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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

DECLARATION OF BRUCE A. GOLDBERGER, PH.D.

I, Dr. Bruce Goldberger, declare and state as follows:

1. I am over the age of 18 and have personal knowledge of the following facts and, if called as a witness, could and would competently testify to them.
2. I am 48 years old, and currently a resident of Newberry, Florida.

I.

QUALIFICATIONS

A. PROFESSIONAL POSITIONS

3. I entered the field of forensic toxicology in 1982 as a bench-level chemist.
4. I worked as an Assistant Toxicologist and Laboratory Manager for the State of Maryland at the Office of the Chief Medical Examiner, as well as a Toxicologist with the National Center for Forensic Science in Baltimore, Maryland.
5. I am currently a Professor and the Director of Toxicology in the Department of Pathology, Immunology and Laboratory Medicine in the College of Medicine at the University of Florida in Gainesville. In addition, I hold a joint Clinical Professor position in the Department of Psychiatry, also in the College of Medicine.
6. I also serve as the Technical and Administrative Director of the Forensic Toxicology Laboratory at the University of Florida, which supports the Medical Examiner's Offices in seven districts throughout the State of Florida. The approximate yearly caseload of this laboratory is 3000 cases. This work involves analysis of human fluids and tissues for presence of over-the-counter, prescription, and illicit drugs. The laboratory also assists the Florida Highway Patrol and the Sheriff's offices throughout the State of Florida in the investigation of drug-related crimes and traffic homicide cases. My laboratory work includes the routine use of the gas chromatography/mass spectrometry (GC/MS).

7. Finally, in addition to providing support to the Medical Examiners' offices, the laboratory provides analytical services for governmental, academic and private organizations.
8. In addition to these academic appointments, I am also the Director of the William R. Maples Center for Forensic Medicine and Program Director for the Florida Emergency Mortuary Operations Response System.
9. My curriculum vitae, attached as Exhibit 1 to this Declaration, contains a complete list of the Professional Positions that I have held over the course of my career.

B. CONSULTING AND RELATED ACTIVITIES

10. During my career, I have been qualified as an expert witness in analytical and forensic toxicology more than 140 times in U.S. federal courts, Florida state courts, Military courts, Canadian courts of law, and Court of Arbitration for Sport arbitration proceedings. My opinion has frequently been sought by local, state and national radio, television and print media, and I have appeared on Good Morning America, CNN, MSNBC, Fox News, Court TV –among other programs, to discuss forensic toxicology matters in the news.
11. Typically, I am called as a State's witness in the prosecution of drug and alcohol cases. Because the lab work at issue in these cases was often conducted at my laboratory, my testimony frequently focuses on the matters at issue here–what techniques and methods were used to support the positive drug or alcohol test, were those techniques performed in accordance with the applicable rules, statutes, regulations, and general scientific best practices, and are they reliable?
12. Since 2006, I have provided consulting services to the National Football League Players' Association on anti-doping matters.

C. EDUCATION

13. I received my Bachelor of Arts Degree in Zoology from Drew University in Madison, New Jersey. I earned both a Master of Science and Doctor of Philosophy degree in Forensic Toxicology from the University of Maryland School of Medicine in Baltimore, Maryland. My curriculum vitae (Exhibit 1) contains a complete educational history.

D. CERTIFICATIONS

14. I am a Diplomate and Vice President-Elect of the American Board of Forensic Toxicology (ABFT), and am certified as a Toxicological Chemist by the National Registry of Certified Chemists (NRCC). I am also a Fellow of the National Academy of Clinical Biochemistry.

15. I have a license to practice as a Clinical Laboratory Director issued by the Florida Board of Clinical Lab Personnel, Department of Business and Professional Regulation.

16. I am certified as a Toxicological Chemist by the National Registry of Certified Chemists, and have in the past been certified as a Forensic Toxicology Specialist, a certification issued by the American Board of Forensic Toxicology.

E. PUBLICATIONS

17. My curriculum vitae, which is attached as Exhibit 1 to this Declaration, contains a current list of my publications. Generally, I have authored and published numerous articles relating to forensic toxicology, and am co-editor of the Handbook of Workplace Drug Testing (AACC Press) and On-Site Drug Testing (Humana Press).

18. Many of my published studies and presentations focus on the isolation of drugs and drug metabolites and the use of mass spectrometry in forensic toxicology laboratories.

19. In addition to authoring my own presentations and studies, I am the Editor-in-Chief of the Journal of Analytical Toxicology. I am also a member of the editorial boards of the Journal of Forensic Sciences and Forensic Science Review.

F. MEMBERSHIPS

20. I am an immediate-past President of the American Academy of Forensic Sciences.

21. I am also a member of the Society of Forensic Toxicologists (SOFT), the American Association for Clinical Chemistry, the California Association of Toxicologists, the Council of Science Editors, International Association for Chemical Testing, National Safety Council's Committee on Alcohol and Other Drugs, and the International Association of Forensic Toxicologists. Of particular note is my participation on the National Committee for Clinical Laboratory Standards' (NCCLS) Gas Chromatography/Mass Spectrometry (GC/MS) Confirmation of Drugs Committee. This committee was responsible for the drafting of GC/MS guidelines in the fields of clinical chemistry and toxicology. While serving on this Committee, I worked with USADA Director, Dr. Larry Bowers, to formulate guidelines for the use of the GC/MS in the testing for the presence of drugs. Since 1995, the National Committee on Clinical Laboratory Standards (now the Clinical and Laboratory Standards Institute (CLSI) has exercised the lead role in managing the work of the ISO's technical committee, ISO Technical Committee 212, charged with focusing on the coordination of international standardization in the clinical laboratory testing field. ISO/TC 212 is responsible for "standardization and guidance in the field of laboratory medicine and in vitro diagnostic test systems."

G. HONORS AND AWARDS

22. In 1988, I was the first recipient of the American Academy of Forensic Sciences Toxicology Section's Irving Sunshine Award.

23. In 1994, I received the American Association for Clinical Chemistry's Outstanding Scientific Achievements by a Young Investigator Award.

24. In 2004, I received the International Association of Forensic Toxicologists' Achievement Award for excellence in forensic toxicology.

25. In 2006, I received the American Academy of Forensic Sciences Toxicology Section's Alexander O. Gettler Award for outstanding contributions to the field and profession of forensic toxicology.

26. I am not being paid for my participation in this appeal. Generally, I would charge for this kind of case and the time I have spent reviewing these materials and testifying. I am participating in this appeal proceeding without any fee because I believe that to uphold an anti-doping sanction on the evidence in this case is a moral and ethical wrong.

II.

OPINIONS

A. INTRODUCTION

27. In preparation for my testimony in this case, I was provided with more than 1500 pages of documents, including the laboratory documentation package prepared by the LNDD. I have also reviewed the accreditation documents for the laboratory. Although initially reluctant to serve as an expert in this case, it was my review of these documents–and my identification of what I consider to be glaring deficiencies in the work done by the LNDD–that convinced me to participate in this case. Of particular importance to me

were the manifest deficiencies in the quality of the chain of custody records and the way that the Testosterone to Epitestosterone test ("T/E test") was performed at LNDD. The work that LNDD performed on Appellant's Stage 17 sample is clear evidence of a laboratory operating with neither validated methods nor the attention to detail needed to ensure that accurate results are being generated. The manifest deficiencies in LNDD's work gives me no assurance that the laboratory results for Appellant's are accurate or reliable. My comments will focus primarily on the issues of laboratory procedure and the flaws in the LNDD's T/E analysis.

B. CHAIN OF CUSTODY

1. Whether they exist in anti-doping labs or forensic labs, chain of custody systems must provide a complete record of every possession and transfer of a sample from collection through final analysis and disposal.

a. Chain of Custody Documentation Format

28. After reviewing the laboratory documents and the arguments made by USADA in its pretrial briefs and its brief in this appeal, I have determined that LNDD does not have a proper chain of custody system in place. Chain of custody is the most important laboratory procedure next to ensuring that the assays performed generate reliable and accurate results. The importance of chain of custody is enhanced when the test results from the samples will be used in a criminal or other disciplinary proceeding. Maintaining proper chain of custody is the best means of ensuring that sample integrity is not compromised.

29. The chain of custody of a sample must be well-documented, or one loses the ability to demonstrate definitively that the results generated can actually be attributed to the

individual involved in the legal proceeding. Thus, the purpose of creating chain of custody documentation is so that an outside observer, be it a judge or an arbitrator, can look at the documentation and be assured that the integrity of the sample has not been compromised. While there are certainly differences among laboratories in how they implement and generate chain of custody documentation, there is but one basic requirement for chain of custody documentation: There must be a link, or "chain," between the people who have handled the sample. In other words, the chain of custody documentation must establish from whom a person received the sample and to whom that person later gave the sample. There must be a sufficient link between people who possessed the sample such that a chain can be formed; i.e., A sample went from Person A to Person B, then from Person B to Person C and so forth until the sample is destroyed. By establishing a link between people who have handled the sample, it is easy to ensure that the integrity of the sample has not be compromised. For example, if the chain of custody documentation only listed the sample going from Person A to Person B, and then from Person B to Person C, with Person C destroying the sample, evidence that Person Z possessed the sample would establish that the chain of custody was broken and the test results from the sample should not be trusted. Likewise, if the chain of custody documentation lists that the sample went from Person A to Person B, but then the next entry indicates that the sample went from Person Z to Person X, the judge or arbitrator will be able to determine that the chain of custody was broken and the sample results are not reliable.

30. An example of proper chain of custody documentation is found by looking at the chain of custody documentation used at the UCLA Laboratory, exhibit GDC0030-31, and at the

Montreal Laboratory, exhibit GDC0032-33. Although the UCLA Laboratory and Montreal Laboratory documentation use slightly different formats and include different information, one constant between the forms is that a link is established between the people who possessed the sample.

31. The necessity of having this link is also required by WADA TD2003LCOC. The technical document requires that a laboratory have a continuous record of individuals in possession of the sample. The requirement of maintaining a continuous record is synonymous with establishing a link between people who have handled the samples.

32. LNDD's chain of custody documentation does not establish this necessary, critical and required link between the people who handle the sample. Remarkably, USADA acknowledges this utter deficiency in LNDD's documentation, but argues that LNDD's chain of custody is still sufficient. This argument is specious, however, as I explain below.

33. LNDD's only chain of custody documentation is a summary sheet that is prepared a significant amount of time after the testing of the sample. And the summary sheet is purportedly recreated using the testing documents contained in the laboratory document packet, similar to that of recreating your activities on a day two months in the past by reviewing your emails. While I will address the deficiencies in how LNDD creates the summary chain of custody documentation later and explain why the summary sheet is not supported by the laboratory documentation, my initial comments will focus on the fact that the summary sheet fails to establish a link between the people who handled Mr. Landis' sample.

34. LNDD's summary chain of custody sheet, Ex. 25, USADA 253-54, simply identifies each person that had custody of the sample individually, e.g., A, B, C, D. The documentation provided by LNDD is more of a "plot of custody" than it is a "chain of custody." As noted above, the proper documentation, and the documentation used by the UCLA Laboratory and the Montreal Laboratory, create a link between the people who handle the sample, e.g., A to B, B to C, C to D.

35. The problems of LNDD's system, and why it should be considered deficient, is best evidenced when analyzed vis-à-vis the purpose of having chain of custody documentation. Since the purpose of having chain of custody documentation is to provide the judge or arbitrator with proof that the sample could not have been altered or tampered with, one must ask what information is conveyed to the judge or arbitrator by LNDD's documentation that provides this assurance. The answer is that LNDD's chain of custody documentation provides absolutely no assurance that the sample integrity has not been jeopardized. By listing each person who had the sample bottle individually, there is no way to for the judge or arbitrator to determine when, where and from whom that person obtained the sample bottle or when, where and to whom the person gave the sample bottle. For example, by simply listing that Person A had the sample at noon and that Person B had the sample bottle at 3:00 o'clock, the judge and arbitrator can not be assured that the sample bottle was not possessed by Person Z at 1:00 o'clock and Person X at 2:00 o'clock. Accordingly, since there is no guarantee that the people on the list were the only people who handled the sample, which is the purpose of having chain of custody documentation, LNDD's chain of custody documentation is deficient. And, since it does not provide a link between the people handling the sample, it is, therefore, in

violation of the technical document's requirement of a laboratory maintaining a continuous record of who had possession of the sample bottle.

36. LNDD's chain of custody documentation requires that the Panel just assume that a person obtained the sample from the person listed above him or her on the summary sheet. However, one should not be forced to make an assumption when reviewing chain of custody documentation. Indeed, the rationale of maintaining accurate and detailed chain of custody documentation is that it alleviates the need to make these assumptions.

37. In its brief, USADA contends that a chain of custody document that provides a link between the people who possessed the sample bottle provides no further assurances against undocumented transfers than the plot of custody method used by LNDD. This argument does not withstand the slightest scrutiny. At the outset, I must note that my testimony that a proper chain of custody document must create a link between people possessing the sample should not be interpreted as a statement that this method provides absolute assurance to a judge or arbitrator that the sample integrity has not been compromised. Like any other control system or method, the chain of custody method is subject to deliberate deception by the laboratory technicians. For instance, even if the chain of custody documentation established a link between the people who possessed this sample, it can fail if the technicians are dishonest and deceptive by not listing the actual person from or to he or she received or gave the bottle. Also, there are some exceptional circumstances that may occur in which the chain of custody method of linking the people who possess the sample fails as well. One of these exceptional theoretical situations is the example provided in Appellee's Brief of when there is an undocumented transfer between Person A to Person C, and then another undocumented transfer in which Person

C transfers the bottle back to Person A, so that when Person A documents a transfer to Person B, it creates a link and masks the undocumented transfer. Nevertheless, this chain of custody documentation at least provides to the judge or arbitrator that absent intentional dishonesty or a unique exceptional circumstance described above, there is some assurance that the sample was not compromised. Comparatively, LNDD's chain of custody documentation is deficient to such an extent that it provides zero assurance, regardless of the situation, that the sample was not compromised.

b. Chain of Custody Method

38. In addition to the fact that LNDD's chain of custody documentation does not establish a link between people who possessed the sample, the method with which the summary chain of custody page is created is unacceptable. LNDD does not maintain a contemporaneous chain of custody record, whether it be in a single form or multiple forms, as required by TD2003LCOC and generally accepted scientific principles. During the AAA proceeding, USADA stated that "LNDD uses multiple separate contemporaneous forms with a summary document prepared at the time the laboratory documentation package is assembled." USADA Pre-Hearing Brief at 16. USADA again made this argument in its appeal brief. Appellee's Brief at 78. However, this statement is misleading. When USADA is referring to "separate contemporaneous forms," based on my review of the documents and my understanding of LNDD's practices, USADA is referring to the laboratory worksheets that are completed by the laboratory technician when a particular task is performed, and will be noted later, some of them are not even contemporaneous. These documents are not created for the purpose of maintaining chain of custody documentation. It is my understanding that several weeks after the tests are

performed, LNDD reviews these laboratory worksheets in attempt to recreate the chain of custody and then drafts the summary page. As I noted above, this process is similar to that of a person attempting to recreate his or her activities in a day one month ago by reviewing the emails and phone records for that day. In light of the importance of the chain of custody documentation, this method of preparing chain of custody documentation is improper and can lead to significant errors.

39. The most obvious deficiency of this method is that the summary page created after the fact will not list the person who had possession of the bottle but did not perform any analytical or other work on the sample, and thus, never completed a worksheet. For example, imagine a situation in which a runner or assistant is used to transfer the sample bottle from one technician to another technician. In other words the sample possession would be from Technician A to Runner, and then Runner to Technician B. However, since this runner or assistant is not actually performing any work with the sample, he or she will likely not complete a worksheet. Therefore, when LNDD weeks later attempts to create a summary chain of custody sheet based on the worksheets, it will not list the fact that the runner or assistant had possession of the sample bottle. Put differently, the summary sheet will not reflect that the runner or assistant had possession of the sample and will only represent that the sample was possessed by Technician A and then possessed at a later point by Technician B. The fact that LNDD's method can lead to this obvious error means that LNDD's summary chain of custody sheet can not be relied upon as being a true and accurate record of who possessed Mr. Landis' sample.

40. LNDD's method of maintaining, or its lack of maintaining, adequate chain of custody documents is also in violation of TD2003LCOC. The technical document requires that

the "entry into the Laboratory Internal Chain of Custody should be completed at the time that any change of possession occurs." In other words, a transfer of the sample must be contemporaneously recorded in some worksheet, logbook, or form with the transferring of the sample. Based on my understanding of the LNDD method, this does not occur. As described above, the technician does not record the transfer of the sample bottle at the time the sample is transferred, the recordation occurs when the technician completes the laboratory worksheet when he or she begins performing work on the sample. Also, using the same example as above, if a runner or assistant is used, there is no contemporaneous document that is completed to represent this transfer.

41. A laboratory's chain of custody documentation methodology is an all-or-nothing system. In order to reap the benefits of a chain of custody, it is necessary to document each transfer, each human possession, and each test that is conducted; documenting only some of these steps compromises the entire chain. LNDD's chain of custody documentation and method do not achieve these benefits.

2. Specific Instances of Summary Document Not Being Supported

42. In addition to the fat that the method in which LNDD creates the summary chain of custody document is improper, contrary to the representations by USADA, the individual laboratory documents do not support the entries made in the summary chain of custody documentation. The discussions below are only some of the glaring unsupported entries in the summary chain of custody document.

43. However, before discussing the specific instances in which the laboratory documentation does not support the documentation, it should be noted that LNDD did not comply with TD2003LDOC. This technical document requires that LNDD provide to the athlete all

documents that support the internal chain of custody in the laboratory document packet. While USADA in its brief stated that all information required by the TD2003LDOC was provided in the laboratory document packet, Appelee's Brief at 8, USADA has cited to several documents not included into the laboratory document packet. USADA Pre-Trial Response Brief at Page 19. Indeed, USADA has admitted that these documents are not normally provide in the laboratory documentation package.

44. The most atrocious error in the chain of custody documentation is that the laboratory document packet has conflicting information. In the summary chain of custody document at USADA 0253, the first entry in for the "A" sample bottle is that it was possessed by Operator 44 at 7:25 a.m. As noted above, because of the form of the documentation, this summary sheet does not establish from whom or from where Operator 44 received the "A" sample bottle. To assume that Operator 44 received the "A" sample bottle from the freezer, because this is the last listed location of the "A" sample bottle, is an improper assumption.

45. In reviewing the documents provided by LNDD, however, there is no document that supports this entry. In fact, there is a document that is in direct contradiction to this entry in the summary document. LNDD 1591 establishes that Operator 42, not Operator 44 as indicated on the summary sheet, removed the bottle from CHFR-1 at 07:30, not at 07:25 as indicated on the summary sheet. This one instance, establishes that the summary chain of custody documentation contains a break and does not accurately reflect the movement of the sample bottle. This alone, is sufficient belie any reliability in the test results.

46. To make matters even worse, there is a document which partially supports the entry in the summary sheet, but is in direct contradiction to the document discussed above.

LNDD1590 purports to indicate that on July 21, 2006, Operator 44 possessed Mr. Landis' sample bottle at 07:25. There is no indication where Operator 44 obtained this sample from, and, more important, it directly contradicts the fact that LNDD 1591 states that the sample bottle was not removed from the freezer until 07:30 by Operator 42. Obviously, it is impossible for LNDD1591 and LNDD1590 to both be correct.

47. This glaring contradiction contained in LNDD 1950 and 1951 is further complicated by the fact that USADA0006, which appears to be a storage log for the samples, fails to include an entry for Mr. Landis' sample bottle either being removed or returned to the freezer or refrigerator. That is, USADA0006, a document which USADA purports to represent that V21 placed the "A" bottle in CH.FR.1 on the night of July 20, 2006, and then also purports to establish other instances when the sample bottle was either removed or returned to a refrigerator, does not indicate that on July 21, 2006, Mr. Landis' sample was removed or returned. This document contradicts both LNDD 1590 and 1591.

48. This one entry on LNDD's summary chain of custody document establishes the utter deficiency in the chain of custody of Mr. Landis' sample. USADA repeatedly posits that the entries in the summary sheet are supported by the laboratory documentation. This is simply not the case. Indeed, the laboratory documentation in this instance actually has three documents that all contradict each other. There is no reasonable way to conclude anything other than that LNDD fails to follow the requirements of TD2003LCOC and generally accepted scientific principals in maintaining adequate chain of custody.

49. While this one entry establishes the failures of LNDD's chain of custody method, a careful examination of the laboratory documents reveals other significant errors in the summary sheet and the underlying laboratory documentation provided.

50. In the documentation package, LNDD provided as a chain of custody a form labeled "E-TE-05 A" which purported to trace the A and B bottles from the reception of the bottles at the laboratory through their disposal. In addition to its failure to do this, as discussed above, this document fails in every meaningful respect that would represent effective chain of custody.

51. USADA 0253 records that the sample bottles were first received at LNDD by an operator coded as V21 at 21h35 on July 20, 2006. USADA cites to USADA 0024 and 0229 as laboratory documents that support this entry, both of which are copies of the same paper. These documents do not support the entry on the summary chain of custody sheet because USADA 0024 and 0229 establish that LNDD received Mr. Landis' sample at 9h35, not 21h35. While it is possible that USADA 0024 and 0229, are the only instance in the entire document in which a 12-hour clock instead of a 24-hour clock was used, even in this case, the LNDD employee failed to record an "AM" or "PM." Thus, there is no way to determine based on the documents when LNDD actually received the Mr. Landis' sample.

