onto the IsoPrime2.[9] The chart showing the results of this reprocessing is Exhibit GDC01350.

III.

THE FUNDAMENTAL FAILURE OF THE GC/C/IRMS TEST: COMPLETELY UNRELIABLE IDENTIFICATION OF TESTOSTERONE METABOLITES

A. LNDD'S IRMS Test Results

LNDD's IRMS test results for Sample 995474 were unreliable and cannot be the basis for any anti-doping rule violation. The IRMS test has two different processes, a process to identify a particular substance in a complex solution with thousands of substances, and a process to measure the isotopic value of the substance previously identified. LNDD's IRMS test for Sample 995474 is subject to a fatal flaw: LNDD failed to properly identify the critical metabolites of testosterone as required by TD2003IDCR. Simply put, LNDD has no ability to establish that the substances measured in Sample 995474 were the critical metabolites of testosterone that were in fact supposed to be measured. Moreover, USADA can introduce no evidence to show that the failure to identify critical metabolites, as required by TD2003IDCR, did not cause the Adverse Analytic Finding.

B. The Theory Of The IRMS Test

The theory behind the IRMS test rests on the difference in the molecular structure of naturally produced (endogenous) or synthetically produced (exogenous) testosterone. Testosterone is composed of Carbon, Oxygen and Hydrogen atoms. However, there are several

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[9] LNDD IRMS technicians did not know how to convert the EDFs into data readable by Masslynx. Therefore, Dr. Davis performed this part of the operation. Tr. of R. at 1764:4-10.

isotopes of Carbon, including the stable isotopes ^{12}C and ^{13}C.[10] Testosterone and its metabolites are composed of a mixture of ^{13}C and ^{12}C. The ratio of ^{13}C and ^{12}C, however, in any individual will vary based on its source. For example, synthetically produced testosterone is produced from soy plants, which are particularly low in ^{13}C, also known as ^{13}C depleted, compared to natural testosterone. Thus, a person who uses synthetic testosterone will have testosterone with fewer ^{13}C atoms. In the context of anti-doping, the IRMS instrument measures the ratio of ^{13}C to ^{12}C, also known as the isotopic ratio or isotopic value, in specific metabolites of testosterone, as explained below.

The IRMS test does not measure the isotopic ratio of testosterone – it examines the metabolized products ("metabolites") of testosterone. The IRMS test measures the following four metabolites of testosterone: Androsterone ("Andro"), Etiocholanolone ("Etio"), 5α-Androstanediol ("5 Alpha") and 5β-Androstanediol ("5 Beta"). The following diagram is illustrative:

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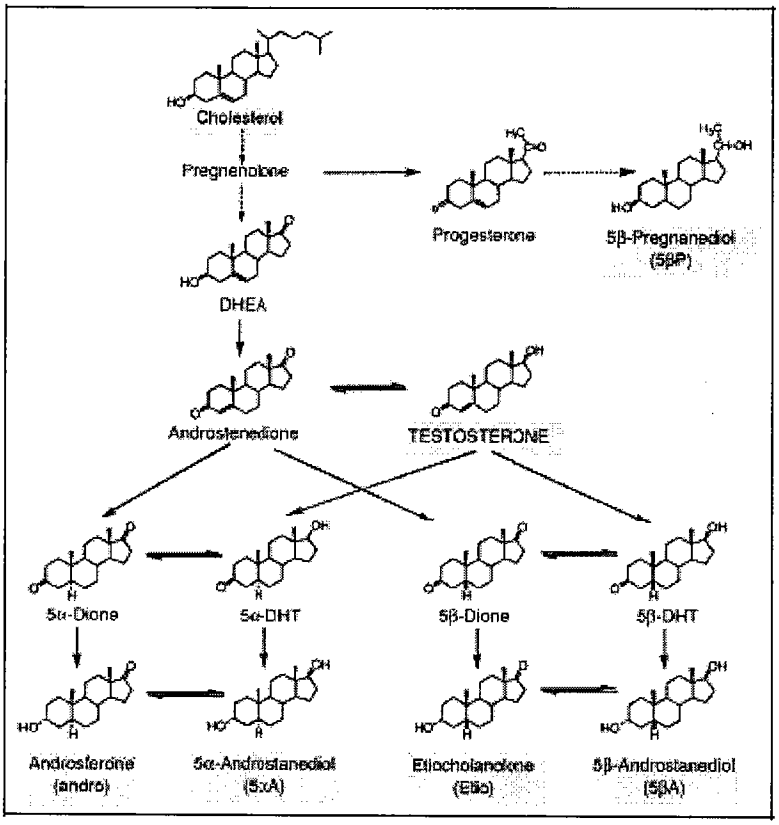
[10] The difference between ^{12}C and ^{13}C is that ^{13}C has one more neutron. Most all carbon on earth is ^{12}C, whereas, approximately 1.1% of all carbon is ^{13}C.