52. Next, USADA 0253 notes that the A bottle was placed in CH.FR.1 at 22h15 on July 20, 2006 by V21. USADA pre-trial response brief directs us to USADA 0006 as support for this entry. USADA Pre-Trial Response Brief at 19. USADA 0006 is what appears to be a storage log and it records a time and date entry of 22h15 on July 20, 2006 by V21 for sample 995474. There is, however, nothing on this log that I can find that indicates that the sample was stored in a refrigerator designated CH.FR.1. There are only two other marks for this entry. The first is a double-headed arrow presumably indicating that this entry applies to all three samples listed on the sheet (995474, 994179 and 994178). The

other is a mark that appears to be an upper-case "R" and a lower-case "n". It is possible that this entry is, in fact, "R1" and that "R1" is shorthand for CH.FR.1, but there is certainly no way from examining the documentation to determine if this is the case. Additionally, there is no indication that the bottle being referred to by the designation 995474 is the sample "A" bottle.

53. Even if USADA 0006 did indicate that the A bottle was stored in CH.FR.1, the document itself is deficient under the rules of TD2003LCOC and generally accepted scientific standards. TD2003LCOC requires, at a minimum, that "[t]he Laboratory Internal Chain of Custody must contain the name or initials of the individual, date of transfer, and purpose of the transfer of possession. The individual's complete signature/name should appear in the documentation at least once." Here, the entry on USADA 0006 has no name or initial, but instead contains merely an operator code.

54. Next, USADA 0253 notes that Mr. Landis' "B" bottle was placed in CH.FR.3 at 22h15 on July 20, 2006 by V21. USADA again supports this contention by citing to USADA 0006. As noted above, this document was used to support the entry that the "A" bottle was stored in CH.FR.1. Beside the entry I described above, there is not another entry for July 20, 2006. This one entry cannot be used to support both the fact that the "A" sample was placed in CH.FR.1 and that the "B" sample was in CH.FR.3.

55. In addition to citing USADA 0006 as support for the "B" bottle being placed in CH.FR.3, USADA also refers to a document produced later in discovery, not part of the document packet, which is an SOP that states that the "B" sample bottle should be placed in CH.FR.3 when it is received by the laboratory. LNDD1592. USADA appears to be supporting LNDD's entry in the summary chain of custody document about the storage

of the "B" bottle with the SOP related to the storage of the "B" bottle. This argument is absurd and completely unsubstantiated. An SOP, can never, under any circumstances be satisfactory as a chain of custody document. A generic instruction sheet indicating what *should* happen cannot possibly establish what, on a particular day, in fact *did* happen. USADA has simply provided no document that would satisfy TD2003LCOC or generally accepted scientific principals that supports the summary sheet entry about the initial storage of the "B" sample bottle.

56. The summary chain of custody sheet next notes that the "A" bottle was opened for the purpose of aliquoting the sample for EPO analysis on July 21, 2006 by Operator 44 in room 107 at 7h25. This is the entry that I discussed above that has three documents that all contradict each other. However, even the documents that USADA suggests support this entry, USADA0007 and LNDD1590, are both deficient. USADA0007 is a results recording sheet that only notes that Operator 44 at some point either performed or recorded the values in the pH, specific gravity and d-refract analysis columns. Further, and importantly, no where on this form does Operator 44's name or initials appear – a requirement for any valid chain of custody document by the language of TD2003LCOC.

57. The second document cited to by USADA is LNDD1590. LNDD1590 indicates, with a date, time and proper initials, that Operator 44 took charge of series 177/07 and 178/07 on July 21, 2006 at 7h25, which as noted above is contrary to LNDD 1591 and USADA0006. While Sample 995474 is part of series 178/07, there is no indication on LNDD1590 that Mr. Landis' samples were indeed removed from the refrigerator as part of this series.

58. The summary chain of custody sheet next indicates that Operator 44 maintains possession of the bottle to aliquot for an EPO test. Though USADA does not indicate a supporting document for this entry in its chart in its pre-trial response brief at page 19, presumably the support for this entry is LNDD1590. This document, however, is subject to the deficiencies mentioned above.

59. The summary chain of custody document next notes that operator 19 in room 006 aliquoted multiple tests from the "A" bottle on July 21, 206 at 9h10. USADA points to LNDD1591 as supporting this entry. Several problems present themselves with this conclusion. First, LNDD1591 is a document that we already know contains information contradicted by LNDD1590 and by USADA006. Second, even if the information on this document is correct, it cannot stand as support as a chain of custody document because there is no name or initials of the operator in question (or any other operator, for that matter) found on this document as required by TD2003LCOC and generally accepted scientific principals. Last, this document again makes reference to a series and not individual sample numbers, and one must assume that because the series 178/07, of which sample 995474 is a part, is mentioned on the document, that the laboratory technician in fact had possession of the "A" sample bottle.

60. In the last several paragraphs, I have discussed the errors of only the first six entries on the summary chain of custody form. It is clear that not only is the method of documenting chain of custody at LNDD confusing and convoluted, but it is in fact incorrect. It is my conclusion that there is not sufficient chain of custody documentation and there is no assurance that the integrity of the sample was not jeopardized. However,

for the convenience of the panel, I will discuss some of the other errors in the summary chain of custody documentation briefly.

- According to the chart in USADA's pre-trial response brief, there are several entries that are supported by USADA0006. However, I have addressed the deficiencies of USADA0006 with respect to another entry. These entries fail for the same reason as that entry failed. Therefore, USADA0006 is deficient and cannot be considered credible evidence to support the entries in the summary chain of custody sheet.
- Similarly, the chart in USADA's pretrial brief also states that entries in the summary chain of custody sheet are supported by LNDD1591. As I have explained above, LNDD 1591 does not satisfy the requirements established by TD2003LCOC for a proper chain of custody document and cannot support the entry in the summary chain of custody documentation.
- I would also like to take this opportunity to re-emphasize a part of my earlier testimony calling now specific reference to USADA0006. USADA has consistently argued that the "plot" method of chain of custody is sufficient under TD2003LCOC and generally accepted scientific principals. USADA has consistently argued that the chain of custody here is, in fact, a complete and unbroken chain because you see Operator A possessing the sample and then you next see Operator B possessing the sample that this means by implication that nothing happened to the sample between the two. USADA0006 makes the failure of this argument obvious.

3. A Laboratory Technician Testimony Contradicts the Summary Sheet

61. The summary chain of custody document purports to state that Operator 49, Cynthia Mongongu, obtained Mr. Landis' Sample "A" bottle on July 22, 2006, at 11h20. See

Exhibit 25, USADA0253. According to the summary chain of custody document, the Operator who had the sample bottle before Mrs. Mongongu was Operator 18, who supposedly had the sample bottle at 10h50 in Room 103. At the hearing, however, Mrs. Mongongu testified that she obtained the bottle from the rack in Room 103, not Operator 18. Tr. of Proceeding at 533:14-15. This establishes that the summary chain of custody documentation does not actually establish the location of the sample bottle or who had possession of it at a given time. That is, there is no indication on the summary chain of custody documentation sheet that Operator 18 divested herself of the sample bottle and put it on the rack in Room 103.

62. Even worse yet, at the hearing, Mrs. Mongongu testified that she "recalled" obtaining the sample bottle at 11h20 on July 22, 2006 and possessed it for only five to ten minutes. Tr. of Proceedings at 535:21-23. But the next entry on the summary chain of custody document is that Operator 18 placed the bottle in storage at 12h45 on July 22, 2006. The entry in the summary chain of custody document and the testimony of Mrs. Mongongu establish that the chain of custody documentation does not establish where the sample bottle is within the laboratory and who possessed the sample bottle at any given time. Accordingly, as I have noted above, the chain of custody documentation maintained by LNDD is not sufficient.

4. Chain of Custody Documents Must Record When Sample is in Control Zone

63. Appellee's Brief posits that all of the above deficiencies in the chain of custody records can be dismissed because once the sample reached the laboratory, it was within the control zone of the laboratory the entire time. Appellee's Brief at 75-76. This broad, sweeping statement is erroneous when the actual language of TD2003LCOC is

considered. The technical document requires that when a sample is not in the possession of a laboratory technician, it should be **documented** that the Sample is within the control zone. Put simply, there must be some document that the laboratory technician completes that documents the fact that the sample is no longer in his or her possession and that it has been place in the control zone.

64. There is no such documentation here. Indeed, the summary chain of custody documentation purports to show that certain laboratory technicians had the sample bottle for several hours at a time. For instance, according to the summary chain of custody, Operator 28 is said to have possession of the "A" sample bottle on July 23, 2006 from 14h30 to 17h00. I find it difficult to believe that Operator 28 had actual possession of the sample bottle during this entire time. Yet, there is no **documented** transfer of the sample bottle from Operator 28 to the control zone. It is not sufficient for USADA to merely argue that since the technician was in the laboratory, that he or she did not have to record the transfer to the control zone. To accept USADA's argument would be to eliminate the chain of custody requirement once the sample arrived at the laboratory.

5. AAA Panel Was Incorrect In Disregarding the Chain of Custody Error

65. The AAA Panel states in ¶264 of its decision that while there appeared to be gaps in the chain of custody summary document, USADA 253-7, when it reviewed the document packet, it was "satisfied" that it could trace the location of the bottles and at all times identify the operator in possession. The panel did not support this proposition with any cites to the record, and, as I have established above, there is no way to trace the movement of the sample bottle based on the document packet. And, indeed, there are contradictory documents about the movement of the sample bottle while at LNDD.

66. Equally, the Panel's conclusion that any alleged breaches in the chain of custody cannot have caused the AAF because the results of the A sample were confirmed by the B sample is fallacious. ¶268. First, it assumes as a threshold matter that gaps in the chain of custody occurred only with the "A" sample. There is reason to believe, as I discussed above, that the failure to record the movement of the bottle or the sample aliquots was not properly accounted for with respect to both the "A" and the "B" sample. Further, the conclusion appears to miss the significance of chain of custody gaps. The fact that the results between the "B" sample also "confirmed" the presence of testosterone does not address the significance of the chain of custody gaps. Reaching the "right" conclusion does not exclude the possibility that both samples were tampered with or compromised in some way. I express no opinion about whether that happened, but no one, including this Panel, can be assured that this did not happen because the chain of custody documentation is lacking significantly.

C. LNDD's T/E method and Carbon Isotope Ratio Test procedure were not ISO-accredited

1. Accreditation Background

67. During my eleven years inspecting laboratories for the National Laboratory Certification Program, I was repeatedly called upon to evaluate a laboratory's documentation, and to evaluate it with reference to certification standards. I have also published in the scientific literature on the issue of method development, and the process of validating a method and proving to accreditation bodies that a laboratory is qualified to conduct a given method of analysis.

68. Laboratory accreditations are an important tool used to ensure that laboratories are able to perform various analytical techniques accurately and reliably. But simply being accredited does not ensure that on a given occasion a laboratory performed certain analytical tests competently or correctly. In fact, due consideration must be given to the scope of the accreditation; i.e., an accreditation that ensures that a laboratory consistently abides by its Standard Operating Procedure ("SOP") is meaningless if the SOP is not scientifically valid.

69. In Appellate Response brief, it repeatedly emphasizes that LNDD was ISO-accredited to perform the various assays used to generate and support the Adverse Analytical Finding ("AAF") for Mr. Landis's Stage 17 sample. LNDD's own documentation belies USADA's argument, however. Before turning to this point, an understanding of how a laboratory obtains ISO accreditation is required.

70. The WADA International Standard for Laboratories mandates that a WADA laboratory obtain an ISO 17025 accreditation. See International Standard for Labs at ¶4.1.1. The International Organization for Standardization ("ISO") develops standards to ensure that products and services are created or performed in such a manner to achieve desirable characteristics at an economical cost. Specifically, ISO 17025 sets forth the general requirements for the competence of testing and calibration labs. Although ISO drafts the standard, it does not actually accredit laboratories. The laboratories are accredited by any one of the more than 750 certification bodies in the world, bodies over which ISO has no control. In France, the ISO accreditation or certification decisions are made by the Comité français d'accréditation (COFRAC). Further, as USADA's counsel, Mr. Young, acknowledged during the proceedings before the AAA panel, an ISO accreditation is not

a global certification that a laboratory is proficient across-the-board. Tr. Of Proceedings, Feb. 23, 2007 Vol. II at 100:4-102:8. Instead, ISO accredits the particular methods used at individual laboratories.

71. Before the laboratory can obtain ISO 17025 accreditation for a particular method, the laboratory must first develop and validate the method for which it wants accreditation. The particular purpose of the laboratory, such as in this case, anti-doping testing, does not change the basic requirements for method development and validation.

72. Method development and validation is the documented process of proving that a selected analytical technique is acceptable for its intended purpose, and that it can be used effectively by the lab in question. The documentation generated during this process is the evidence that would eventually be provided to an accreditation body to prove that a lab has chosen analytical techniques that it has demonstrated that it is able to implement in a manner that generates accurate and reliable results. Specifically, the method development documentation demonstrates that a lab has adopted a method only after assessing general reliability factors like stability, precision, specificity, linearity, accuracy and sensitivity. Particular assays, such as the T/E assay, include several additional assessments. The laboratory should ensure in the method development phase that it can adequately and consistently recover the analyte from the matrix, and that it has established the ruggedness and reliability of the assay process. All of these steps are necessary to validate a method, and the documentation generated in this process is what the lab will show to an accrediting body in order to earn additional accreditations. This process is discussed in more detail in my peer-reviewed paper, "Commonly Practiced Quality Control and Quality Assurance Procedures for Gas Chromatography/ Mass

Spectrometry Analysis in Forensic Urine Drug-Testing Laboratories," B.A. Goldberger et al., Forensic Sci. Rev. 9:59; 1997. While the article references drug-testing labs in particular, the general principles are equally applicable in the anti-doping lab context, where the goal is the same, to generate reliable, valid and accurate results with evidentiary value. ISL §1.0.

73. These validation studies are critical because while a particular assay may be generally accepted in theory, e.g., the T/E testing theory, each laboratory performing this assay may have different instruments, personnel and variations in the method that can drastically affect the reliability and accuracy of the particular assay. For instance, one specific laboratory may perform the GC/MS assay with a method that produces a measurement of uncertainty different from the measurement of uncertainty of another laboratory. Indeed, a specific laboratory may have different methods it uses for a particular assay, and each one of these methods may result with a different measurement of uncertainty. Once a laboratory develops and validates the method, the laboratory drafts a SOP to memorialize the method.

74. It is only after the SOP is drafted that a laboratory can obtain ISO accreditation. The review process for ISO accreditation is not as it is described in USADA's Response Appellate brief. To obtain ISO accreditation, the accreditation body only looks to see if the laboratory has a written SOP documenting the previously validated method and whether there are proper management controls in place to address deviations from the SOP and for updating the SOP if necessary. The ISO accreditation body DOES NOT review the validation study to ensure that it is scientifically accurate and does not ensure that the method or SOP is in compliance with governing regulations such as the ISL. To

borrow a phrase from Appellee's Brief, the ISO accreditation body does not step into the shoes of the scientists to determine whether the method is scientifically valid.

2. LNDD lacked ISO accreditation to perform the T/E analysis for the purpose of determining the T/E ratio of Mr. Landis's urine sample.

75. LNDD performs several assays or processes in the laboratory, and for some assays, LNDD has multiple methods it uses. LNDD's T/E assay is one of the assays with multiple methods. While some of the T/E methods have been validated and are accredited by COFRAC, the T/E method used in performing the T/E assay on Mr. Landis' sample was not accredited, and based on my review of the documents produced, the validation study, if any, was not provided.

76. LNDD's laboratory documents, at USADA 104, reflect that it has a T/E method for determining a T/E ratio identified as assay EC24D. This assay was used by LNDD to determine the T/E ratio on Mr. Landis' Stage 17 samples. *See* USADA 256-7, USADA 189, 365. However, LNDD is not accredited by ISO/COFRAC to use the EC24D assay as the COFRAC accreditation documents accredit assays EC24B and EC24C. *See* LNDD 0085.

77. The EC24D method likely has not been validated by LNDD either. In my review of the documents provided by LNDD to Mr. Landis, I only located a validation study for the EC24C assay, not EC24D. See LNDD 461-471. Without this method being validated, there can be no confidence that the results obtained using this method were reliable or accurate, even if the LNDD laboratory technicians performed the test in compliance with the method.

78. The failure to validate the EC24D, and obtain an ISO accreditation for this method, is in violation of ISL ¶ 5.4.4.2. Further, the failure to validate and accredit a method, but still use the method on a sample, causes me great concern about the results of Mr. Landis' Stage 17 T/E test results.

3. LNDD's Carbon Isotope Ratio Test performed on Mr. Landis' Stage 17 urine sample was not accredited.

79. The method used for the CIR test performed on Mr. Landis' State 17 urine sample was not accredited by COFRAC either. Unlike the T/E method accreditation issue above, in which the method used simply was not listed in the COFRAC accreditation documents, the CIR method accreditation deficiency is far more interesting. The COFRAC accreditation documents accredit by method identification number, the CIR test method; however, the description of the method on the accreditation documents is different than the method described in the laboratory document packet provided by LNDD. *Compare* LNDD 0097-98 *with* USADA 124-26; 303-05. Additionally, the measurement of uncertainty on the accreditation document in effect at the time the Stage 17 sample was analyzed was 20%, whereas, the December 2006 accreditation documents note that the measurement of uncertainty is .8%. *Compare* LNDD 0086 *with* LNDD 0097-98.

80. The May 2006 accreditation documents accredit a CIR test identified as EC31. This method is defined as including the following sub-methods: an extraction method, M-Ex-24 (USADA 295-8), an analytical method, M-An-41 (USADA 329-30), and a method setting forth the parameters for the portion of the test performed on the GC/C/IRMS instrument.

81. The C.I.R. test performed on Mr. Landis' Stage 17, while identified as EC31, contains an additional step not included in the definition of the EC31 method in the COFRAC accreditation documents. Indeed, the document in the laboratory document packet setting forth the individual sub-methods for the EC31 method is different than the sub-methods set forth in the accreditation documents. The C.I.R. test performed on Mr. Landis' Stage 17 sample included a sub-method for when the samples are run on the GC/MS instrument, the sub-method "M-AN-52." USADA 303-05 ("B" sample) and USADA 124-26 ("A" sample). Indeed, not only is the "M-AN-52" sub-method not included in the EC31 accreditation, this sub-method does not appear anywhere in the COFRAC accreditation documents.

82. It is curious that the accredited C.I.R. test, EC31, is not the same EC31 method described in the laboratory document packet. Nevertheless, disregarding the method identification, the actual method, including the sub-methods, for Mr. Landis' Stage 17 C.I.R. test was not accredited. Further, and critically, in my review of the documents produced by LNDD, I have not found a validation study for the EC31 method as it was performed by LNDD in testing Mr. Landis' Stage 17 sample. Performing a test without proper validation violated ISL § 5.4.4.2, and generally accepted scientific principles and methodology. Accordingly, the C.I.R. tests results are unreliable, not valid and cannot be used to support the allegation that Mr. Landis committed an anti-doping rule violation.

4. LNDD was not accredited to perform IRMS analysis at the appropriate level of uncertainty.

83. As I noted above, a laboratory's validation of an assay method is important in ensuring that the method produces reliable, valid and accurate results. In fact, one of the critical

measurements the laboratory determines during the validation study is the measurement of uncertainty for that particular method. This point has been acknowledged by USADA during the AAA proceeding. [Tr. of Proceedings, February 23, 2007, Vol. II at 100:4–102: 8].

84. I have serious concerns regarding the validation study and accreditation for the C.I.R. assay with respect to the measurement of uncertainty.

85. The ISO-accreditation issued by COFRAC and actually in force at the time LNDD performed the C.I.R. assay on Mr. Landis' Stage 17 sample for the EC31 assay (which as noted above lacks all of the sub-methods from the method used for Mr. Landis' Stage 17 sample) noted the measurement of uncertainty at "20%". See LNDD 0086. The 20% uncertainty level contained in this COFRAC accreditation document at LNDD 0086 also appeared in earlier COFRAC accreditation documents, specifically those generated by COFRAC staff at the last LNDD audit occurring before the 2006 Tour de France, the February, 2006 audit. See LNDD 414, LNDD 429.

86. At the AAA proceeding, Dr. Christiane Ayotte testified that she believed the accreditation listing 20% uncertainty was a "mistake." See Tr. of Proceedings at 878-9. A belief that this was a mistake is hardly tenable in light of the fact that COFRAC had listed this same uncertainty level on other documents. LNDD 00414, 00429.

87. Despite the accreditation at the time listing the measurement of uncertainty for the EC31 method as 20%, LNDD used a .8‰ level of uncertainty in interpreting Mr. Landis' C.I.R. test results. See USADA 186, 352; Tr. of AAA Hearing, 464:16-465:4. The use of a different measurement of uncertainty than what is listed in the accreditation documents raises serious questions as to what the actual measurement of uncertainty was at the time

the Stage 17 samples were analyzed. According to Ms. Cynthia Mongongu, a LNDD laboratory technician, the measurement of uncertainty was adopted after a validation study was performed at LNDD. Tr. of Hearing 464:16-466:1. The only validation study produced by LNDD that I have reviewed, LNDD 451-460, however, is neither signed nor dated, and is not presented on an official LNDD form. Indeed, the format of the C.I.R. test validation test is markedly different from the format of the T/E validation method [EC24C]. LNDD 461-471. Thus, I cannot determine whether the validation study produced by LNDD had been conducted by LNDD before Mr. Landis' Stage 17 samples were produced. Nevertheless, assuming that such a validation study was completed, it is unclear to me why COFRAC would have repeatedly listed the measurement of uncertainty as 20%.

88. While COFRAC did eventually issue an ISO accreditation for method EC31 that listed the measurement of uncertainty for this method at 0.8‰, this accreditation did not take effect until December 15, 2006, after Mr. Landis' Stage 17 sample had been tested. See LNDD 0098. The reason for such a correction was because LNDD's Adeline Molina sent to Mr. Robin Leguy of COFRAC on December 14 an email requesting that COFRAC "correct" the 20% measurement of uncertainty in the previous accreditation for method EC31 to 0.8‰ based on the undated validation study. That request, incidentally, was made by LNDD some time after Mr. Landis commenced his legal challenge to LNDD's findings

D. POSITIVITY CRITERIA NEEDS TO BE VALIDATED

89. During the AAA proceeding, USADA argued that LNDD did not have to validate the C.I.R. test with respect to the positivity criteria because the WADA Technical Document

has defined what the positive criteria is for the C.I.R. test. While I do not express an opinion generally on the positivity criteria contained in the Technical Document, USADA's argument that such a document relieves a laboratory from validating its method is specious.

90. As noted above, the purpose behind validating a method is to ensure that a laboratory can consistently obtain reliable, valid and accurate results. The need to validate method is no less applicable because WADA has issued a Technical Document setting forth a positivity criteria. The reason for the validation study is because not all laboratories have identical instruments or methods. These differences affect the test results that are obtained from the assay, e.g., one laboratory has a measurement of uncertainty of 0.4% whereas another laboratory for the same test may have a 0.8% measurement of uncertainty. A one size fits all approach is not possible.

91. Using the same example as above, assuming based on the validation studies for each laboratory, the T/E test at Laboratory A is 0.4% and Laboratory B it is 0.8%. If WADA issues a technical document stating that the uncertainty level for the T/E test is 0.4%, it would be illogical for Laboratory B to start analyzing its test results with a 0.4% measurement of uncertainty when it knows, based on its validation study that its method produces a measurement of uncertainty of 0.8%. Likewise, if in validating its C.I.R. test, the laboratory can only produce consistently reliable and accurate results when it uses two metabolites to declare a positive test, it would be improper for the laboratory to institute a positivity criteria based on one metabolite simply because the technical document allows it to.

92. To put this concept differently, the WADA Technical Document sets the floor for the positive criteria. The laboratories, however, then need to validate their method to see, for their particular method, what positivity criteria generates consistently reliable and accurate results.

93. USADA's expert and WADA laboratory head, Dr. Ayotte, concurred with my position during the AAA proceeding. Dr. Ayotte clearly conceded that TD2004EAAS did not relieve the laboratory of validating the WADA positivity criteria before implementing it. Tr. at 856-858

94. The argument that a laboratory can be relieved of its duty to validate its methods simply because WADA dictated a particular measurement of uncertainty or positivity criteria is in contradiction to the ISL, specifically ¶¶ 5.4.4.2.1 and 5.4.4.2.2, and generally accepted scientific practices and methodology. Further, this argument is not supported by USADA's own expert.

95. In my review of the documentation, I have not located a validation study in which LNDD has validated its positivity criteria. Instead of producing the validation study, USADA has repeatedly argued that since the C.I.R. test is accredited, this Panel can assume that the positivity criteria has been validated. Appellee's Brief at 22, USADA's Pre-Trial Response Brief at 26. This argument rings hollow, however.

96. First, as I have noted above, the EC31 method used by LNDD is not the same as the accredited EC31 method described in the accreditation documents. Second, ISO accreditation only means that there is either a SOP or multiple SOPs documenting the method that has been validated. However, in accrediting a method, the positivity criteria for the method does not need to be documented in an SOP. Thus, the method can be

accredited without any reference to the positivity criteria or a validation for the positivity criteria.

97. Further, while I am not an expert in the C.I.R. test, the need to validate the positivity criteria of the laboratory is best illustrated by the illogical difference between the acceptance criteria for the alleged quality controls run during the C.I.R. test and the positivity criteria suggested by WADA and accepted by LNDD. Based on my review of the laboratory document packet and the briefs in this case, it is my understanding that with respect to the purported quality control measures during the C.I.R. test, the Mix Cal Acetate and the Mix Cal IRMS, LNDD requires the isotopic ratio for only three out of the four compounds in each of these substances to be within the expected specifications. In other words, with respect to these supposes quality controls, LNDD concludes that the GC/C/IRMS instrument is working properly even though the isotopic ratio for one of the results is essentially incorrect. Remarkably, however, the positivity criteria used by LNDD, the same positivity criteria suggested by WADA, for the C.I.R. test only requires one of the four delta-delta values to be more negative than -3.00‰.

98. The positivity criteria compared with the acceptability criteria for the supposed quality controls reveals a paradoxical situation. A quality control is acceptable if one isotopic ratio falls outside of the expected range; whereas, if one delta-delta value is more negative than -3.00‰, the laboratory considers the sample positive. To put it simply, based on the acceptance standard for the quality controls, the laboratory expects that the isotopic ratio for one of the compounds in the quality control will fall outside the specified expected range; however, the laboratory then expects that every isotopic ratio obtained in the samples is correct. This is simply nonsensical. If the laboratory cannot

obtain accurate isotopic ratios for every compound in the quality control, it is unlikely that the laboratory should expect to obtain accurate isotopic ratios for all target analytes.

99. That WADA has suggested a positivity criteria does not mean that the laboratory does not have to validate the positivity criteria. The apparent inconsistency between the quality control acceptance criteria and the positivity criteria is indicative of this fact. Assuming that the quality control acceptance criteria has been validated, which I cannot confirm because no validation study was produced, it would be illogical to then accept the one metabolite positivity criteria suggested by WADA when the laboratory expects that the isotopic ratio for one compound in the quality control will be out of specifications.

E. Sample number errors.

1. No Documents Support Receipt of Mr. Landis' Sample

100. Each sample provided by an athlete at the Tour de France is provided a unique sample number. This unique sample number allows the sample to be traced from the time it is provided after the race to the destruction of the sample at the laboratory. This sample number can also be later cross referenced with the person who provided the sample. Additionally, this sample number is used to identify documents that pertain to the sample, for example, if a T/E test is run on Sample 12345, the worksheet and test results corresponding to this T/E test will indicate that they are for Sample 12345. Failure to input the correct sample number on a document, be it a transfer document or laboratory analysis document, is a serious error in the chain of custody, and frequently fatal to the success of any legal proceeding intent upon penalizing the person whose sample is at issue.

101. The first sample number error occurred in the documents purportedly reflecting the transfer of samples to the LNDD from the field collection station after the completion of Stage 17. First, the specimen transfer record, USADA 0024 and 229, contains a statement indicating that the group of samples were being transferred to LNDD without a delivery document ["Cas d'un TRANSPORT AU LABORATOIRE par chauffeur sans document de livraison"]. This, in itself, is in violation of generally accepted scientific best practices. Second, Mr. Landis' Stage 17 sample was given the sample number 995474. The official transfer record documents USADA provided, with the name and signature of both the delivery person and the person who received the samples at LNDD, does not list Mr. Landis' sample number. While there is a sample number that is numerically close to Mr. Landis' sample number, 995476, precision is required in the context of chain of custody and in all other laboratory procedures. Indeed, in the Appellate Brief, USADA simply ignores this error in citing these transfer documents as the only evidence that Mr. Landis' sample was transferred to LNDD. *See* Appellate Brief at 19 (citing USADA 0024 and USADA 0229 to establish receipt of bottle 995474 at LNDD).

102. Additionally, while there is a document in the document package on LNDD letterhead that notes the receipt of a sample 995474, USADA 0023, this document fails to comply with the requirements of ISL ¶5.2.1.3, which requires that a transfer documents bear the "name and signature . . . of the Person delivering or transferring custody of the shipped Samples, the date, the time of receipt, and the name and signature of the Laboratory representative receiving the Samples . . . ." The document at USADA 0023 contains none of that information required. Therefore, the laboratory documentation

package provided by the LNDD to Mr. Landis appears to contain no chain of custody documents or specimen transfer records that both accurately reflect the transfer of Mr. Landis's urine specimen – #995474 – to the LNDD, and comply with the ISL requirements at ¶ 5.2.1.3.

103. In light of the error described above, the anti-doping organization, AFLD, should have taken corrective action to ensure the integrity of the samples it received. Pursuant to the International Standard of Testing, when LNDD received a sample without proper accompanying documentation, the anti-doping organization should have confirmed that there was proper chain of custody and should have considered voiding the sample. ¶ 9.3.6. Mr. Landis' sample was not received at LNDD with proper accompanying documentation, because the documentation failed to list Mr. Landis' sample number. The French Anti-Doping Agency, AFLD, should have confirmed that there was proper chain of custody, and if there was not, the sample should have been voided. There has been documentation provided to establish that the AFLD took such action or somehow confirmed the chain of custody of Mr. Landis' sample.

104. Further, LNDD was required to take corrective action as well when it received Mr. Landis' sample without proper accompanying documents. ISL ¶ 5.2.2.3 requires that a laboratory document conditions that exist at the time the sample was received. Indeed, one of the listed irregularities in the ISL when the "Sample identification is unacceptable. For example, the number on the bottle does not match the Sample identification number on the form." LNDD has provided no documents establishing that it documented the irregularity with Mr. Landis' sample.

2. Laboratory Documents Have Improper Sample Number

105. Documents prepared by LNDD staff and offered as evidence in support of LNDD's AAF also fail to reflect Mr. Landis' sample number. In addition to the sample number, 995474, Mr. Landis' was also given a series number when it was received by the laboratory, 178/07. See USADA 023.

106. On USADA 0288, a laboratory document containing the results of the T/E analysis on what is purported to be Mr. Landis' "B" sample, the sample number and control number are both incorrect. This document reports data for sample 994474, not sample 995474, and reflects the series number of 478/07, not 178/07. Yet, the document is offered as evidence against Mr. Landis.

107. Another document in Mr. Landis' laboratory document packet that lists an incorrect sample number is a barely legible document that appears to be a registration document evidencing the retention and/or destruction of various samples. USADA 008. While this document refers to samples 995475 and 995676, the document does not contain any reference to Mr. Landis' sample number, 995474. The significance of this error is evidence by the fact that LNDD has acknowledged that there was a sample 995475 that was related to a different 2006 Tour de France cyclist and 995676 was also a sample being tested at the time. LNDD0380, USADA0007.

108. Yet another document in the laboratory document packet containing a sample number error is found at USADA 009. Unlike the above documents which simply have a different sample or series number, this document contains an overwritten sample number. It is not clear what the original sample number was, but the document clearly shows that the third number was altered and overwritten to make it Mr. Landis' sample number. As

will be discussed below, correcting a mistake by overwriting is not permitted under the ISL. But in addition to the forensic correction violation, the true concern comes from not knowing who, why, or when this correction occurred.

109. Remarkably, another document, USADA0079, contains both improper forensic correction of the series number and lists a different sample number than Mr. Landis' sample number. The series number was changed from 188/07 and overwritten with 178/07.

F. Improper Forensic corrections

110. LNDD's documentation supporting its test results is riddled with improper "forensic" corrections. The ISL memorializes a generally accepted scientific practice that any correction on a document related to a sample should be done by putting a single line through the incorrect information, and initialing and dating the correction. In no instance should the incorrect information be erased or otherwise obliterated. WADA TD2003LCOC. This is not a merely technical rule. Laboratory work, from the actual testing method to the documentation of the test, must be beyond reproach. Anyone examining the laboratory document packet should be able to read every entry. If a mistake is made on of the documents supporting a test and an entry is correct, a third party should be able to ask the person who made the correction why the correction is made. By not obliterating the mistake, the person reviewing the documents can know what the mistake was and then verify why the mistake needed to be corrected. The forensic correction rule is not a trivial one and should not be treated as one.

111. There are several instances in the document packet where LNDD personnel did not comply with the requirement regarding forensic corrections.

- USADA 009 reflects an improper forensic correction made on a sample number, a serious break in the chain of custody.
- USADA 200 contains at least six forensic corrections that do not comply with WADA rules or ISO 17025.
    - The sample number was corrected to #995474, however, the correction was not dated.
    - In a box called "Echantillon Blanc" followed by columns marked "donneur," "densite," "facteur de dilution." The box marked "donneur" contains a marked-out 16, replaced by a 31. Again, there is no initial or date.
    - In the "Heure de la PE" box, there is a mark in the box that was crossed out but not initialed or dated.
    - In the middle of the document there is a substance table that has a heading titled "Volume preleve en *u*L," with six numbered columns. In column 1, the initial entry for epitestosterone was corrected from a 2 to a 4. The correction is not dated or initialed.
    - In the same table, column 3, there is a "60" that has been crossed out and placed in a different box on the next line down in the column. This change was not initialed or dated.
    - In the substance table in the columns entitled "Conc ref dans PE en ng/mL," columns 1-6, we can see that in column 3, an entry for epitestosterone was marked out. Again, this change was not initialed or dated.

- The Operation table contains an altered date in the "Mise a pH" box; again, no initials or date were provided.[1]

- USADA 0079 also contains two improper corrections. As noted above, this is the document that had both Mr. Landis' rider and series number incorrect. In correcting the series number, however, the laboratory wrote over the pervious incorrect control number and did not date or initial the change. The second improper forensic correction on USADA 0079 appears in a box marked "Paraphe" appearing on the right-hand side of the page near the top. The initials of one analyst are crossed out and the initials of another analyst are inserted in the table toward the top of the document which sets forth the pH measurements. The change does not contain the initials of the individual making the change and it does not reflect the date upon which the forensic change was made.

112. The failure of the laboratory to maintain clear and compliant records raises significant concerns about the laboratory practices. While cliché, where there is smoke there is fire. Sloppy work in one area of the laboratory is likely illustrative of sloppy work in other areas.

113. USADA dispenses with the numerous forensic correction errors by minimizing the severity of these mistakes by referring to them as "unfortunate." *See* Appellate Brief at 80. USADA states, without benefit of supporting evidence or citation to documents, that each forensic correction can be traced to an original document in the document package, and therefore the errors cast no doubt on the validity of the lab's findings. It is

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[1] It is worth noting that this document, riddled with forensic errors, also incorrectly reports the concentration for the reference solutions printed on this page. To give one example, methyltestosterone SI3-046 is listed at a concentration of 4 mg/L, but the reference solution log appearing at LNDD 263 clearly states that the 046 methyltestosterone from the SI3 series is concentrated at 8 mg/mL.

difficult to imagine, however, how USADA would demonstrate that a sample number that has obviously been overwritten or altered with document correction fluid [see USADA0009] can be "traced back to an original document" contained in the LNDD document package. Thus, once again, USADA's argument is specious.

G. LNDD failed to conduct the GC/MS testing used to calculate Mr. Landis's testosterone: epitestosterone ratio in the manner required by the ISL.

114. The screening test performed by LNDD for the presence of testosterone in a sample is the T/E test, which uses the Gas Chromatography/Mass Spectrometry ("GC/MS") instrument. The T/E test measures the amount of testosterone and epitestosterone in the sample, which is then used to determine the testosterone to epitestosterone ratio. A T/E ratio of 4:1 is considered suspect by the ISL.

115. Not only was LNDD's T/E test method unaccredited, as noted above, it was performed in violation of the ISL. Despite vehemently arguing that the T/E test was performed in accordance with the ISL, USADA now concedes in this appeal that the T/E test was in violation of the ISL. USADA Appellate Brief at n.5 ("The AAA Panel correctly concluded that LNDD's T/E ratio analysis did not satisfy all the technical requirements of the International Standard for Laboratories ("ISL"). While I will not go into detail about the scientific theory underlying the T/E test or the procedures for performing a T/E test, I am going to highlight some of the egregious errors committed by LNDD while performing the T/E test. I believe that the errors committed by LNDD should not be limited to the T/E test context, but are indicative of a laboratory that fails to comply with ISL and chooses not to perform assays in accordance with generally accepted scientific principles and methodology. For instance, as will be discussed next,

one of the violations of the ISL during the T/E test was the failure of LNDD to properly identify the compounds in the Sample. This same failure to identify compounds in accordance with the ISL also occurred during the Carbon Isotope Ratio test, as will be discussed by other experts. Accordingly, the errors committed by LNDD with respect to the T/E test cannot simply be put aside because USADA now does not want to introduce T/E evidence; rather, these errors must be given due weight in analyzing the credibility of the laboratory with respect to all the test results used to support the AAF.

1. Compound Identification

116. The identification of a target substance during a T/E test is based on the retention time and ion ratios of the substance. Oversimplified, the retention time of substance is simply the time it takes a compound to pass through the column of the GC/MS instrument. However, the retention time of substance, standing alone, is sufficient to ensure that the substance measured is the target substance. This is because retention times are not unique and there are a number of different compounds that may have the same or very similar retention times. To ensure that the compound found at the specific retention time is the target analyte, the ISL requires the laboratory to perform a method called selected ion monitoring. *See* WADA TD2003IDCR. Selected ion monitoring essentially requires the laboratory to acquire and identify at least three different and unique ions. The underlying rationale and scientific theory for why a laboratory needs to obtain three diagnostic ions to ensure proper identification is not necessary for the purposes of this discussion; however, a detailed explanation is contained in my testimony before the AAA panel and in Mr. Landis' pre-trial hearing brief. Suffice it to say, LNDD

did not acquire three ions as required by the ISL.[2] Additionally, there is evidence that LNDD was capable of acquiring the three ions required, but for some reason, never did. Thus, LNDD never properly identified the substances it measured in the T/E test were in fact testosterone and epitestosterone, in violation of the ISL and generally accepted scientific principles and methodology.

2. Performing T/E Confirmation in Triplicate

117. The ISL has a straightforward rule requiring that a laboratory must perform all T/E confirmation tests, whether on the "A" sample or "B" sample, in triplicate. ISL ¶ 5.4.4.1.2, TD2004EAAS. LNDD could not comply with this requirement either. The confirmation T/E test performed on Mr. Landis' Stage 17 "A" sample was not performed in triplicate. The failure to follow a straightforward rule such as this is indicative of the way in which this laboratory operates.

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[2] The following exhibits reveal that LNDD, instead of acquiring and analyzing *three* diagnostic ions when conducting T/E confirmation analyzed (and sometimes acquired) only *one* diagnostic ion:

- the Data Analysis Parameters for the first attempt to confirm the A sample T/E results show the acquisition of a single diagnostic ion at m/z 432.40. Ex. 24, USADA 0086;
- The chromatogram for the successful A confirmation shows the acquisition of a single diagnostic ion at m/z 432.40. Ex. 24, USADA 0093.
- The Data Analysis Parameters for the second A confirmation show the acquisition of a single diagnostic ion at m/z 432.40. Ex. 24, USADA 0207.
- The chromatograms for the first, unsuccessful A confirmation show the acquisition of the same diagnostic ion at m/z 432.40. Ex. 24, USADA 0213, 0215.
- The Data Analysis Parameters for the B confirmation show the acquisition of a single diagnostic ion at m/z 432.40. Ex. 25, USADA 0270.
- The chromatograms for the B confirmation show the acquisition of a single diagnostic ion at m/z 432.40. Ex. 25, USADA 0277, 0280, 0282, 0284.

3. CHROMATOGRAPHY

118. A chromatogram in both the T/E test and Carbon Isotope Ratio test is the graphic representation of the raw data obtained from the sample. In these tests, the chromatograms have retention time on the x-axis, but the y-axis differs depending on the test. The chromatograms, or the data underlying the chromatograms, are the foundation for the analysis and calculations that eventually lead to the ultimate test results. Accordingly, the quality of the chromatogram affects the reliability and accuracy of the later calculations, and ultimately, the test results. Put differently, if the quality of the chromatogram is poor, even if the later calculations are performed properly, the test result will be inaccurate and unreliable. For example, imagine that the raw data from a sample was not produced as a chromatogram, but was rather a simple data set with two numbers. However, further imagine that the quality of the print is so poor that it cannot be determined whether one of the numbers is a "3" or an "8," and it could not be determined what the second number was because part of the number was cut off. Even if the only calculation required was to add these two numbers, the laboratory technician would not be able to perform this calculation without having to guess whether the blurred number was a "3" or an "8," and just speculating what the second number should have been. That the technician had to guess in performing the calculation means that the result would be unreliable and maybe inaccurate. Similar to the blurred number and cut off number in the example above, chromatograms have particular defects that affect the reliability, validity and accuracy of the later calculations that lead to the final test results.

119. I review chromatograms on a daily basis as a regular part of my duties as director of a forensic laboratory and I have also published papers discussing the interpretation of

chromatograms. *See* "Commonly Practiced Quality Control and Quality Assurance Procedures for Gas Chromatography/ Mass Spectrometry Analysis in Forensic Urine Drug-Testing Laboratories," B.A. Goldberger et al., Forensic Sci. Rev. 9:59; 1997. In reviewing and interpreting chromatograms, there are a number of threshold criteria that should considered to ensure that the chromatogram is of sufficient quality that it can be used as the foundation for the later analysis.

120. The first criteria to consider is the shape of the curve of each peak. Optimally, the peaks should be a classic Gaussian curve. This means that there should be no shoulders or tailing. A shoulder is simply a bump in the curve wall and tailing is when the back half of the peak trails off to the right. The presence of a shoulder or a tail is a clear indication that two substances are co-eluting, which means that two or more substances have the same or nearly the same retention time. If two substances are co-eluding, the peak with the shoulder or tail is a graphic representation of either both, or some combination of both, of the substances found at that retention time. Put differently, the peak with a shoulder or tail is a graphic representation of both the target compound and an irrelevant compound. Accordingly, any later calculations based on this peak are unreliable and will lead to inaccurate results.