11 **Figure 131. Metabolic pathways of testosterone. From Maitre.** [24]

The carbon framework of the testosterone metabolites will maintain essentially the same isotopic value as the testosterone from which they originated. Therefore, measuring the isotopic ratio of the metabolites is tantamount to measuring the isotopic ratio of testosterone.

There are several individual variables that can cause endogenous testosterone and its metabolites to become ^{13}C depleted that are unrelated to using exogenous testosterone, such as diet. To account for these individual variables, the IRMS test compares the $^{13}C/^{12}C$ ratio of a testosterone metabolite to the $^{13}C/^{12}C$ ratio of an endogenous reference compound ("ERC"). By

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11 Maitre et al., Urinary Analysis of Four Testosterone Metabolites and Pregnanediol by Gas Chromatography–Combustion–Isotope Ratio Mass Spectrometry after Oral Administrations of Testosterone, Journal of Analytical Toxicology, Vol. 28, September 2004, USADA0799.

comparing the difference in the $^{13}C/^{12}C$ ratio between a testosterone metabolite and an ERC, if performed properly, indicate the likelihood of testosterone being from an exogenous source.

In theory, for any individual at any one time the $^{13}C/^{12}C$ ratio of an ERC should be close to that of a testosterone metabolite. If a person is using exogenous testosterone, however, there will be a detectable and significant difference between the $^{13}C/^{12}C$ ratio in a testosterone metabolite and an ERC. In other words, if a person is taking exogenous testosterone, his or her $^{13}C/^{12}C$ ratio for a testosterone metabolite will be different than the ratio for an ERC.[12]

That there is some detectable difference between the $^{13}C/^{12}C$ ratio between the metabolite and the ERC does not result in a positive test, however. Once the $^{13}C/^{12}C$ ratio for the ERC is subtracted from the testosterone metabolite, referred to as the $\delta^{13}C‰$ value or the delta-delta value, it must be compared to the positivity criteria mandated by WADA. The WADA positivity criteria for IRMS is as follows:

> The results will be reported as consistent with the administration of a steroid when the $^{13}C/^{12}C$ value measured for the **metabolite(s)** differs significantly i.e. by 3 delta units or more from that of the urinary reference steroid chosen. In some *Samples*, the measure of the $^{13}C/^{12}C$ value of the urinary reference steroid(s) may not be possible due to their low concentration. The results of such analysis will be reported as

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[12] A good summary of the IRMS theory is provided at Maitre et al., Urinary Analysis of Four Testosterone Metabolites and Pregandiol by Gas Chromotography-Combustion-Isotope Ratio Mass Spectrometry After Oral Administration of Testosterone, 28 Journal of Analytical Toxicology (Sept. 2004).

IRMS allows measurements of slight differences in the carbon isotope ratio ($^{13}C/^{12}C$) of the exogenous and endogenous testosterone. Synthetic testosterone is produced from precursors derived from plants with low ^{13}C content, whereas the ^{13}C and ^{12}C content in the natural endogenous form depends on the isotopic carbon composition of the food in a person's diet and is influenced by additional effects of human biological processing.

"inconclusive" unless the ratio measured for the metabolite(s) is below -28‰ based on non-derivatized steroid.[13]

See Exhibit WADA0011-0021, at 3.