121. In addition to a Gaussian curve, peaks should be well resolved. A well resolved peak occurs when the peak starts at the baseline and then ends at the baseline. If the valley between peaks on a chromatogram fail to reach baseline, the peak are not classified as well resolved. However, absolute peak resolution, while a goal, is not required, but the more the peaks are unresolved, the more unreliable and inaccurate the test results will be. A related concept to well resolved peaks is to have good baseline

separation of the peaks such that there is a clear end of one peak and start of the next peak.

122. The chromatograms generated by LNDD that are the foundation of the T/E and C.I.R. test contain peaks with shoulders and tailing, and are not well resolved. The quality of the chromatograms are so poor that any calculations, and ultimately, the test results, are not reliable, valid and are inaccurate. The T/E chromatograms are found at USADA 0093, 0213, 0277, 0280, and 0282. All of these chromatograms, to some degree, show peaks that have shoulders and tails, and are not well resolved or baseline separated.

123. The T/E confirmation for the "A" sample, USADA 93 (bottom left) shows poor baseline separation as to both the testosterone and the epitestosterone peaks, the retention time obscures the epitestosterone peak, and it is not at all clear that the automatic peak integration performed by the Agilent Chem Station was correct. Further, the chromatogram for the internal standard, methyltestosterone, USADA 93 (top right) also exemplifies a resolution problem. There is a peak at 21:21 which is co-eluting with the internal standard at 20.98. These peaks are clearly not baseline resolved.

124. More deficiencies of the same sort can be seen by looking at USADA 213 (bottom right), which is the chromatogram from the first, unsuccessful, T/E confirmation on Mr. Landis's "A" sample. Again this chromatogram shows poor baseline separations and questionable peak integration.

125. This same poor chromatography can be seen in the three confirmation "B" sample T/E tests. The first confirmation T/E test chromatogram on the "B" sample is at USADA 277 (bottom right). This chromatogram is simply horrible with respect to the

epitestosterone. There is no baseline resolution, no peak separation, and, put simply, the epitestosterone is indistinguishable from neighboring peaks. The testosterone peak is better, however, there is a shoulder that indicates probable co-elution. The internal standard, USADA 277 (top right) has significant co-elution as well – the peak at 21.22 is co-eluting with the internal standard eluting at 20.98. These same chromatographic deficiencies are also present in the chromatograms for the second confirmation and third confirmation test, which are found at USADA 280 and 282.

126. The comparison of the T/E chromatography generated by LNDD and the T/E chromatography generated by the UCLA Olympic Analytical Laboratory further illustrate the poor chromatography generated by LNDD. The UCLA laboratory chromatogram for the UCLA Laboratory is found at GDC 524. This chromatogram shows peaks with a Gaussian curve, no shoulders or tailing, and well resolved peaks and baseline separation.

4. Matrix Interference

127. The sample provided by Mr. Landis after Stage 17 was a urine sample, which is also described as a urine matrix. Urine, by its nature, is a matrix that contains numerous compounds that are being excreted. Further, Mr. Landis did not provide the urine sample in a sterile environment, which allows for the introduction of other compounds to be introduced in the sample.

128. Both the T/E and the C.I.R. tests require that a chemical process be performed on the sample to remove the irrelevant compounds from the sample. If the laboratory does not prepare the sample properly, significant matrix interference will be shown in the chromatogram. Matrix interference is graphically depicted in the chromatogram by a jagged baseline or a sloping baseline. As noted above about the effects of poor curve

shape and unresolved peaks, the presence of matrix interference in the chromatogram cause unreliable, invalid and inaccurate results.

129. In fact, the ISL mandates that when a lab validates a particular method for use in confirming the presence of threshold substances like testosterone and epitestosterone, matrix interference "must" be limited. ISL §5.4.4.2.2. During the AAA proceeding, USADA argued that this ISL did not apply to the testing of actual samples as it should be limited only to validation studies. This argument is absurd. If a validation study, a study to establish that the laboratory's method consistently achieves reliable and accurate results, requires limited matrix interference, so should the actual method in practice. To interpret the ISL otherwise would be to allow a laboratory to apply a validated method in circumstances for which it is not validated for.

5. Finding an Internal Standard when it did not exist

130. Another remarkable error by LNDD is that in one T/E test the laboratory found a substance that was not actually present in the sample. In the method for preparing the sample for a T/E screening test, LNDD inserts deuterated androsterone as an internal standard in the T/E screen test, but LNDD does not add this internal standard in the confirmation method. Yet in a T/E test performed on a sample prepared with this confirmation method, one without deuterated androsterone, actually found that the deuterated androsterone was in the sample. The Panel appeared to believe that the automatic identification of deuterated androsterone by the instrument in no way reflected mistakes on the part of the lab. Whether it is a mistake or not a mistake, it establishes that the laboratory results are not reliable.

H. Incorrect Column Identification

131. A critical piece of equipment in both the GC/MS and the GC/C/IRMS instrument is the gas chromatograph. The gas chromatograph separates molecules by sending these molecules through a column, which is essentially a tube coated with complex hydrocarbons. However, there are numerous types of columns with different chemical compositions that can be used in any particular machine. By having a different chemical composition, the amount of time it takes a particular compound to travel through the column, or retention time, will vary. In other words, the type of column used has a direct impact on the molecules retention time.

132. As will be explained in the declarations of Dr. Keith Goodman, Dr. Wolfram Meir-Augustine and Dr. Simon Davis, the C.I.R. test uses two instruments, the GC/MS and the GC/C/IRMS. To ensure that the retention time provided by the gas chromatograph in the GC/MS instrument is comparable to the retention time provided by the gas chromatograph in the GC/C/IRMS instrument, both gas chromatographs must have the same column, in addition to the same method file. Failure to have the same column and method file will result in the retention times of the target analytes being different between the GC/MS instrument and the GC/C/IRMS instrument such that trying to compare the retention times between the two instruments would be similar to trying to compare apples and oranges.

133. According to the laboratory document packet provided by LNDD for Sample 995474 that I reviewed, the columns in the GC/MS instrument and the GC/C/IRMS instrument at the time of Mr. Landis' Stage 17 sample was tested were not the same. The

column used in the GC/MS instrument was Agilent HP-5ms, USADA 0124, 0303, and the column used in the GC/C/IRMS phase is Agilent DB-17ms. USADA 0153.

134. The importance of having the same column in the GC/MS and GC/C/IRMS instrument was acknowledged by the majority of the AAA panel, yet, contrary to evidence noted above, the AAA Award found that "[t]he GC Column is, of course, the same in both instruments." Majority Award, ¶ 186. This assertion is simply not true based on the evidence provided in the laboratory document package for Sample 995474.

135. LNDD's improper use of two different columns in the GC/MS and the GC/C/IRMS instruments, and the AAA Panel's incorrect factual finding, was noted in Appellant's Brief. In its brief, USADA in essence concedes that LNDD's laboratory document packet notes that different columns were used in the GC/MS and GC/C/IRMS instruments, but that this was caused by a "mistake in the printouts of the informational operation summary." Appellee's Brief at 43. USADA then contends that despite these errors in the documentation, the proper column was used in the GC/MS instrument during the Carbon Isotope Ratio test. USADA explains that during a service of the GC/MS instrument by Agilent, Mr. Gerard Le Petit, a technician from Agilent (the manufacturer of the column) did not change the operating summary on the GC/MS instrument after performing his diagnostic testing using a different column. Appellee's Brief at 44.

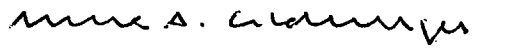
136. Even assuming the truth of USADA's contention that the same column was used in both the GC/MS and GC/C/IRMS, the fact that there is an error in the laboratory documentation packet provided by LNDD causes me great concern. As noted above, the purpose of all laboratory documentation is to provide a third party who reviews the documentation with all necessary information to evaluate the reliability and accuracy of

the test results. Indeed, the ISL states that "the record should be such that in the absence of the analyst, another competent analyst could evaluate what tests had been performed and interpret the data." ISL § 5.2.6.1. This "purported" mistake is yet another error in the laboratory document packet, which is supposed, standing alone, support the finding of an adverse analytical finding. Further, this mistake is again indicative of a laboratory that refuses to follow the ISL and other generally accepted scientific principles and methodology. In sum, this error, compounded with the other errors, is the work of a generally incompetent laboratory, which, in my opinion, seriously jeopardizes the accuracy and reliability of the results reported by the laboratory.

I. Conclusion

137. For the foregoing reasons, the T/E and C.I.R. test results are not reliable, not valid, are inaccurate, and should not be given in any evidentiary weight.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. This declaration was executed on Friday, March 07, 2008 in Newberry, Florida.



BRUCE A. GOLDBERGER

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CURRICULUM VITAE

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EDUCATION

May, 1982

B.A. degree in Zoology
Drew University
Madison, New Jersey

August, 1985

M.S. degree in Forensic Toxicology
University of Maryland School of Medicine
Department of Pathology, Division of Forensic Pathology
Baltimore, Maryland

Thesis: "*In vitro* and *in vivo* studies of the collection and delayed analysis of the alcohol content in breath."

January, 1993

Ph.D. degree in Forensic Toxicology
University of Maryland School of Medicine
Department of Pathology, Division of Forensic Pathology
Baltimore, Maryland

Dissertation: "Measurement and interpretation of heroin, 6-acetylmorphine and morphine concentrations in biological tissues obtained from heroin users and heroin-related deaths."

PROFESSIONAL POSITIONS

July, 2005 to present	Professor, Clinical Track Department of Pathology, Immunology and Laboratory Medicine Department of Psychiatry University of Florida College of Medicine Gainesville, Florida
November, 2002 to June 2005	Associate Professor, Clinical Track Department of Psychiatry University of Florida College of Medicine Gainesville, Florida
July, 2001 to June 2005	Associate Professor and Director of Toxicology, Clinical Track Department of Pathology, Immunology and Laboratory Medicine University of Florida College of Medicine Gainesville, Florida
July, 1999 to June, 2001	Assistant Professor and Director of Toxicology, Clinical Track Department of Pathology, Immunology and Laboratory Medicine University of Florida College of Medicine Gainesville, Florida
October, 1994 to June, 1999	Assistant Professor and Director of Toxicology Department of Pathology, Immunology and Laboratory Medicine University of Florida College of Medicine Gainesville, Florida
September, 1987 to September, 1994	Toxicologist National Center for Forensic Science a division of Maryland Medical Laboratory Baltimore, Maryland
September, 1989 to May, 1992	Assistant Toxicologist and Toxicology Laboratory Manager Toxicology Laboratory Office of the Chief Medical Examiner Baltimore, Maryland
July, 1986 to September, 1989	Assistant Toxicologist Toxicology Laboratory Office of the Chief Medical Examiner Baltimore, Maryland

September, 1982 to September, 1987	Laboratory Technologist Clinical Toxicology Department Maryland Medical Laboratory Baltimore, Maryland

CERTIFICATIONS

Diplomate. American Board of Forensic Toxicology, Certificate Number 218 (3/1/99-6/30/09)
Clinical Laboratory Director. Board of Clinical Lab Personnel, Department of Business and Professional Regulation, State of Florida, License Number DI 0033647 (5/18/95-8/31/08)
Forensic Toxicology Specialist. American Board of Forensic Toxicology, Certificate Number 5001 (11/1/92-2/28/99)
Toxicological Chemist. National Registry of Certified Chemists (previously known as the National Registry in Clinical Chemistry), Certificate Number 2254 (1991-2009)

HONORS AND AWARDS

Educational Research Award. Society of Forensic Toxicologists, 1984 and 1986
Sunshine Award. Toxicology Section, American Academy of Forensic Sciences, 1988
Toxicology Section Scholarship. American Academy of Forensic Sciences, 1991
Outstanding Scientific Achievements by a Young Investigator Award. American Association for Clinical Chemistry, 1994
Mid-Career Achievement Award, The International Association of Forensic Toxicologists, 2004
Alexander O. Gettler Award, Toxicology Section, American Academy of Forensic Sciences, 2006

CAMPUS ACTIVITIES

Teaching

College of Medicine:

General Pathology and Immunology (BMS 5608) – Lectures in Chemical Carcinogenesis and Forensic Pathology
Systemic Pathology and Laboratory Medicine (BMS 5600) Case Study Mentor
Principles of Drug Action (GMS 6002) – Forensic Pharmacology (Grand Rounds)
Special Topics in Pathology: Cellular & Molecular Basis of Liver Disease (GMS 6381) – Lecture in Pharmacogenomics and Drug Toxicity
Translational Neuroscience: Junior Honors Medical Program (MEL 4001) – Forensic Medicine
Laboratory Rotation Mentor, Interdisciplinary Graduate Program
Pathology Resident Rotation (Preceptor)

College of Pharmacy:

Selected Topics in Pharmacy (The Role of the Pharmacist in Substance Abuse Education and Prevention; PHA 4933) – Lecture in Forensic Toxicology

College of Law:

Handling Drug/Alcohol Crimes Seminar – Lecture in Forensic Toxicology

Thesis/Doctoral Dissertation Committee Member:

Michael W. Belford, Department of Chemistry, 2001-2003
Matthew W. Warren, Department of Psychiatry, 2003-2006
Timothy L. Naylor, Department of Physiological Sciences, 2003-2005
Frank Kero, Department of Chemistry, 2004-present
David Khey, Department of Criminology, Law and Society, 2005-present
Marilyn Prieto, Department of Chemistry, 2007-present

Student/Fellowship Training:

Name	Program	Date
Diana Garside	Post-Doctoral Fellowship in Forensic Toxicology	1994-1997
Jeri Ropero-Miller	Graduate Student – Doctoral	1994-1998
Ruth Winecker	Graduate Student – Doctoral	1994-1996
Jason Byrd	Graduate Student Rotation	1996
Bart Wacek	Graduate Student Intern	1996
Mary Rucker	Graduate Student – IDP Lab Rotation	1998
Richard Fox	Center for Precollegiate Education and Training	1998
Gretchen Miller	Graduate Student – Master's	1998-1999
Beth Ladlie	Graduate Student – IDP Lab Rotation	1998
Tara Sabo	Graduate Student – IDP Lab Rotation	1999
Andria Hobbs	Undergraduate Student – University Scholars Program	1999-2000
Kristofer Rau	Graduate Student – IDP Lab Rotation	1999
Jessica Walrath	Graduate Student – IDP Lab Rotation	2000
Bruno De Martinis	Visiting Scientist (Brazil)	2000-2001
Karen Vieira	Graduate Student – IDP Lab Rotation	2001
Michele Merves	Graduate Student – Doctoral/Post-Doctoral	2001-present
Sheng-Meng Wang	Visiting Scientist (Taiwan)	2001
María Antonia Martínez González	Visiting Scientist (Spain)	2002
Rebecca Murray	Pharmacy Student	2002-2003
Ansley Gascoigne	Undergraduate Intern (UCF)	2004
Kelly MacDougall	Graduate Student – IDP Lab Rotation	2005
Rebecca Fidler	Undergraduate Intern (UCF)	2005
Jennifer Hoyer	Undergraduate Intern (UCF)	2005

Christopher Moody	Undergraduate Intern (UCF)	2005
Melissa Clarady	Undergraduate Intern (UCF)	2006
Kimberly Fitzgerald	Medical Student (UF College of Medicine)	2006
Melanie Atkinson	High School Student (PK Young)	2006
Jenna Chin	Undergraduate (UF Senior Research)	2006-2007
Sarah Guilmain	Graduate Student – IDP Lab Rotation	2006
Diana Sum	Pharmacy Student	2007

Administration

College of Medicine

Member, Medical Selection Committee, 2005-present

Department of Pathology, Immunology and Laboratory Medicine:

Director, William R. Maples Center for Forensic Medicine
Unit Director of Toxicology, Diagnostic Referral Laboratories
Member, Diagnostic Referral Laboratories Executive Committee
Member, Diagnostic Referral Laboratories Quality Assurance Group
Chairman, Biosafety Committee
Biologic Safety Officer
Member, Clinical Research Committee
Member, Rocky Points Labs, Building & Safety Committee

Interdisciplinary Toxicology Graduate Training Program (Center for Environmental and Human Toxicology):

Faculty Member
Graduate Coordinator for Pathology
Member, Toxicology Graduate Specialization Committee

University of Florida University Athletic Association:

Member, University Athletic Association Substance Abuse Committee

GRANTS AND CONTRACTS

State of Florida, Department of Health, Office for Emergency Operations, Florida Emergency Mortuary Operations Response System (FEMORS), $1,964,300, 2002-present.

An Exhaled Breath Detection System for Environmental Tobacco Smoke Exposure, James & Esther King Biomedical Research Program, State of Florida, University of Florida, 2004-2005.

Dynamic Signal Processing and Information Extraction for E-Noses, National Science Foundation, Subcontract from Convergent Engineering to Goldberger, $37,813, 2005-2007.

Detection of Ethanol in Human Breath: Mini-GC Use and Exhaled Breath Condensate, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Subcontract from Xhale Diagnostics to University of Florida, $134,091 (pending).

OTHER ACADEMIC ACTIVITIES

Adjunct Assistant Professor in Clinical Chemistry. University of Maryland School of Medicine, Department of Medical and Research Technology, Baltimore, Maryland, 1991-1992 and 1993-1994

Thesis Advisor. College of Graduate Studies, Thomas Jefferson University, Philadelphia, Pennsylvania, 1994

External Examiner for Sarah Kerrigan. Faculty of Graduate Studies, The University of British Columbia, Vancouver, B.C. Canada, 1997

PROFESSIONAL MEMBERSHIPS AND ACTIVITIES

American Academy of Forensic Sciences (AAFS), Fellow, 1983-present

Academy Activities

- Program Committee, Poster Session Chairman, 1994
- Nominating Committee, 1996-1997
- Council, 1995-1997
- Program Committee, Breakfast Seminars Chairman, 1997-1998
- Program Committee, Poster Session Chairman, 1998-1999
- Strategic Planning Committee, 1997-1998
- Long Term Planning Committee, 1998-present
- Board of Directors (Toxicology Section Representative), 1999-2002
- Academy-Wide Luncheons, Moderator, 2000
- Program Committee, Workshop Chairman, 2000-2001
- Forensic Sciences Foundation Nominating Committee, 2000-2001
- Program Committee, Program Co-Chairman, 2001-2002
- Program Committee, Program Chairman, 2002-2003
- Policy and Procedure Committee, 2002-present
- AAFS Website Redesign Task Force (Chairman), 2002-2003
- AAFS Website Content Oversight Task Force, 2003-2004
- Vice President, 2003-2004
- Membership Committee, Chairman, 2003-2004
- Treasurer, 2004-2006
- Executive Committee, 2004-present
- Finance Committee, 2006-present
- Forensic Sciences Foundation Nominating Committee, 2005-2006
- President-Elect, 2006-2007
- Trustee, Forensic Sciences Foundation, 2006-2008
- President, 2007-2008

Toxicology Section Activities
- Workshop Co-Chairman, 1992-1995, 1999
- Program Committee, 1992-1996
- Program Chairman, 1994-1995
- Secretary, 1995-1996
- Chairman, 1996-1997
- Chairman, Nominating Committee, 1997-1998
- Abstract Guidelines Committee, 1995-1996
- Editor, *News and Views*, 1993-1996
- Steering Committee, 1994-present
- Minutes Review Committee, 1994-1999
- Awards Committee, 1997-1999, 2001-present
- *ad hoc* Membership Guidelines Committee, 1994-1999

American Association for Clinical Chemistry (AACC), Member, 1984-present
- TDM/Tox LIP Committee, 1991-1996; Chairman, 1995-1996
- FUDT/LIP Committee, 1997-present; Chairman, 1999
- Toxicology News Committee, Chairman, 2000-2001
- Workshop Leader, 1993-1994
- TDM and Clinical Toxicology Division, representative to the Joint Committee on Education and Training in Toxicology, 1993-1996

American Board of Forensic Toxicology (ABFT)
- Board of Directors, 2000-present
- Treasurer, 2002-present
- Promotion Committee, 1998-present
- Examination Committee, 1999-2004
- Chair, Finance Committee, 2002-present

California Association of Toxicologists (CAT), Associate Member, 1993-present

Council of Science Editors, 2001-present

National Academy of Clinical Biochemistry, Fellow, 2003-present

International Association for Chemical Testing (IACT), Member, 1999-present

National Committee for Clinical Laboratory Standards, Member, 1993-2002
- Gas Chromatography/Mass Spectrometry (GC/MS) Confirmation of Drugs Committee

National Registry of Certified Chemists (NRCC)
- Board of Directors, 2001-2003
- Examination Committee, 2001-2003

National Safety Council, Committee on Alcohol and Other Drugs, Member, 1988-present
- Education and Training, Co-Chairman, 1990-1991
- Education and Training, Chairman, 1992-1997
- Executive Board, 1992-2007
- Action Programs Subcommittee, 1998-present
- Web-Site (ad hoc) Subcommittee, Chairman, 2002-present

Society of Forensic Toxicologists (SOFT), Member, 1984-present
- Advisory Committee on Hair Analysis, 1991-1992
- Annual Meeting Program Committee, 1993-present
- Chairman, SOFT Web-site Committee, 1997-present
- Chairman, SOFT Logo Redesign Committee, 1997

Board of Directors, 1998-2000
Special Issue Editor, Journal of Analytical Toxicology, 1999
Board of Directors (ex officio), 2005-present
The International Association of Forensic Toxicologists (TIAFT), Member, 1991-present
T'2007 Scientific Advisory Committee

EDITORIAL TASKS

Clinica Chim Acta – Member, Editorial Board, 1999-2003
Clinical Chemistry - ad hoc reviewer, 2006
Clinical and Forensic Toxicology News (AACC Newsletter) – Chairman, Editorial Advisory Board, 1999-2001
Drug Court Review – ad hoc reviewer, 2005
Forensic Science International – ad hoc reviewer, 2004-2006
Forensic Science Review – Member, Board of Editors, 2002-present
Journal of Analytical Toxicology –
Editor-in-Chief, 2001-present
Member, Editorial Advisory Board, 1997-2000
Invited Reviewer, 1995-1996
Society of Forensic Toxicologists Special Issue Editor, October, 1999
Journal of Forensic Sciences – Member, Editorial Board, 1997-present
Science & Justice – ad hoc reviewer, 2005
Therapeutic Drug Monitoring and Toxicology (AACC In-Service Training and Continuing Education Publication) – Chairman, Editorial Board, 1995-1996
Clarke's Analysis of Drugs and Poisons (3rd Edition), Pharmaceutical Press – Member, Editorial Advisory Board, 2000-2004
Clarke's Analysis of Drugs and Poisons (4th Edition), Pharmaceutical Press – Member, Editorial Advisory Board, 2007-present

CONSULTANT AND OTHER RELATED ACTIVITIES

Expert Witness/Consultant in Forensic Toxicology. Qualified as an Expert in Forensic Toxicology in Federal, State of Florida, Canadian, and Military Courts of Law
Laboratory Inspector. National Laboratory Certification Program, Substance Abuse and Mental Health Services Administration, DHHS, 1989-2000
Chairman. Florida Department of Law Enforcement/Institute of Police Technology and Management Implied Consent Rules Committee, 1999-2000
Chairman. Substance Abuse Committee, Athletic Programs, Santa Fe Community College, 1997-present
Co-Chair, Methadone Associated Mortality: A National Assessment Workshop, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, Arlington, Virginia, May 2003
Member, Florida Task Force on Suicide Prevention, Office of Drug Control, Office of the Governor, State of Florida, 2003-2007
Consultant, Drug Enforcement Administration (Arlington, VA), 2004-present
Consultant, National Football League Players Association (Washington, D.C.), 2006-present

Planning Committee, Methadone Mortality: A Reassessment, Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, Arlington, Virginia, July 2007

Member, State of Florida Suicide Prevention Coordinating Council, Office of Drug Control, Office of the Governor, State of Florida, 2003-present

REVIEW OF GRANTS AND CONTRACTS

Consultant. Counterdrug Technology Assessment Center Demand Reduction Advisory Board, Office of National Drug Control Policy, Executive Office of the President, 1993

Consultant. Maternal Lifestyle Study, National Institute of Child Health and Human Development, National Institutes of Health, 1992-1993

Consultant. Measurement of Caffeine, Paraxanthine and Osmolality in Serum from the Collaborative Perinatal Project, National Institute of Child Health and Human Development, National Institutes of Health, 1996

ad hoc Committee Member. Molecular, Cellular and Chemical Neurobiology Research Review Subcommittee [NIDA/B], National Institute on Drug Abuse Initial Review Group, National Institutes of Health, 1996-1997

ad hoc Reviewer. Clinical Protocols, Addiction Research Center, National Institute on Drug Abuse, National Institutes of Health, 1998

ad hoc Committee Member. Epidemiology and Prevention Review Committee [NIDA/G], National Institute on Drug Abuse Initial Review Group, National Institutes of Health, 1998

ad hoc Reviewer. NIDA/INVEST Research Fellowship Program, National Institute on Drug Abuse, National Institutes of Health, 2000

Reviewer. FY 2005 General Forensics Research and Development Solicitation, Office of Science and Technology, National Institute of Justice, U.S. Department of Justice, 2005

Reviewer. FY 2006 Forensic Toxicology Research and Development (R&D) Solicitation, Office of Science and Technology, National Institute of Justice, U.S. Department of Justice, 2006

INVITED LECTURES

The Use of Quality Control by Forensic Urine Drug Testing Laboratories. Hewlett-Packard Clinical/Forensic Seminar, Rockville, Maryland, April, 1989.

Principles of Forensic Toxicology. Forensic Toxicology Workshop, Department of Health and Rehabilitation Services, State of Florida, Orlando, Florida, April, 1990.

Drug Testing in the 1990s. 1991 Hewlett-Packard User's Group Meeting, American Society of Mass Spectrometry, Nashville, Tennessee, May, 1991.

Optimization of GC/MS. Hewlett-Packard User's Group Meeting, Baltimore, Maryland, October, 1991.

FPDT: Forensic Pelage Drug Testing (Breakfast Seminar). American Academy of Forensic Sciences, New Orleans, Louisiana, February, 1992.

Optimization of GC/MS. Forensic and Clinical Drug Analysis by GC/MS. Hewlett-Packard Sponsored Workshop, American Association for Clinical Chemistry, Chicago, Illinois, July, 1992.

Confirmation. Preparing for the NIDA NLCP Inspections: Problems Commonly Encountered by Inspectors. Society of Forensic Toxicologists, Cromwell, Connecticut, October, 1992.

Hair Testing: The Growing Way to Test for Drugs of Abuse. The Pittsburgh Conference, Atlanta, Georgia, March, 1993.

Disposition of Heroin and 6-Acetylmorphine in Hair. Clinical Pharmacology/Toxicology Forum, Baltimore, Maryland, March, 1993.

Testing for Abused Drugs in Human Hair. 1993 Hewlett-Packard User's Group Meeting, American Society of Mass Spectrometry, San Francisco, California, May, 1993.

Hair. Drug Analysis of Unusual Biological Tissues. American Association for Clinical Chemistry, New York, New York, July, 1993.

Heroin and Metabolites in Biological Tissues Obtained from Heroin Users and Heroin-Related Deaths. Roche Diagnostics Seminar, Branchburg, New Jersey, August, 1993.

Seminar: Measurement and Interpretation of Heroin, 6-Acetylmorphine and Morphine Concentrations in Biological Tissues. Department of Medical and Research Technology, University of Maryland School of Medicine, Baltimore, Maryland, September, 1993.

Study of the Effect of "UrinAid" on HHS Regulated Urine Specimens. Drug Testing Advisory Board, Division of Workplace Programs, Substance Abuse and Mental Health Services Administration, Bethesda, Maryland, September, 1993.

Current Status of Hair Drug Testing. Capital Section, American Association for Clinical Chemistry, Baltimore, Maryland, November, 1993.

Optimization Techniques for GC/MS. The In's and Out's of Capillary Gas Chromatography: Routinely Utilized Inlet and Detector Systems. American Academy of Forensic Sciences, San Antonio, Texas, February, 1994.

Opiates. Forensic Toxicology. Armed Forces Institute of Pathology, Vienna, Virginia, April, 1994.

Adulteration Issues-Laboratory Checks and Balances. Substance Abuse Workshop. Department of Energy, Alexandria, Virginia, May, 1994.

Hair. Drug Analysis of Unusual Biological Tissues. American Association for Clinical Chemistry, New Orleans, Louisiana, July, 1994.

Pharmacology of Heroin and Related Opiates in Hair. SOFT Conference on Drug Testing in Hair, Tampa, Florida, October, 1994.

Opiates. Fundamentals of Forensic Toxicology: A Basic Course. Society of Forensic Toxicologists, Baltimore, Maryland, October, 1995.

Testing for Drugs in Hair. Seminar. Departments of Pharmacodynamics and Pharmaceutics, University of Florida College of Pharmacy, Gainesville, Florida, October, 1995.

Postmortem Toxicology. Advances in Alcohol and Drug Testing-Significance for Legal Proceedings. Toxicology Consultants Forensic Science CLE Seminar Series. Fort Lauderdale, Florida, December, 1995.

The Analysis of Anabolic Agents in Sports. Amateur Athletic Drug Testing – Substance Abuse Policy. American Academy of Forensic Sciences, Nashville, Tennessee, February, 1996.

Drugs of Abuse Testing. Boehringer Mannheim Corporation 1996 Preferred Partners Meeting and Product Fair. Orlando, Florida, March, 1996.

Drug Free Workplace Seminar - Lab Procedures. Gainesville Area Chamber of Commerce, Gainesville, Florida, May, 1996.

Testing for Cocaine in Hair: New Clinical and Forensic Applications. Department of Pathology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, Florida, June, 1996.

Drug Testing for Drug Courts: Components of Reliability. Gaining Momentum: Drug Courts in Florida. Supreme Court of the State of Florida, Office of the State Courts Administrator, Naples, Florida, June, 1996.

Rohypnol and Rape Prevention. Rape & Crime Victim Advocate Program, Alachua County Department of Community Services, Gainesville, Florida, July, 1996.

Medical Examiner Toxicology, Analysis of Unusual Biological Tissues, and Forensic Chemistry. Introduction to Forensic Toxicology. American Association for Clinical Chemistry, Chicago, Illinois, July, 1996.

High Sensitivity CEDIA Benzodiazepine DAU: New Solutions for the Nineties. Boehringer Mannheim Corporation 1996 Industry Workshop at the AACC Annual Meeting. Chicago, Illinois, July, 1996.

Forensic Toxicology. 1996 Clinical Chemistry and Toxicology Audioconference Series - Teleconference Network of Texas. Gainesville, Florida, August, 1996.

Forensic Toxicology Sites on the World Wide Web. Forensic Toxicology and the Internet. Society of Forensic Toxicologists, Denver, Colorado, October, 1996.

Drug Free Workplace Seminar – Lab Procedures. Gainesville Area Chamber of Commerce, Gainesville, Florida, October, 1996.

Forensic Science: A Living Science – Amniotic Fluid and Breast Milk. American Academy of Forensic Sciences, New York City, New York, February, 1997.

Forensic Toxicology: QA/QC Considerations. NFSTC Forensic Toxicology Workshop, Gainesville, Florida, August, 1997.

Implementation of a PT Program for Hair Testing in Florida. HHS Drug Testing Advisory Board, Scientific Meeting on Drug Testing of Alternative Specimens and Technologies, Arlington, Virginia, September, 1997.

Signs of Impairment & Physiology and Pharmacology, Breath Test Instructor Course, Institute of Police Technology and Management, University of North Florida, Jacksonville, Florida, January, 1998.

Cocaine Analyses in Breast Milk and Nails. Seminar. Department of Pharmaceutics and Pharmacodynamics, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, March, 1998.

Hewlett-Packard Seminar on Drug Testing and Forensic Analyses. Wilmington, Rockville, Atlanta, and Tampa, March, 1998.

Results from the First Round of the State of Florida Hair Proficiency Testing Program. Drug Testing Advisory Board, Division of Workplace Programs, Substance Abuse and Mental Health Services Administration, Bethesda, Maryland, June, 1999.

Physical Effects of Abuse. The GHB, GBL and 1,4 Butanediol Working Group Meeting. Sponsored by Orphan Medical Group, National Forensic Science Technology Center, St. Petersburg, Florida, July, 1999.

Case Studies in Forensic Toxicology. Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, Florida, August, 1999.

Forensic Toxicology. Microbiology and Cell Science Student Organization. University of Florida, Gainesville, Florida, September, 1999.

Hewlett-Packard Seminar on Drug Testing. Fundamental and Critical Procedures Used in the Analysis of Drugs of Abuse in Urine by GC/MS. Mexico City, Mexico, November, 1999.

Leading Edge Seminar – The Future of Forensic Medicine at the University of Florida, University of Florida Department of Conferences and Seminars, Division of Continuing Education, Gainesville, Florida, February, 2000.

Forensic Toxicology of Opiate Alkaloids and Synthetic Analgesics – Metabolism of Opioids. American Academy of Forensic Sciences, Reno, Nevada, February, 2000.

Post-Mortem Forensic Toxicology (Part 1), Shands Hospital Laboratories Continuing Education Program, Gainesville, Florida, March, 2000.

Drug Testing: An Important Element in Substance Abuse Prevention – Today's Drugs, Beating the Test and Other Myths. American Alliance for Health, Physical Education, Recreation and Dance, Orlando, Florida, March, 2000.

Contemporary Practice in Clinical Toxicology – Opiates. American Association for Clinical Chemistry, Alexandria, Virginia, June, 2000.

Assessment of Alternative Specimens in Forensic Toxicology. Society of Forensic Toxicologists, Milwaukee, Wisconsin, October, 2000.

Post-Mortem Forensic Toxicology (Part 2), Shands Hospital Laboratories Continuing Education Program, Gainesville, Florida, November, 2000.

The Drunk and Drugged Driver: Understanding Toxicology, Advanced DUI Seminar, Florida Prosecuting Attorneys Association, Ocala, Florida, March, 2001.

Effects on the Body, Florida Statewide Conference on Designer Drugs, Florida Department of Law Enforcement, Orlando, Florida, April, 2001.

Club Drugs, Florida Association of Medical Examiners, Daytona Beach, Florida, November, 2001.

Forensic Toxicology, Florida Homicide Investigators Association, Gainesville, Florida, November, 2001.

Chemical Agents, Community Bioterrorism Summit, Shands HealthCare, Gainesville, Florida, November, 2001.

Analytical Toxicology Considerations in Drugs and Driving Cases, The Effects of Drugs on Human Performance and Behavior, Robert F. Borkenstein Center for Studies of Law in Action, Indiana University, Bloomington, Indiana, March, 2002.

Chemical Agents of Terrorists, The Challenge of Bioterrorism, Florida League for Nursing, University of Florida, Gainesville, Florida, April, 2002.

Chemical Agents, Shands Hospital Laboratories Continuing Education Program, Gainesville, Florida, August, 2002.

Club Drugs. Microbiology and Cellular Science Student Organization. University of Florida, Gainesville, Florida, September, 2002.

Analytical Toxicology Considerations in Drugs and Driving Cases, The Effects of Drugs on Human Performance and Behavior, Robert F. Borkenstein Center for Studies of Law in Action, Indiana University, Bloomington, Indiana, March, 2003.

Drug and Deaths in Florida, Grand Rounds, Department of Psychiatry, University of Florida College of Medicine, March 2003.

Forensic Pharmacology, Consumer Chemistry (CHM 1083), University of Florida, April 2003.

The Role of the Toxicology Laboratory in the Prosecution of Drugged Driving Cases, International Association for Chemical Testing, Cocoa Beach, Florida, April, 2003.

The Challenge to the Forensic Community. Methadone Associated Mortality: A National Assessment Workshop, Center for Substance Abuse Treatment Substance Abuse and Mental Health Services Administration, Arlington, Virginia, May, 2003.

Methadone Deaths in Florida. Methadone Associated Mortality: A National Assessment Workshop, Center for Substance Abuse Treatment Substance Abuse and Mental Health Services Administration, Arlington, Virginia, May, 2003.

Drug Testing Update, Department of Community Health and Family Medicine. University of Florida College of Medicine, Gainesville, Florida, September, 2003.

Forensic Toxicology of Methadone – Methadone and Death Investigations. Society of Forensic Toxicologists, Portland, Oregon, October, 2003.

Methadone Overdose Deaths. National Association of Drug Diversion Investigators, Fort Lauderdale, Florida, November, 2003.

Pursuing a Career in the Forensic Sciences. Biomedical Research Career Development Seminar, University of Florida Interdisciplinary Program in Biomedical Sciences, Gainesville, Florida, January, 2004.

Methadone-Associated Mortality: Report of a National Assessment – Toxicological Issues, The 6th International Conference on Pain & Chemical Dependency, Brooklyn, New York, February, 2004.

Ephedrine: Drug or Supplement? Ephedrine Related Compounds and the Debate on Their Potential for Contribution to Injury – Analytical Issues of Ephedrine and Related Compounds in Possible Injury Cases. American Academy of Forensic Sciences, Dallas, Texas, February, 2004.

Developing Global Strategies for Identifying, Prosecuting, and Treating Drug-Impaired Drivers – Chemical Sensing of Exhaled Breath, Tampa, Florida, February, 2004.

Ninth Annual Southern Coastal International Conference – Breath, Blood and Urine Testing, Jekyll Island, Georgia, March, 2004.

Club Drugs, Shands Hospital Laboratories Continuing Education Program, Gainesville, Florida, April, 2004.

Analytical Toxicology Considerations in Drugs and Driving Cases, The Effects of Drugs on Human Performance and Behavior, Robert F. Borkenstein Center for Studies of Law in Action, Indiana University, Bloomington, Indiana, September, 2004.

Club Drugs, Shands Hospital Laboratories Continuing Education Program, Gainesville, Florida, December, 2004.

Forensic Toxicology Reference Laboratory and Public Service, Southeastern Association of Pathology Chairs and Department Administrators, St. Petersburg, Florida, January, 2005.

Evidenced Based Forensic Science: Interpreting Postmortem Toxicology in the Light of Pathologic Findings – Interpreting Postmortem Opioid Measurements. American Academy of Forensic Sciences, New Orleans, Louisiana, February, 2005.

Drugs and Drug Deaths in Florida. University of Florida Committee on Alcohol and Other Drug Education and Policy, Gainesville, Florida, April, 2005.

OTC and Prescription Stimulants, Stimulants Workshop (sponsored by Society of Forensic Toxicologists), Orlando, Florida, April 2005.

Pharmaceutical Abuse, Annual Training for Demand Reduction Program Coordinators, Drug Enforcement Administration, Orlando, Florida, August, 2005.

Update in Forensic Toxicology: Selected Topics in Death Investigation – Case Studies in Analytical & Forensic Toxicology, North American Congress of Clinical Toxicology 2005, American Academy of Clinical Toxicology, September, 2005.

An Epidemic of Drug Deaths in Florida, Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, Florida, September, 2005.

Forensic Toxicology Update – Opiates. Society of Forensic Toxicologists, Nashville, Tennessee, October, 2005.

Interpretation of Toxicological Analysis in the Elderly – Opioids in the Elderly. American Academy of Forensic Sciences, American Academy of Forensic Sciences, Seattle, Washington, February, 2006.

Pediatric Postmortem Toxicology Session – Toxicological Findings of a Mother and Fetus in a Fatal DUI. American Academy of Forensic Sciences, American Academy of Forensic Sciences, Seattle, Washington, February, 2006.

Annual Conference on Addictions – An Epidemic of Opioid-Related Deaths in Florida, Florida Society of Addiction Medicine, Lake Mary, FL, March, 2006.

Methamphetamine: A Deadly Formula – Methamphetamine: Toxicology, Pathology and Treatment, Second Annual Prevention Summit, DISC Village, Inc., Tallahassee, FL, March, 2006

Analytical Toxicology for Impaired Driving Programs – Laboratory Aspects, The Effects of Drugs on Human Performance and Behavior, Robert F. Borkenstein Center for Studies of Law in Action, Indiana University, Bloomington, Indiana, April, 2006.

Forensic Toxicology, Ninth Forensic Science Educational Conference (FSEC) (sponsored by the American Academy of Forensic Sciences and Court TV), Florida Gulf Coast University, Fort Myers, Florida, May, 2006.

CE Committee: How Does Your QA/QC Program Measure Up? – Analytical Toxicology – QA/QC Laboratory Aspects Society of Forensic Toxicologists, Austin, Texas, October, 2006.

Alcohol Use Disorders Colloquium – Alcohol and Drugs in Trauma Cases, Shands at the University of Florida and the University of Florida, College of Medicine, Division of Acute Care Surgery, Gainesville, FL , February, 2007.

DUI and DUI Drugs: State of the Art, Florida Society of Addiction Medicine, Gainesville, FL, March, 2007.

Analytical Toxicology for Impaired Driving Programs – Laboratory Aspects, The Effects of Drugs on Human Performance and Behavior, Robert F. Borkenstein Center for Studies of Law in Action, Indiana University, Bloomington, Indiana, April, 2007.

Multidisciplinary Trauma Conference – Alcohol and Drugs in Trauma Cases, Trauma Services Department, Shands at the University of Florida, May, 2007.

Methadone-Related Deaths in Florida, Methadone Mortality – A Reassessment. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Washington D.C., July, 2007.

Clinical and Translational Science Seminar Series, University of Florida, College of Medicine, Department of Epidemiology & Health Policy Research, Addiction – Forensic Medicine, Gainesville, Florida, September, 2007.

Toxicology Jeopardy – A Practical Approach to DUID Testing – Confirmation - Method Validation, Society of Forensic Toxicologists, Durham, North Carolina, October, 2007.

Stop Drugged Driving, The John P. McGovern Lecture, Institute for Behavior and Health, Washington D.C., November, 2007.

The Cocaine Epidemic, Drug Policy Advisory Council, Florida Office of Drug Control, Tallahassee, Florida, November, 2007.

Pharmacology - Alcohol and Drug Impaired Driving, 2007 DUI Adjudication Lab, Florida Judiciary Education, St. Augustine, Florida, December, 2007.