As noted above, there are several metabolites whose isotopic values are measured by the IRMS instrument (Androsterone, Etiocholanolone, 5α-Androstanediol[14] and 5β-Androstanediol[15]), along with the isotopic value of two ERCs (11-Ketoetio and 5β-Pdiol). LNDD in theory identifies and measures all of these metabolites and ERCs. However, the relevant delta-delta numbers are calculated by subtracting the delta value of 11-Ketoetio (ERC) from the delta value of Etiocholanolone and Androsterone (metabolites) and from subtracting the delta value of 5β-Pdiol (ERC) from the delta value of 5β-Adiol and 5α-Adiol (metabolites).

On July 24, 2006, LNDD conducted the IRMS test on Mr. Landis's A Sample from Sample 995474. The delta-delta values were as follows:

Etiocholanolone – 11-Ketoetio	-2.58‰
Androsterone – 11-Ketoetio	-3.99‰
5β-Adiol - 5β-Pdiol	-2.15‰
5α-Adiol - 5β-Pdiol	-6.14‰

On August 3, 2006, LNDD began the IRMS test on the "B" sample. The delta-delta values were as follows:

[13] In the case of LNDD, it has already been conceded that, due to a measure of uncertainty of 0.8‰, the LNDD positivity criteria is a delta-delta value that is more negative than -3.8‰.

[14] Also referred to as 5α-Adiol.

[15] Also referred to as 5β-Adiol.

Etiocholanolone – 11-Ketoetio	-2.02‰
Androsterone – 11-Ketoetio	-3.51‰
5β-Adiol - 5β-Pdiol	-2.65‰
5α-Adiol - 5β-Pdiol	-6.39‰

C. How The IRMS Test Operates

The IRMS test consists of three main steps (1) sample preparation, (2) pre-IRMS compound identification by GC/MS and (3) IRMS analysis. Each one of these steps must be performed properly in order to obtain accurate delta-delta values.

1. Sample Preparation

The IRMS test begins with sample preparation. First, an aliquot is made from the sample; additionally, an aliquot made from blank urine,[16] which is taken from a pool of urine known not to contain synthetic testosterone (it is often the urine pooled from lab technicians). These aliquots are then cleaned through several physical, enzymatic and chemical treatments. The reason for this step is obvious – urine is a waste product, a "dirty" matrix, in which many other substances, in addition to testosterone and its metabolites, will be present. In order to ensure the accuracy of the IRMS results, the sample must be stripped of those other substances so that it is clear that the laboratory is not measuring/analyzing the wrong substances.

The aliquots are then separated into three fractions using further physical treatments. The three fractions created are as follows: (1) the F1 fraction, containing 11-Ketoetiocholanolone (11-Keto), (2) the F2 fraction, containing Etiocholanolone (Etio) and Androsterone (Andro) and

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[16] Additionally, the blank urine aliquot is used during the test as a "known negative" control.

(3) the F3 fraction, containing 5α-Androstanediol (5α-Adiol), 5ß-Androstanediol (5ß Adiol) and 5ß Pregnanediol (5ß Pdiol).

One of the last steps in sample preparation is the addition of an "internal standard." The internal standard, which in this case was 5 Alpha Androstanol Acetate, is a substance with a known isotopic value. It therefore serves as a quality control mechanism (to test whether the IRMS instrument is working properly) and also serves as an anchor to calculate relative retention times, which will be discussed in detail below.

2. The Instrument

As described below, the IRMS test uses two different instruments - the GC/MS instrument and the GC/C/IRMS instrument. Two instruments are needed because neither instrument can perform both the necessary functions to complete the test – identification and measurement. The GC/MS instrument cannot measure isotopic values, it can only identify substances; whereas, the GC/C/IRMS instrument can measure isotopic values, but it cannot identify substances. In some anti-doping laboratories, the GC/MS instrument is attached to, and part of, the IRMS instrument. However, at LNDD, two different and non-attached instruments were used.

3. The GC/MS Analysis: Compound Identification

Once the fractions are prepared, the first phase of IRMS testing – compound identification with the GC/MS instrument – begins.

The GC/MS instrument is composed of two major components: the gas chromatograph and the mass spectrometer. The gas chromatograph is used to separate molecules by sending these molecules through a column, which is essentially a tube coated with complex hydrocarbons. This coating is called the "stationary phase." Based on the interaction of each