STATE AND NATIONAL MEDIA APPEARANCES

In Search of Jesse James, A&E and History Channel, 1996
Party Drug, Fatal Drug, 48 Hours, CBS News, 2001
PMA, Channel One News, 2001
Addicted: An OxyContin Tragedy, 48 Hours, CBS News, 2002
Ecstasy – Nothing to Rave About, Florida's News Channel, 2002
Hooked On Club Drugs, VH1, 2002
State of Florida v. Rachel Sercey Trial, Court TV, 2003
State of Florida v. Laura Roberts, Inside Edition, 2004
Secrets from the Grave, 48 Hours, CBS News, 2005
Caffeine in Decaf Coffee, Today Show, 2006
Caffeine in Energy Drinks, National Public Radio, 2007
Death of Daniel Smith, CNN and MSNBC, 2007
Death of Anna Nicole Smith, Fox News and Court TV, 2007

PUBLICATIONS

Books

1. Liu RH and Goldberger BA (eds). Handbook of Workplace Drug Testing. AACC Press, 1995 (380 pages) [second printing 1996 – 396 pages; Chinese translation 1997 – 448 pages].

2. Jenkins AJ and Goldberger BA (eds). On-Site Drug Testing. Humana Press, Inc., 2002 (276 pages).

Chapters

1. Goldberger BA and Cone EJ: Heroin. *in* Encyclopedia of Analytical Science. Academic Press, 1995 (pp. 3861-3866).

2. Inoue T, Seta S and Goldberger BA: Analysis of drugs in unconventional samples. *in* Handbook of Workplace Drug Testing. AACC Press, 1995 (pp. 131-158).

3. Garside D and Goldberger BA: Determination of cocaine and opioids in hair. *in* Drug Testing in Hair. CRC Press, Inc., 1996 (pp. 151-180).

4. Winecker RE and Goldberger BA: Urine specimen suitability for drug testing. *in* Drug Abuse Handbook. CRC Press, Inc., 1998 (pp. 764-772).

5. Goldberger BA and Jenkins AJ: Drug Toxicology. *in* Sourcebook on Substance Abuse: Etiology, Epidemiology, Assessment, and Treatment. Allyn & Bacon, 1999 (pp. 184-196).

6. Kerrigan S and Goldberger BA: Opioids. *in* Principles of Forensic Toxicology. AACC Press, 1999 (pp. 202-220). {revised – 2003}

7. Magura S, Laudet A and Goldberger BA: Improving the validity of behavioral drug abuse research through drug testing. *in* Drug Testing Technology: Assessment of Field Applications. CRC Press, 1999 (pp. 215-233).

8. Garside D and Goldberger BA: Forensic and Medicolegal Issues. *in* Atlas of Hair and Nails. Churchill Livingstone, 1999 (pp. 227-232).

9. Kerrigan S and Goldberger BA: Drugs of Abuse - Body Fluids. *in* Encyclopedia of Forensic Sciences. Academic Press, 2000 (pp. 616-626).

10. Ropero JD and Goldberger BA. Opioids. *in* The Clinical Toxicology Laboratory - Contemporary Practice in Clinical Toxicology. AACC Press, 2001 (pp. 73-96).

11. Caplan YH and Goldberger BA: Blood, Urine and Other Fluid and Tissue Specimens for Alcohol Analyses. *in* Medical-Legal Aspect of Alcohol, fourth edition. Lawyers & Judges Publishing Company, 2003 (pp. 149-159).

12. Merves ML and Goldberger BA: Heroin. *in* Encyclopedia of Analytical Science, second edition. Elsevier Press, 2005 (pp. 260-266).

13. Kerrigan S and Goldberger BA: Forensic Toxicology. *in* Forensic Nursing. Elsevier Mosby Publishing, 2005 (pp. 123-139).

14. Kerrigan S and Goldberger BA: Substance Misuse – Alternative Body Fluids Analysis. *in* Encyclopedia of Forensic and Legal Medicine. Elsevier Press, 2005 (pp. 192-201).

15. Isenschmid DS and Goldberger BA: Workplace Testing – Analytical Considerations and Approaches for Drugs. *in* Drug Abuse Handbook, second edition. CRC Press, Inc., 2007 (pp. 775-799).

16. Merves ML and Goldberger BA: Quality Assurance, Quality Control, and Method Validation in Chromatographic Applications. *in* Chromatographic Methods in Clinical Chemistry and Toxicology. John Wiley & Sons, Ltd., 2007 (pp. 1-14).

17. Merves ML and Goldberger BA: Forensic Toxicology. *in* Forensic Chemistry. John Wiley & Sons, Inc. (in press).

18. Kerrigan S and Goldberger BA: Specimens of Maternal Origin – Amniotic Fluid & Breast Milk. *in* Drug Testing in Alternative Biological Specimens. Humana Press, Inc. (in press).

Monographs

1. Goldberger BA: Acetaminophen, Caffeine, Chloramphenicol, Lithium and Procainamide Drug Monographs. *in* Drug Monitoring Data Pocket Guide II. AACC Press, 1994.

2. Goldberger BA: Opiates. Abused Drugs Monograph Series. Abbott Diagnostics, 1994.

3. Goldberger BA, Ropero-Miller JD, Zawta B and Jackson R: Drugs of abuse testing. Questions and Answers. Boehringer Mannheim Corporation, 1998. {revised and reprinted by Roche Diagnostics in 1999}

4. Hammett-Stabler C, Goldberger BA and Ropero-Miller JD: Abused drugs. *in* Medical Toxicology Self Study. American Association for Clinical Chemistry, 1998.

5. Ropero JD, Garside D and Goldberger BA. Opiates. *in* Contemporary Practice in Clinical Toxicology. American Association for Clinical Chemistry, 1998. {second edition, 2000}

6. Goldberger BA (ed.): Hair Analysis: Drugs of Abuse, Therapeutic Drugs, and Steroids {reprints of selected articles from the Journal of Analytical Toxicology}, 2001.

Journal Articles (Refereed)

1. Black DL, Goldberger BA, Isenschmid DS, White SM and Caplan YH: Urine cannabinoid analysis: An integrated multi-method approach. J. Analyt. Toxicol. 8: 224-227, 1984.

2. Goldberger BA and Caplan YH: Infrared quantitative evidential breath-alcohol analyzers: *In vitro* accuracy and precision studies. J. Forensic Sci. 31: 16-19, 1986.

3. Goldberger BA, Caplan YH and Zettl JR: A long-term field experience with breath ethanol collection employing silica gel. J. Analyt. Toxicol. 10: 194-197, 1986.

4. Goldberger BA and Caplan YH: *In vitro* accuracy and precision studies comparing direct and delayed analysis of the ethanol content of vapor. J. Forensic Sci. 32: 48-54, 1987.

5. Black DL, Goldberger BA and Caplan YH: Enzyme immunoassay method for comprehensive drug screening in micro-samples of urine. Clin. Chem. 33: 367-371, 1987.

6. Caplan YH, Levine B and Goldberger B: Fluorescence polarization immunoassay evaluated for screening for amphetamine and methamphetamine in urine. Clin. Chem. 33: 1200-1202, 1987.

7. Levine B, Goldberger BA and Caplan YH: Evaluation of the Coat-A-Count radioimmunoassay for phencyclidine. Clin. Chem. 34: 429, 1988.

8. McMullen NT, Goldberger B, Suter CM and Glaser EM: Neonatal deafening alters nonpyramidal dendrite orientation in auditory cortex: A computer microscope study in the rabbit. J. Comp. Neurology 267: 92-106, 1988.

9. McMullen NT, Goldberger B and Glaser EM: Postnatal development of lamina III/IV nonpyramidal neurons in rabbit auditory cortex: Quantitative and spatial analyses of golgi-impregnated material. J. Comp. Neurology 278: 139-155, 1988.

10. Jenkins AJ and Goldberger BA: Forensic chemistry: The analysis of controlled substances. Therapeutic Drug Monitoring and Toxicology In-Service Training and Continuing Education Program, American Association for Clinical Chemistry 13(1): 7-15, 1991.

11. Goldberger BA, Caplan YH, Maguire T and Cone EJ: Testing human hair for drugs of abuse. III. Identification of heroin and 6-acetylmorphine as indicators of heroin use. J. Analyt. Toxicol. 15: 226-231, 1991.

12. Levine BS, Wu SC, Goldberger BA and Caplan YH: Two fatalities involving haloperidol. J. Analyt. Toxicol. 15: 282-284, 1991.

13. LoDico CP, Levine BS, Goldberger BA and Caplan YH: Distribution of isoniazid in an overdose death. J. Analyt. Toxicol. 16: 57-59, 1992.

14. Goldberger BA and Jenkins AJ: Testing of abused drugs in urine by immunological techniques. Therapeutic Drug Monitoring and Toxicology In-Service Training and Continuing Education Program, American Association for Clinical Chemistry 13(8): 7-18, 1992.

15. Heller PF, Goldberger BA and Caplan YH: Chloral hydrate overdose: Trichloroethanol detection by gas chromatography/mass spectrometry. Forensic Sci. International 52: 231-234, 1992.

16. Ripple MG, Goldberger BA, Caplan YH, Blitzer MG and Schwartz S: Detection of cocaine and its metabolites in human amniotic fluid. J. Analyt. Toxicol. 16: 328-331, 1992.

17. Ramcharitar V, Levine BS, Goldberger BA and Caplan YH: Bupropion and alcohol fatal intoxication: Case report. Forensic Sci. International 56: 151-156, 1992.

18. Goldberger BA, Darwin WD, Grant TM, Allen AC, Caplan YH and Cone EJ: Measurement of heroin and its metabolites by isotope-dilution electron-impact mass spectrometry. Clin. Chem. 39: 670-675, 1993.

19. Klette KL, Levine B, Dreka C, Smith ML and Goldberger BA: Cholinesterase activity in postmortem blood as a screening test for organophosphate/chemical weapon exposure. J. Forensic Sci. 38: 950-955, 1993.

20. Cone EJ, Holicky BA, Grant TM, Darwin WD and Goldberger BA: Pharmacokinetics and pharmacodynamics of intranasal "snorted" heroin. J. Analyt. Toxicol. 17: 327-337, 1993.

21. Goldberger BA, Cone EJ, Grant TM, Caplan YH, Levine BS and Smialek JE: Disposition of heroin and its metabolites in heroin-related deaths. J. Analyt. Toxicol. 18: 22-28, 1994.

22. Jenkins AJ and Goldberger BA: New antidepressants. Therapeutic Drug Monitoring and Toxicology In-Service Training and Continuing Education Program, American Association for Clinical Chemistry 15: 79-87, 1994.

23. Goldberger BA and Caplan YH: Letter. The effect of glutaraldehyde (UrinAid) on the detection of abused drugs by immunoassay. Clin. Chem. 40: 1605-1606, 1994.

24. Goldberger BA and Cone EJ: Review. Confirmatory tests for drugs in the workplace by GC/MS. J. Chromatogr. A 674: 73-86, 1994.

25. Goldberger BA, Watts VW and Simonick TF: Analysis of volatiles by headspace gas chromatography. Therapeutic Drug Monitoring and Toxicology In-Service Training and Continuing Education Program, American Association for Clinical Chemistry 15: 231-236, 1994.

26. Goldberger BA, Loewenthal B, Darwin WD and Cone EJ: Technical brief. Intrasubject variation of creatinine and specific gravity measurements in consecutive urine specimens of heroin users. Clin. Chem. 41: 116-117, 1995.

27. Goldberger BA, Cone EJ and Kadehjian L: Letter to the editor. Unsuspected ethanol ingestion through soft drinks and flavored beverages. J. Analyt. Toxicol. 20: 332-333, 1996.

28. Ropero JD, Garside D and Goldberger BA: Synthetic and semisynthetic opioid analgesics. Therapeutic Drug Monitoring and Toxicology In-Service Training and Continuing Education Program, American Association for Clinical Chemistry 17: 261-271, 1996.

29. Winecker RE, Goldberger BA, Tebbett I, Behnke M, Eyler FD, Conlon M, Wobie K, Karlix J and Bertholf RL: Detection of cocaine and its metabolites in amniotic fluid and umbilical cord tissue. J. Analyt. Toxicol. 21: 97-104, 1997.

30. Garside D, Goldberger BA, Preston KL and Cone EJ: Rapid liquid-liquid extraction of cocaine from urine for gas chromatographic-mass spectrometric analysis. J. Chromatogr. 692: 61-65, 1997.

31. Ropero-Miller JD, Garside D and Goldberger BA: Technical brief. Automated on-line hydrolysis of benzodiazepines improves sensitivity of urine screening by a homogeneous enzyme immunoassay. Clin. Chem. 43:1659-1660, 1997.

32. Jenkins AJ and Goldberger BA: Identification of unique cocaine metabolites and smoking by-products in postmortem blood and urine specimens. J. Forensic Sci. 42:824-827, 1997.

33. Goldberger BA, Huestis MA and Wilkins DG: Commonly practiced quality control and quality assurance procedures for gas chromatography/mass spectrometry analysis in forensic urine drug-testing laboratories. Forensic Sci. Review 9:59-80, 1997.

34. Garside D, Ropero-Miller JD, Goldberger BA, Hamilton WF and Maples WR: Identification of cocaine analytes in fingernail and toenail specimens. J. Forensic Sci. 43:974-979, 1998.

35. Goldberger BA, Darraj AG, Caplan YH and Cone EJ: Detection of methadone, methadone metabolites, and other illicit drugs of abuse in hair of methadone treatment subjects. J. Analyt. Toxicol. 22:526-530, 1998.

36. Ropero-Miller JD and Goldberger BA: Recreational drugs: Current trends in the 90's. Clin. Lab. Med. 18:727-746, 1998.

37. Preston KL, Goldberger BA and Cone EJ: Occurrence of cocaine in urine of substance abuse treatment patients. J. Analyt. Toxicol. 22:580-586, 1998.

38. McCusker R, Paget-Wilkes H, Chronister C, Goldberger BA and ElSohly MA: Analysis of gamma-hydroxybutyrate (GHB) in urine by gas chromatography/mass spectrometry. J. Analyt. Toxicol. 23:301-305, 1999.

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Commonly Practiced Quality Control and Quality Assurance Procedures for Gas Chromatography/Mass Spectrometry Analysis in Forensic Urine Drug-Testing Laboratories

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Commonly Practiced Quality Control and Quality Assurance Procedures for Gas Chromatography/Mass Spectrometry Analysis in Forensic Urine Drug-Testing Laboratories

REFERENCE: Goldberger BA, Huestis MA, Wilkins DG: Commonly practiced quality control and quality assurance procedures for gas chromatography/mass spectrometry analysis in forensic urine drug-testing laboratories; *Forensic Sci Rev* 9:59; 1997.

ABSTRACT: Forensic urine drug-testing laboratories operate in a prescribed scientific and administrative manner to ensure accurate test results. All specimens positive by an initial immunoassay test must be confirmed by gas chromatography/mass spectrometry (GC/MS). To provide adequate control and verification of these analytical processes, laboratories must implement appropriate policies and procedures to be used in routine practice. This review describes the following topics regarding GC/MS analyses: method validation, instrument performance, assay calibration, quality control, criteria for designating a positive test result, sample and batch acceptance criteria, and GC/MS data review.

KEYWORDS: Accuracy, calibration, carryover, gas chromatography/mass spectrometry, GC/MS, internal standard, laboratory certification, limit of determination, limit of quantitation, linearity, precision, quality assurance, quality control, sensitivity.

INTRODUCTION

Laboratories accredited by the National Laboratory Certification Program of the United States Substance Abuse and Mental Health Services Administration (SAMHSA, formerly the National Institute on Drug Abuse, NIDA), Department of Health and Human Services (HHS) and the College of American Pathologists (CAP) must perform urine drug testing in a prescribed scientific and administrative manner. Testing of specimens under the CAP and HHS Guidelines requires initial testing by an immunoassay, followed by confirmation of all positive initial test results by gas chromatography/mass spectrometry (GC/MS) [70,72].

To provide adequate control and verification of the analytical process, laboratories must implement appropriate policies and procedures regarding GC/MS analysis. This review is intended to discuss the following topics: method validation, instrument performance, assay calibration, quality control, criteria for designating a positive test result, specimen and batch acceptance criteria, and GC/MS data review. Although this review focuses upon those aspects of quality control and quality assurance pertinent to the regulated drug-testing laboratory, many of the components specified below are directly applicable to any laboratory performing drug testing in biological specimens. Indeed, many of the guidelines reviewed below have been adapted from recommended practices for pharmaceutical methods from the Food and Drug Administration (FDA) and the United States Pharmacopoeia (USP), as well as recommendations resulting from a 1988 Ad Hoc Committee Report to the American Academy of Forensic Sciences (Toxicology Section) and a 1995 Mass Spectrometry and Good Laboratory Practices Workshop organized by the American Society for Mass Spectrometry [9,69,73,74,80].

I. METHOD VALIDATION

A. Assay Characterization

Method development is a process of documenting or proving that an analytical method is acceptable for its intended purpose. For analytical methods to be implemented in laboratory-based regulatory drug-testing programs, the laboratory must be able to demonstrate that the chosen analytical method has the ability to provide *accurate* and *reliable* data. These data can then be used to identify drug presence in a urine specimen according to pre-established administrative reporting limits (cutoff concentrations). Therefore, it is critical that the laboratory identify the key assay characteristics which it will validate prior to implementation of the method into routine use. Also, the laboratory must clearly define the evaluation criteria for each of the key assay characteristics it has selected as part of its validation. It has been suggested that at a minimum, the key assay characteristics to be established and evaluated should include: the accuracy, precision, linearity, specificity, sensitivity, carryover potential, and ruggedness of the analytical method [29]. Additional

characteristics to be evaluated may include: the stability of the analyte under various analytical and storage conditions, identification and concentration of the internal standard(s) for the method, validation of use of partial (diluted) sample volumes, and estimated recovery of the analyte from the matrix [18].

Specific evaluation criteria for method validation generally accepted by the scientific community for an analytical method can vary depending on the particular technique used (i.e., HPLC, GC/MS, LC/MS), as well as its particular application. Much of the available published information with respect to details of validation protocols, such as the number of batches to be evaluated, the number of replicates, and specific acceptability criteria, is based upon chemical analyses performed on autoanalyzers, or HPLC systems, rather than GC/MS systems [2,18,38,41, 78]. Therefore, the application of quality control principles to GC/MS analysis of urine specimens has been based largely upon professional consensus, or "generally accepted laboratory practice" in the drug-testing community. This is in some contrast to a formally and experimentally developed, literature-based approach to implementation of quality control principles to a specific technology. Nevertheless, as individual GC/MS methods for drugs of abuse in urine matrices have been developed and published in the literature, quality control principles have been selected and applied in a variety of ways to assist in the validation of methods and increase confidence in the data that are obtained.

B. Accuracy and Precision of the Analytical Method

Two of the most important assay characteristics to be determined during method validation are accuracy and precision. Together, accuracy and precision determine the error of an analytical measurement. Accuracy and precision are frequently considered together because they are interdependent in assessing the acceptability of a method. The *accuracy* of a method, as used in biopharmaceutical or drug-testing analysis, refers to the closeness of the measured value to the true value for the sample. More specifically, it is a measure of the degree to which a mean obtained from a series of experimental observations agrees with the "true" or "accepted" value of the quantity to be measured. *Precision*, on the other hand, refers to the variability of measurements within a set. It is most often used to demonstrate scatter or dispersion between numeric values in a set of measurements that have been determined under the same analytic parameters.

The accuracy and/or precision of an assay can be determined by comparing test results utilizing laboratory-prepared standards and controls with those obtained with an established reference method and/or by analysis of standard reference materials, such as those available from the National Institute of Standards and Technology (NIST) and CAP [3,17,22,23,66]. Secondary checks may involve reanalyses of performance test specimens and comparison of laboratory results with target means obtained via alternate methods already known to be accurate. (Reanalysis of performance test samples, however, may be prohibited unless the laboratory has obtained prior approval from the submitting agency.)

Accuracy is generally expressed as the percentage difference from the actual value (%DFA) as shown below:

$$\%DFA = [(Mean - Spiked) / Spiked] \times 100$$

An alternate way to determine accuracy is to determine whether the measured mean value is statistically different from the actual value using a *t*-test at 95% confidence [37]. The assessment of accuracy must be carried out on mean values which have been calculated from replicate measurements of reference materials containing known concentration of analyte. At a minimum, triplicate measurements are necessary to establish a single mean value and standard deviation (SD) for any single target concentration. During validation of the assay, it is generally accepted practice to assess accuracy at two to three different concentrations of analyte.

The specific concentrations used for the accuracy evaluation are selected to test accuracy across the range of the standard curve (calibration curve) of the assay. It has recently been recommended that accuracy be assessed using a minimum of 9 determinations over a minimum of three concentrations (e.g., 3 concentrations with 3 replicates each) [65,68]. Other authors have recommended a minimum of 36 determinations over a minimum of 6 concentrations (e.g., 6 concentrations with 6 replicates each) [78].

As stated earlier, the acceptability criteria for accuracy and precision for an assay should be preselected by the laboratory. Generally, accuracy acceptability ranges in forensic urine drug-testing laboratories do not exceed 20% (by convention) of the target concentration. Many laboratories routinely use lower ranges, such as 10%. It should be noted that the acceptable accuracy range selected for initial method validation may differ from that selected for routine use (batch acceptance criteria). For example, a laboratory may require that accuracy be within 10% of the known concentration during method validation, and then choose to increase the acceptable range to 20% for routine daily analysis to accommodate both random and systematic error [38].

Precision of an analytical method is usually assessed in two ways: analysis of multiple measurements during a single analytical run (within-run precision) and analysis of single, or mean, measurements over many runs (between-run precision). Precision is expressed as the percentage relative standard deviation (%RSD), also referred to as the coefficient of variation (CV), as shown below:

$$\%RSD = [Standard\ deviation / Mean] \times 100$$

Within-run precision can be considered a measure of the precision of an analytical method under optimal conditions. The between-run precision, however, is likely to be a better representation of the precision one might observe during routine performance of the assay because these data are generally subjected to a greater number of sources of variability. The lower the calculated CV, the greater the precision of the assay. Precision of an assay at concentrations below, at, and above the assay cutoff concentration can be determined by repeated analyses of quality control samples on a within- and between-batch basis. One approach to assessing between-run precision of the method is to perform triplicate measurements on three separate concentrations of analyte, across three separate analytical batches. Subsequently, the laboratory evaluates the acceptability of the precision of the method using a criterion selected *a priori*. Generally, within-run and between-run coefficient of variation values of <15% are considered acceptable [2,18,29,33,78]. However, because greater variability is to be expected as analyte concentrations approach the limit of detection (LOD) of the analytical method, the laboratory might choose to increase the acceptability criterion to 20% at its lowest measured concentrations [37].

Finally, an additional technique for evaluation of between-run precision data is to apply a one-way analysis of variance (ANOVA) of the data to ensure that results do not significantly differ between analyses [37,42].

C. Linearity of the Analytical Method

The full range of linearity of a method should be established during initial assay characterization and periodically thereafter with specimens containing drug analytes over a wide range of concentrations. Further, the practical range of linearity, referred to here as the daily linear range, should be documented with every batch based upon data obtained with standards and/or controls [29,65]. Acceptance criteria for evaluating linearity data must include review of chromatographic appearance, retention time, and ion ratio or full-scan spectra matching criteria, for example. Although some analytical procedures may require nonlinear calibration, it is conventional for forensic urine drug-testing laboratories to utilize a linear model and univariate regression for GC/MS analysis. In this model, the independent variable is concentration (X) and the dependent variable is response (Y), i.e., the value determined by the value of the independent variable. Recommendations for linearity studies are noted below; issues with respect to acceptability of daily assay calibration (range) are considered in a subsequent section of this paper.

In practice, linearity should be established via visual evaluation of a plot of signals (response) as a function of analyte concentration. If a linear relationship appears probable by inspection of such a plot, test results should be evaluated by an appropriate statistical method, such as the method of least squares regression [6,7,29]. Other statistical approaches must be clearly justified by the laboratory. Data from the regression line, such as the correlation coefficient (r), coefficient of determination (R^2), slope, and residual sum of squares, can also provide useful mathematical estimates of the degree of linearity obtained with the analytical method. In addition, since it is not uncommon to expect an increase in variance as a function of concentration, it may be more appropriate to perform a weighted (rather than unweighted) regression analysis to improve accuracy at the lowest concentrations studied [8].

During initial method validation, the laboratory typically analyzes a series of standards (calibrators) that have been prepared at known concentrations of analyte. Data are plotted and analyzed as just described to determine the upper and lower boundaries of linearity. A frequently used criterion for determining the upper and lower boundary limits in the pharmaceutical industry is the point at which the slope of the line deviates from the overall slope by not more than 5% [20]. However, this recommendation is not originally based upon GC/MS analysis. An alternative is to "reverse calculate" the individual concentrations of each standard using the generated regression line and determine whether each is in compliance with the acceptance criteria established for evaluation of quality control samples (e.g., such as ±20% of the target value). Outliers may be identified as those concentrations of analyte at either extreme (high or low) which are outside the 20% criterion. Acceptable linearity, therefore, is demonstrated when the correlation coefficient exceeds a defined value, such as 0.990, and quantitative concentration of each point falls within ±20% of the target value. The discussion regarding evaluation criteria for linearity can be found in Section III.

The laboratory uses this information to establish the range, or concentration interval, which will routinely be used for analysis of samples. Validating the method over a wider range than that used in daily practice provides increased confidence that the routine standard concentrations are well removed from nonlinear response concentrations. If the laboratory elects to perform the linearity

assessment on more than one occasion, a statistical test of linearity can be performed for each standard curve separately using a weighted ANOVA [8,42].

D. Specificity of the Analytical Method — Interference Studies

Specificity refers to the ability of the analytical method to accurately measure an analyte response in the presence of all potential sample components. All methods should at a minimum be investigated for potential interference by endogenous matrix components, as well as common compounds that are structurally similar to the analyte of interest. A complete review of interference studies published regarding forensic urine drug-testing analytes is beyond the scope of this paper; however, some examples are provided below to illustrate general principles.

The potential interference of endogenous urine components with the assay is most frequently assessed by evaluation of urine specimens from several sources (donors) that are known to be drug-free for the analyte of interest. Assessment of interference from structurally related compounds can be determined by fortification of urine with high concentrations (e.g., 1 mg/mL) of potentially interfering analytes and cutoff concentrations of target analytes, or with concentrations of analytes that are expected under therapeutic conditions. For example, possible interference with the measurement of amphetamine and methamphetamine may occur due to the presence of sympathomimetic amines such as ephedrine, pseudoephedrine, phenylpropanolamine, and phentermine [32]. Further, interference with the measurement of morphine and codeine due to the presence of opiate metabolites and synthetic 6-keto-opioids such as dihydrocodeine, hydromorphone, hydrocodone, oxymorphone, and oxycodone has also been described [25].

The determination of potential interferents that are *not* structurally related to the analyte of interest is more difficult to establish. However, the urine drug-testing laboratory may consider evaluating the potential interference of common over-the-counter products, as well as frequently encountered compounds which produce fragment ions also produced by the analyte of interest. In addition, the laboratory may refer to literature reports for interferences experienced by other investigators and assess their method with the potential interfering substances [34,59,67,79]. Although a laboratory cannot be expected to anticipate all potential interferents with its analytical method, it should make its best effort to characterize them whenever feasible.

The problem of interfering substances may be addressed by employing more selective extraction methods, chromatographic separations, or detection methods. For example, to eliminate potential-false positive amphetamine/methamphetamine results due to the presence of other sympathomimetic amines, aliquots of specimens can be treated with a solution of 0.035 *M* sodium periodate at room temperature, then subjected to extraction. In the presence of periodate, α-hydroxyamines undergo oxidative cleavage removing the potential interferant [24]. Recent evidence indicates that periodate oxidation should be conducted at pH 7 or lower to prevent possible formation of low levels of amphetamine from extremely high levels of methamphetamine that may be present in the specimen [57]. In addition, lowering the injection port temperature of the gas chromatograph, coupled with other preventative measures, eliminates artifactual production of methamphetamine in the presence of high concentrations of ephedrine and/or pseudoephedrine [24,57,67]. It should be noted that some reported interferences may be method-specific and thus will need to be evaluated by the laboratory on an individual basis, as appropriate.

E. Sensitivity of the Analytical Method — Relationship to Limit of Detection and Quantitation

An analytical method is determined to be *sensitive* if small changes in concentration cause large changes in analytical response. It is directly related to, and frequently defined as, the slope of the standard curve [38]. However, this definition does not account for the variability of a measurement. The limit of detection (LOD) and limit of quantitation (LOQ) are terms which are used to express the ability of the assay to detect small concentrations of analyte, as well as attempting to account for variability of measurement.

The *limit of detection* of a method is the lowest analyte concentration that produces a response detectable above the noise level of the system. The *limit of quantitation* is the lowest concentration of analyte that can be accurately and precisely measured. The LOD and LOQ of a method are dependent upon several factors, such as the electron multiplier voltage, the volume of specimen analyzed, the detector threshold, the type and condition of the chromatographic column, the concentration of analyte, the amount and type of internal standard, the extraction efficiency, and the individual instrument [54]. A significant change or modification to any of these factors will require reassessment of the LOD and LOQ for the method.

There are several approaches for establishing the LOD and the LOQ of an analytical method [1,44,48,65]; at least two of these are routinely used in forensic urine drug-testing laboratories. Recent publications have defined issues of concern regarding LOD and LOQ determination methods, and have described and compared the two most commonly used methods [1,44].

The first approach to establishing the LOD and LOQ of an assay is based on the measurement of the magnitude of analytical background noise. It is performed by analyzing an appropriate number of blank (drug-free) samples and calculating the standard deviation of these responses. In practice, determining LOD using this approach involves the analysis of negative urine specimens (obtained from at least ten different donors) over time. In this paradigm, the LOD is calculated as the mean of the detected amount or signal intensity plus three standard deviations ($\overline{X}$ + 3 SD) [48], where 3 is a factor for a 99.9% level of confidence. Similarly, LOQ is calculated as the mean of the detected amount or signal intensity plus ten standard deviations ($\overline{X}$ + 10 SD). An obvious limitation of this approach is that while this may be an adequate measure of the theoretical LOD of a method, actual concentrations of analyte in biological samples measured at this calculated LOD would be indistinguishable from zero measurements by a large probability [38].

The second commonly employed approach for the determination of LOD and LOQ is based on a signal-to-noise comparison [65]. Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with low concentrations of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. In this context, a minimum of a signal-to-noise ratio of 3:1 or greater is generally agreed to be acceptable for LOD assessment; a signal-to-noise ratio of 10:1 or greater is generally agreed to be acceptable for LOQ assessment. In practice, this approach involves analysis of a series of samples containing low concentrations of analyte.

For GC/MS analysis in urine drug-testing laboratories, SAMHSA defines the lowest analyte concentration that meets signal-to-noise, chromatographic, retention time, and ion ratio or full-scan matching criteria, as the LOD. The lowest concentration, that meets all of the above criteria and quantitates within ±20% of the target concentration and measures within a specified coefficient of variation, is designated as the LOQ.

The first two approaches described above are routinely utilized in laboratories performing regulated urine drug testing, although the second approach is preferred over the first approach since it is based upon measurement of an actual analyte response, rather than the absence of a response. A third approach to determination of LOD and LOQ values is based on the standard deviation of the analyte response and the slope of the standard curve. In this case, the LOD is expressed as 3.3 times the standard deviation of the response divided by the slope (S) of the calibration curve (3.3 × SD/S). The LOQ is expressed as 10 times the standard deviation of the response divided by the slope of the calibration curve (10 × SD/S). The slope is estimated from the standard curve of the analyte, and the standard deviation is estimated by analysis of blank specimens, as described for the first approach. Alternatively, the residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation. It has been recommended that if the detection limit of an assay has been estimated by calculation or extrapolation, such as with the first or third approach described above, this estimate should be subsequently evaluated and validated by the independent analysis of a suitable number of samples known to be prepared near or at the detection limit [65].

The LOD is an important assay parameter due to the use of this value to evaluate retest results. The LOQ is important for defining the minimum accurate quantitative value of the assay. For example, dilutions that produce results less than cutoff but equal to or greater than the LOQ may be utilized with the appropriate dilution factor to calculate test results if the LOQ control included in the batch is found to be acceptable. Dilutions that produce results below the LOQ are not acceptable; specimens must be reassayed at a lower dilution. At least one publication [18] recommends that the assessment of the LOQ be obtained using LOQ samples that are prepared *independently* from that included in the standard curve because the LOQ standard that is included in the standard curve influences the regression equation (and thus is no longer an independent measure). Also, since the LOD and LOQ values are influenced by a variety of factors, such as the individual instrument or detector, it may be advisable for the laboratory to assess these parameters on each instrument used for a particular assay, although a general consensus on this issue has not yet been reached.

Interestingly, there are no requirements and few specific recommendations regarding the number of analyses or analytical runs to be evaluated for LOD and LOQ determination. Suggested numbers of replicates of any single blank or standard range from 10 to greater than 20 [19,55,56]. However, from a statistical standpoint it may be advisable to perform these replicate measurements of each blank or standard, in three separate batches, followed by *t*-tests or one-way ANOVA to determine if the calculated LOD and LOQ values differ significantly over time. A two-way ANOVA may be used to determine if a bias is present between instruments.

Finally, in an effort to reduce interlaboratory LOD and LOQ variation, and to introduce a sample that assesses minimum performance in each confirmation batch,

SAMHSA suggested that the LOQ achieved by the laboratory must be a value equal to or less than 40% of the assay cutoff concentration [71]. To ensure acceptable performance, it is desirable to challenge the limit of sensitivity in each batch by including a quality control sample at this concentration to monitor day-to-day instrument and assay variance.

F. Carryover

The term "carryover" is used to refer to the contamination of a sample by a sample analyzed immediately prior to it [35,63]. In the urine drug-testing laboratory, the term "carryover limit" is used to delineate the concentration of analyte in a sample above which contamination may reasonably be expected to occur. There is at least one common approach to performing such studies that involves the analysis of standards prepared at increasingly higher concentrations of analyte, preferably reflecting the highest concentrations which a laboratory typically encounters during routine analysis of samples. Each standard should be injected separately, followed by injection of a blank or solvent to determine if a signal (response) characteristic of the analyte is present in the sample above a pre-established limit (typically the LOD of the analytical protocol). Once the concentration at which carryover occurs is determined, the laboratory establishes its carryover limit at the next lowest concentration which *does not* have evidence of carryover in the blank or solvent. More precisely, upon completion of carryover studies, a laboratory should define the range of analyte concentrations at which carryover does not occur.

The laboratory should also ensure that the quantitative value for the carryover limit established in the carryover study falls within the linearity of the assay to ensure that the quantitative value is accurate. It is also advisable to evaluate carryover of an assay on each instrument system, including autosamplers, on which the method is to be performed, although there is no general consensus on this issue. This is to ensure that the established carryover limit is properly applied to data obtained on each system routinely used in the laboratory.

To minimize potential carryover, one or more of the following approaches can be utilized:

1. Use extensive solvent wash procedures between injections.
2. Inject solvent between all subject specimens.
3. Dilute the specimen prior to extraction.
4. Periodically determine or reassess the minimum carryover concentration.
5. Assay specimen extracts in ascending concentration order (according to initial immunoassay test results).
6. Reinject all highly concentrated specimens followed by solvent blanks or negative quality control samples.
7. Assay a carryover standard followed by a solvent blank or negative quality control sample with each batch to assess carryover at the time of testing.
8. Frequently monitor the level of solvent available in the rinse vial for the autosampler to ensure that a sufficient quantity is available for the entire run.

It is important that criteria be established for evaluating the acceptability of solvent blanks or negative quality control samples that have been inserted to assess possible carryover [80]. If carryover is suspected, a potentially contaminated specimen should be re-extracted, rather than reinjected, because the extract vial may have already been contaminated.

G. Other Factors

Other factors, such as selection of a derivatizing reagent, selection of the internal standard(s) for the assay, selection of ions to monitor for selected-ion monitoring or full-scan analysis, stability of the analyte under various storage conditions, estimation of recovery of the analyte from the matrix, and evaluation of the ruggedness of the analytical protocol, should also be determined during the validation of an analytical method [10,18,29,37,38,78].

Selection of a *suitable derivative* is a critical component of assay development and method validation. There are at least three major reasons for using a derivatized compound. First, the analyte can often be made sufficiently volatile to allow its introduction to the mass spectrometer by gas chromatography, permitting optimal separation of the analyte from possible interfering substances. This, in turn, usually increases the specificity, precision, and sensitivity of the assay. Second, the stability of the analyte during storage, isolation, and thermal volatilization can be enhanced via formation of the derivatized product. Third, the increase in molecular mass resulting from derivatization may be beneficial, providing ions which, by virtue of their higher mass, are more specific for the analyte [28,43]. In cases where two or more derivatives are possible, each should be tested to assess its stability, chromatographic peak shape, and mass spectral properties in the biological matrix. The ideal derivatization procedure should be convenient and rapid to perform, form a consistent and stable product in high yield, require small volumes, be selective for the analyte of interest, be safe to handle, and should not form byproducts that interfere with the analysis [4,5,39,40,52].

The selection of a *suitable internal standard* is highly linked to the appropriate selection of a derivative for the assay (if necessary), as well the particular ions to be monitored for analyte identification and quantitation. An ideal internal standard behaves identically to the analyte throughout the extraction, chromatographic separation, and ionization processes. Stable isotope internal standards appear closest to meeting these criteria. The isotope label exerts only a slight effect on the physical properties, yet the higher mass of the isotope-labeled ions of the internal standard permits them to be readily distinguished from analyte ions by the mass spectrometer [16,26,50,58]. Deuterium-labeled analogs [^{2}H] are most frequently used as internal standards in urine drug-testing laboratories; other isotope-labeled analogs, such as ^{13}C or ^{15}N, are not commonly used.

Several factors are important to consider when selecting the deuterium-labeled internal standard to be used in an assay. The isotope should not undergo exchange under any of the conditions under which it will be used, such as the extraction, derivatization, or chromatographic separation procedures, as well as at the mass spectrometer's ion source [26]. In addition, the isotope must be stable under routine storage conditions, so that exchange of deuterium and hydrogen does not occur [50]. The isotopic variant selected should have a molecular weight three or more mass units greater than the unlabeled compound because the naturally occurring heavy isotope content of organic compounds in general produces ions of significant intensity at one or two mass units above each carbon-containing compound in the analyte's mass spectrum [26,45–47]. It is therefore critical that the isotopic variant is of high purity (>99%) to prevent interference with the analyte of interest during the analysis. Also, the labeling should be in such a manner that the isotopic atoms are located in proper molecular structure so that, after the fragmentation or ionization process, a sufficient number of high-mass ions that retain the label are present in significant intensities and will not interfere with the intensity measurement of the corresponding ions derived from the analyte [46].

The laboratory must carefully evaluate the concentration of internal standard used in its assay to ensure that there is no contribution to analyte signal itself. In effect, the substance ratio of internal standard material to analyte should be selected to give the least imprecision of quantitative analysis and to afford equal ion signal responses during mass spectrometric analysis of the analyte. Under certain conditions, improved sensitivity may be observed by the addition of a large excess of isotopically labeled analogue to reduce adsorptive losses ("carrier effect"). However, this approach is not generally preferred in urine drug-testing laboratories, where a specific administrative cutoff value must be applied. When excess deuterated internal standard is used, analytical precision usually suffers [43], which would not be desirable when a specific quantitative cutoff is needed. Therefore, it is recommended that the laboratory eliminate or minimize adsorptive losses, rather than add excessive amount of internal standard.

The choice of *ion or ions to be monitored* for GC/MS assays has an important influence on analytical specificity. Generally, ions of high, even mass-to-charge ratios have fewer possible origins and are therefore more likely to be characteristic of a particular analyte. The laboratory initially performs a preliminary ion selection based on full-scan mass spectrometric analysis. Ions of high mass-to-charge ratios and good intensity are the first choice for use in routine assays. It is recommended that laboratories using selected-ion monitoring utilize at least three characteristic ions for the analyte of interest, and a minimum of two characteristic ions for the internal standard [72].

Laboratories using full-scan GC/MS must identify those ions with sufficient signal intensity and high-mass to use for qualitative identification of the compound ("matching criteria"). The laboratory should be able to demonstrate that the full-scan spectra it achieves, and plans to use on a routine basis, is stable and reliable over time. Further consideration of these requirements is discussed in Section V.

While most forensic urine drug-testing laboratories are using electron impact ionization (EI) for GC/MS assays, chemical ionization (CI) MS may also be utilized as the mode of detection to improve assay sensitivity and specificity. Chemical ionization MS typically produces an intense molecular ion and only a few fragment ions; therefore, one or two analyte ions may be monitored. A further discussion of these two methods of ionization are beyond the scope of this paper; however, the use of CI is acceptable only if the selectivity, accuracy, and precision of the CI process and method have been fully evaluated [26,81].

Another important parameter to assess during the method validation phase is that of *stability of the analyte*. This includes stability of stock solutions of analyte as well as stability of the analyte in biological matrix. Stability studies will typically be performed to assess stability under different temperatures (storage conditions) and different lengths of time (in-process stability and long-term stability). Stability of the analyte can be assessed at room temperature, refrigerated, and frozen storage conditions. The length of time under each storage condition to be evaluated can range from days to weeks. It is recommended that the laboratory at least establish analyte stability under its own anticipated storage and processing conditions. Although there are many different approaches to the performance of stability studies, a common approach is to use quality control materials prepared at known concentrations to assess stability [18].

Recovery of the analyte from a biological matrix must be determined to ensure that it is adequate and consistent. It is recommended that recovery studies be performed across the range of the standard curve, preferably at the lowest, mid-range, and highest concentrations encompassed by the curve [18,61,78]. Typically, a set of samples of known concentrations is prepared in triplicate at three different concentrations, internal standard is added, and the sample then extracted, derivatized, and analyzed by the GC/MS procedure. A second set of samples is also concurrently analyzed; however, the internal standard is not added until just prior to derivatization. Recovery is then calculated by comparing the calculated concentrations of the two sets of samples and expressing total recovery of the method as a percent. Intermediate points in the extraction process may also be evaluated.

The *ruggedness and reliability of the assay* should be established. Critical assay steps need to be identified, including assessing the importance of pH, solvent mixtures, derivatizing reagents, and temperature and incubation times utilized during the hydrolysis and derivatization processes. In addition, the level of expertise required to perform the analysis needs to be assessed. It must be determined whether the assay can be stopped and restarted, and how long the derivatized analytes are stable. A system for monitoring assay performance variables such as the number of rejected batches, calibration curve parameters (including slope, *y*-intercept, and correlation coefficient), and quality control results must be established [42,65,78].

II. INSTRUMENT PERFORMANCE

A. Instrument Checks

In addition to developing validated assays for the purpose of identifying and quantitating drugs in urine, it is an essential quality assurance component that the laboratory monitor and document that all analytical instruments involved in the analysis are maintained and operated properly. The laboratory must establish that the instrument used for a particular analysis is operating adequately and within expected performance specifications. Prior to the start of an assay, the condition of the GC/MS system must be evaluated. The GC/MS operator should check the injection port, detector and oven temperatures, and carrier gas pressure, and perform routine maintenance, as needed, such as clipping of the GC column and replacement of the injector septum and liner. In addition, on a periodic basis, or when a new column is installed, the carrier gas flow rate should also be measured.

Routine maintenance should be performed at least as often as recommended by the manufacturer. Additional maintenance and instrument check schedules should be developed by the laboratory according to its workload and type of assay performed. For example, the laboratory may choose to routinely replenish or replace vacuum pump oil on a quarterly basis. Or, the laboratory may choose to replace injection port liners daily. Other types of maintenance procedures include replacement of filaments, cleaning of the ion source, and replacement of electron multiplier or ion gauge. The specific schedule developed by the laboratory will be dependent upon the type of GC/MS instrument used (e.g., traditional quadrupole, ion-trap), as well as the nature of the extracts analyzed on a particular system. The GC/MS laboratory must maintain records of all routine and nonroutine maintenance performed prior to analysis of specimens, as well as written standard operating procedures for the performance of these tasks [9,26,31,53,80]. Record keeping for maintenance procedures is vitally important to demonstrate the validity of the analysis [31].

B. Instrument Performance Evaluation and Tuning

On a daily basis, it is a good practice to check the *pressure in the ion source* and in the analyzer, as well as the GC column head pressure to assure that no major system leaks have occurred. For quadrupole operation, a pressure of 10^{-4} torr or better is required so that significant interaction between the ion beam and residual gas molecules does not occur (which causes scattering of the ion beam and loss of sensitivity). For GC/MS, an even lower pressure of 10^{-5} torr is necessary to reduce residual gas in order to prevent significant distortion of mass spectra and reduce background interference. Chemical ionization MS typically requires higher source pressure than EI MS.

Following this initial pressure check, the laboratory should verify that there are *no significant air/water leaks* in the system by monitoring the intensity of the following ions: *m/z* 28 (N_2^+), 32 (O_2^+), 40 (Ar^+), and 44 (CO_2^+). If these peaks are abnormally large, an air leak may be indicated. In addition, evaluation of water vapor in the system can be checked by monitoring *m/z* 18 (H_2O^+) and 19 (H_3O^+). Appropriate instrument maintenance must be conducted before analysis is permitted to proceed.

A GC/MS "*tuning procedure*" ensures that appropriate mass-to-charge assignments and abundances of specific ions have been established, as well as indicating the need for instrument preventative maintenance. In order to verify proper calibration and operation of the mass spectrometer, the instrument must be tuned daily with an appropriate tuning compound (e.g., perfluorotributylamine, PFTBA) for proper unit resolution and mass assignment. "Resolution" refers to baseline separation between consecutive integral mass peaks. In mass spectrometry, resolution and sensitivity are inversely related. Tuning should be performed at the operating temperature of the ion source.

Autotune procedures typically utilize a preselected set of criteria across a range of mass-to-charge ratios (e.g., *m/z* 69 to 502 for PFTBA) to optimize source and quadrupole potentials. Alternatively, manual tunes can be used to increase sensitivity over a narrower mass range. Autotune procedures, or optimization of tuning parameters across a wide *m/z* range using a manual tune, are most useful for analysis of unknown specimens. Narrow-range manual tunes can be useful for some low-level target compound analyses. In this case, either of the abundant ions at *m/z* 219 or 414 can be used to optimize source potentials, depending on which is closest to the analyte and internal standard ions that will be monitored. Manual tuning is acceptable as long as the MS operator is appropriately trained, the tune procedure is fully documented, and the laboratory's standard operating procedure (SOP) manual describes the task clearly and accurately. It is most common, however, for urine drug-testing laboratories to perform an autotune across the entire mass range (e.g., *m/z* 69 to 502) at approximately 70 eV [9,26,31,43].

All tune reports should be reviewed thoroughly by the operator before testing is initiated to support compliance with manufacturer and laboratory specifications. Acceptable limits should be established for the ion focus, ion appearance and peak width, abundance of selected ions, isotope ratios, and mass slope, as appropriate for the GC/MS instrument. Critical tune values should be monitored on a regular basis, and all tune reports, including unacceptable ones, should be archived as important supporting forensic documents. Autotune, or manual tune, information should be available during review of the batch to ensure that instruments were performing as expected prior to analysis of specimens. These records may be filed with the pertinent batch, or filed in a manner to permit easy retrieval [72].

C. Chromatographic Performance

The chromatographic performance of an assay should also be assessed before the analysis of specimens. This is achieved readily by the injection of an unextracted performance standard including analyte(s) and internal standard(s). Use of an unextracted standard removes sources of variation due to the extraction procedure and matrix interferences. In addition to permitting evaluation of the quality of the chromatographic system, the analysis of an unextracted standard serves to verify that the analyte(s) of interest elute at the expected retention time, that all MS acquisition windows are appropriately set, and that no unexpected adsorptive system losses have occurred. Evaluation criteria in the SOP manual should include a thorough description of peak shape, resolution, and signal abundance requirements.

One approach to evaluation of acceptable chromatography for a single specimen and/or an entire batch of specimens may be defined and assessed by the following criteria:

1. The analyte of interest is present at the correct retention time.
2. The peak of interest obtained from the total ion chromatogram and each individual ion chromatogram is inspected visually for geometric symmetry. A gaussian peak shape (see **Figure 1**) is required and shall have no greater than 50% tailing using the following procedure:
   a. Draw a vertical line from the apex through the center of the peak to the baseline.
   b. Draw a line parallel to the baseline at 10% of the peak height.
   c. Measure the distance "a" from the leading edge to the centerline.
   d. Measure the distance "b" from the centerline to the tailing edge.
   e. Calculate the ratio of distance "a" and distance "b".
   f. If the ratio is greater than 2 or less than 0.5, performance is unacceptable.
3. The peak of interest is inspected visually for the presence of unresolved peaks. The maximum allowable valley between two adjacent peaks must not exceed 10% of the analyte peak height.
4. Abundance or signal-to-noise levels of the internal standard ions must meet established minimum criteria.

Failure to meet any of these criteria may provide cause for reinjection or reextraction of a specimen. A complete review of methods for evaluation of chromatographic performance is beyond the scope of this paper; however, acceptable alternative criteria for evaluation of chromatographic acceptability can be found in many textbooks and other reference materials [30,36,49,51,60,63]. Some instrument software designers are also developing programs for automated evaluation of chromatography.

In addition to daily chromatographic checks prior to batch analysis, performance of the chromatographic column should be evaluated upon installation and periodically thereafter. This can be accomplished by the analysis of a variety of "test mixtures," such as a Grob's Test Mix

[30], to assess column performance. These mixtures generally contain several compounds (e.g., early and late eluters) which are selected to evaluate certain aspects of chromatographic performance, including peak shape and sensitivity. From a practical perspective, the forensic urine drug-testing laboratory may also choose to evaluate acceptable chromatographic performance for selected drug analytes (e.g., amphetamine, phencyclidine, 6-acetylmorphine, codeine) after column installation. Deterioration in performance can then be followed by comparison of the initial chromatogram with subsequent chromatographic data.

III. ASSAY CALIBRATION

The term "*assay calibration*" refers to the process of developing a mathematical model that attempts to predict the value of an independent variable (e.g., concentration) based on the value of the dependent variable (e.g., peak height, peak area ratios). Calibration has sometimes been referred to as inverse prediction or discrimination. This is in contrast to the term "regression," which was described earlier in this paper with respect to linearity of the analytical method. *Regression* refers to a functional relationship between two or more correlated variables [6,21]. In forensic urine drug-testing laboratories, assay calibration is necessary to determine whether an analyte is present in an unknown sample at or above a pre-established administrative cutoff value, as well as to determine the accurate quantitative concentration of the analyte under certain circumstances [72]. Currently, it is most common to calibrate the assay for quantitative measurement using a single, abundant ion fragment that is characteristic of the analyte of interest. Additional ions, referred to as qualifying ions, are used to support the qualitative identification of the analyte in the unknown sample.

Three approaches to assay calibration are commonly utilized in forensic urine drug-testing laboratories: multi-point calibration curves, single-point calibration curves, and historical calibration curves. The first and probably the most widely employed method of calibration is the preparation of a *multi-point calibration* curve. Experimentally derived multi-point calibration curves are used to cover the concentration range of the samples to be measured, thereby improving the confidence limits associated with the calibration itself. Calibration samples (standards) are prepared from mixtures of different amounts of known concentration of analyte with a fixed amount of internal standard. Specific ion-abundances are measured for the analyte and internal standard, a ratio calculated, and a calibration curve generated using a simple least squares regression model, for example. If the laboratory elects to use a multi-point calibration curve, it must include calibrators that bracket the cutoff concentration. Although many laboratories include a calibrator at the cutoff concentration, it is not required [72].

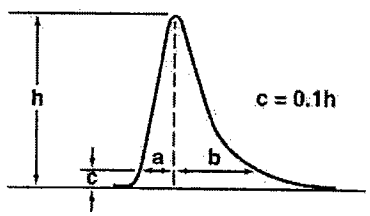


Figure 1. Theoretical chromatographic peak.

The calculated concentration of all standards utilized to construct the calibration curve should be within ±20% of their respective target concentrations. If more than three standards are utilized to construct a calibration curve, it is permissible to delete one calibrator for cause (e.g., poor recovery) provided it is not a calibrator at the cutoff concentration. It is not acceptable to eliminate a calibration point solely in order to bring the quality control results within range, although there is some disagreement on this issue since one might expect that the probability of detecting/obtaining an "outlier" will increase as the number of calibrators analyzed in a batch increases [15,72].

Evaluation criteria for linearity of the multi-point calibration curve include the correlation coefficient (r), coefficient of determination (R^2), the slope (m), y-intercept (b), and quantitative value of each data point. The *correlation coefficient* is a measure of the intensity of association between two variables, X and Y. In calibration, the correlation coefficient ranges from 0 to 1; 0 indicates no correlation and 1 indicates a perfect correlation. A correlation coefficient may indicate a high degree of relation between variables, but the generated model (regression equation) may give an inadequate fit for the data. In contrast, the *coefficient of determination* is a measure of "goodness of fit" and is the proportion of variation in the data explained by the regression model. It also ranges from 0 to 1, with 0 indicating a complete lack of fit and 1 indicating a perfect fit. Generally accepted criteria for acceptable linearity using deuterated internal standards for calibration include a correlation coefficient and/or coefficient of determination of at least 0.990, and a y-intercept close to zero, although slightly positive or negative y-intercept values are also acceptable. Because of the potential for negative and positive bias, y-intercept

values should be monitored on a regular basis and tracked for development of trends.

For assay calibration, the laboratory must also establish whether the regression line will be forced through the origin (a "no-intercept" model) or will not be forced through the origin (an "intercept" model). In the intercept model, R^2 is the proportion of variance explained by the model. In contrast, R^2 produced by the no-intercept model is a measure of the degree of dispersion around *zero* and describes the proportion of variance around zero explained by the model [7]. Most GC/MS software programs allow for the user to select between these two approaches. The selection of the appropriate model to be used for a particular assay will depend on several factors, including the type and sensitivity of instrument, the analytical method, the method of ionization, the required analyte detection, and reporting limits. As a general rule, it has been suggested that one should assume that an intercept model is correct until proven otherwise via statistical testing of the intercept [6-8,14]. If statistical testing of the intercept indicates that it is not different from zero (e.g., b = 0), then the no-intercept model is appropriate and should be used. However, selection of a no-intercept model implies that the assay limit of detection is *zero*, which is not the case for GC/MS urine drug-testing assays due to instrument and matrix background effects. Therefore, in most instances regression through the origin should not be used in assay calibration.

The second most commonly employed approach to assay calibration is a *single-point calibration*. In this case, a single standard containing analyte at the assay cutoff concentration is used to establish the cutoff concentration in order to determine whether a specimen is positive or negative. Laboratories then include quality control materials at concentrations below, at, and above the cutoff concentration to demonstrate linearity. The quantitative results for the quality control samples used in single-point calibration must fall within ±20% of their respective target concentrations.

The third approach to assay calibration uses construction of a *historical multi-point calibration curve*. The laboratory establishes the calibration (as above) and verifies that the calibration has not changed between batches via analysis of control samples, one of which is at the cutoff concentration. Use of historical calibration curves is acceptable only if the laboratory has demonstrated linearity and precision of the calibration curve over time. If shifts in response ratios are observed or new internal standard materials are employed, a new standard curve must be prepared. In addition, all batches must include at a minimum a blank and two controls, one at or near the cutoff.

During assay calibration, the laboratory also establishes acceptance ranges for retention time and ion ratios. These acceptance ranges are then used to evaluate each calibrator, control, and unknown specimen in the batch (*see* Section V). For single-point calibration assays, the acceptable limits are determined from the calibrator at the cutoff. For multi-point or historical calibration curves, acceptable limits may be determined from either the calibrator at the cutoff *or* from the average of all the calibrators analyzed. If historical calibration curves are used, verification of correct retention time and ion ratios is performed by examination of the "at or near cutoff" quality control sample. In this case, the retention time and ion ratios of this sample must fall within the ranges established by the historical curve, or the assay must be recalibrated [72]. Any of the approaches for determining retention time and ion ratio criteria discussed above are considered acceptable; however, the laboratory must apply the acceptable ranges consistently to all calibrators, controls, and specimens in the batch.

IV. QUALITY CONTROL

A. Required Quality Control Samples

Each assay batch must include a minimum total of 10% open and blind positive and negative quality control samples in an appropriate urine matrix [70]. External blind quality control samples are not required, but are highly recommended. Quality control samples may be purchased commercially or prepared from a different source or lot of standard material other than that used to prepare calibrators. The use of different sources and lot numbers is recommended in order to eliminate systematic quantitative bias in the GC/MS assay that may otherwise go undetected. However, at a minimum, quality control materials should be prepared using standard material prepared from a different weighing or vial of source material other than that used to prepare the calibrators. The target concentration of at least one control must be within approximately 125% of the cutoff concentration; other controls should be prepared at appropriate concentrations in order to regularly assess accuracy below and/or above the assay cutoff concentration. It is recommended that a highly concentrated control sample be diluted in a similar manner as diluted specimens during aliquoting in order to verify the accuracy of the dilution technique, if one is routinely used to prepare presumptive positive specimens for confirmation [72].

In order to evaluate the efficiency of the hydrolysis process, cannabinoid and opiate control samples containing conjugated 11-nor-Δ^9-tetrahydrocannabinol-9-car-

boxylic acid and morphine, respectively, should be assayed. Negative urine samples spiked with these reference materials can be prepared, or as an alternative, hydrolysis control samples can be prepared from a combined urine pool of previously confirmed specimens. (It is not acceptable to use regulated specimens for this or any other purpose until after completion of the required storage time.)

Finally, it is highly recommended, but not required, that the laboratory use quality control materials that include the addition of potentially interfering substances in its GC/MS assays. These might include compounds that are structurally related to the analyte of interest, or closely eluting compounds. For example, the laboratory may choose to include a control containing hydrocodone, hydromorphone, or oxycodone in its opiate assay to demonstrate that codeine and morphine are correctly identified and accurately quantitated in the presence of potential interferents. Another example is that of the inclusion of a control containing phenylpropanolamine, ephedrine, phentermine, and/or pseudoephedrine in GC/MS assays that utilize a periodate procedure.

B. Verification of Quality Control Materials

Prior to the use of reference materials to prepare calibrator, control, or internal standard material in the laboratory, the laboratory is required to verify, *independently* from the supplier, that its chemical identity is correct and that it is of acceptable purity and concentration. The laboratory may perform this verification itself, or may refer it to another laboratory. At a minimum, most laboratories perform a full-scan GC/MS analysis to verify the chemical identity and purity of the material and compare the obtained spectra with that of available library spectra to determine that significant impurities are not present in the material which might interfere with the method. The appropriate derivatization procedure for the analyte of interest is employed, as well as the GC conditions routinely used for the assay.

The isotopic purity of the internal standard can also be verified with the same procedure described above. In addition to full-scan analysis, the laboratory may also evaluate the deuterated internal standard in selected-ion monitoring (SIM) mode prior to use.

Additional methods for verification of chemical identity and purity may involve measurement of physical constants, such as melting point or refractive index, as well as use of other analytical techniques (HPLC, IR, NMR, TLC, or UV/VIS) to detect nonpolar or nonvolatile impurities [63]. Verification of concentration is most often evaluated indirectly by preparation of calibrators or controls at known concentrations and analysis in routine batches.

The laboratory must establish specific evaluation criteria for reference materials, such as spectral match requirements, percent isotopic purity required, and quantitative results. The laboratory must retain documentation of all verification procedures performed [72]. The laboratory may then use the reference material to prepare calibrators for controls for routine use. Of course, these new calibrators and controls must then be themselves validated for concentration (e.g., ±20% of the target concentration) prior to routine use.

C. Evaluation of Quality Control Results

There are two major approaches to evaluation of quality control results applied to urine drug testing. The first approach is the use of a fixed-criterion quantitative acceptance range. In this case, the measured concentration of control samples must be within ±20% of the target concentration. A more detailed discussion of the rationale underlying this criterion has already been discussed in Section I-B.

The second approach is to use modifications of Westgard Quality Control Rules to evaluate results. In this approach, the laboratory establishes warning limits and out-of-control limits for the assay based upon the validated mean and standard deviation for the control sample. A thorough description of Westgard rules may be found in several sources [15,35,36,75–77]. Westgard rules are usually not directly applicable to GC/MS forensic testing due to the limited number of quality control data points obtained in a batch, the large number of independent variables associated with GC/MS systems, and the acceptance of potentially out-of-range data. However, if *coupled* with a fixed quantitative accuracy requirement of ±20% for control materials, the rules can be extremely useful for the purposes of evaluating the GC/MS assay for development of trends and systematic biases [38]. Also, other approaches to the evaluation of quality control data, including an ANOVA approach, have been described [37,42].

The laboratory's SOP manual must thoroughly describe the quality control evaluation criteria to be used and must include a policy for the required course of corrective action if quality control sample results fail to meet acceptance criteria. In order to assess laboratory performance, all control data, including out-of-limit data, should be recorded in the quality control log in Levey-Jennings or Shewart chart format [15,27,62,72,75–77]. Out-of-limit data should include documentation of required corrective action. It may be acceptable to reinject a quality control sample one additional time. If the results are still unacceptable, other minimally acceptable protocols include:

1. Reinjection of calibrators, followed by reprocessing of *all* quality control samples and routine specimen data against the new calibration, *if* the time since the last injection is not excessive and the instrument has not been retuned;
2. Reinjection of all calibrators, quality control samples, and routine specimens; and
3. Acceptance of negative test results that are less than the LOD and reextraction of all other specimens in the batch.

V. CRITERIA FOR DESIGNATING A POSITIVE TEST RESULT

A. Chromatographic Criteria

Criteria for designating a positive test result include chromatographic and spectral identification. Chromatographic identification of an analyte requires comparison of the retention time of the specimen with that of a calibrator at the cutoff or the average of multiple calibrators (either approach is considered acceptable). Generally, the retention time of the analyte should be within ±2% of the retention time as established by the calibrator(s) [11–13,72].

B. Ion Ratios

Further, identification of an analyte requires comparison of ion ratios or full spectral data of the unknown with preestablished ion ratios or full-scan mass spectra, respectively. Acceptable ion ratios for the analyte and its corresponding internal standard are usually calculated using ion abundance data obtained for the standard prepared at the cutoff concentration or by determining the mean ion ratios for all calibrators. It has been demonstrated statistically that while full-scan mass spectrometric data provide the maximum confidence for analyte identification, a minimum of three structurally significant ions generated under electron ionization conditions appear to provide adequate information for an identification [12,64]. If the regulated urine drug-testing laboratory uses EI, it is currently required to use a minimum of two ion ratios for identification of the analyte and at least one ion ratio for the internal standard [72]. Of course, CI-generated spectra do not always meet the three-ion criteria because less extensive fragmentation is generally observed with this technique. However, this limitation is offset by the production of high *m/z* ions characteristic of the analyte and increased specificity with selection of appropriate reagent gases [11,12,26,81].

The ion ratios for the analyte and its corresponding internal standard obtained for the unknown should not differ by more than ±20% of the target ion ratio and acceptance criteria must be uniformly applied to all specimens within the batch [72]. The establishment of this 20% acceptance criteria for ion abundance ratios has been determined to be appropriate based on ion statistics [11–13,64]. Different ion ratio criteria cannot be applied to different specimens, calibrators, or controls within the batch.

C. Mass Spectral Match

To ensure adequate mass spectral match quality for laboratories utilizing full-scan acquisition, unknown mass spectra must be compared with reference spectra, and fit or match quality values must be computed. The laboratory should determine allowable limits of acceptability in accordance with laboratory studies and manufacturer's recommendations (e.g., 950 or greater out of a scale of 1,000). It is known that reference spectra in spectral libraries may at times differ from that obtained from analysis of actual specimens. This may be due to the type of instrument used, the particular algorithms used to generate a match, the number of ions used to establish a match, type of reagent gas, electron energy, or type of derivatization employed, among other factors. Therefore, the laboratory may consider establishing its own spectral library for analytes of interest, providing that manufacturer's specifications continue to be met and that generated spectra do not differ *significantly* from published reference sources.

In addition to spectral match requirements, the signal-to-noise ratio at the apex of the integrated peak of the analyte and its internal standard should be equal to or greater than a minimum of 10:1 at the assay's LOQ.

D. Quantitative Result

Regardless of the detection technique, in order to be designated as positive, the measured concentration of a specimen must be equal to or exceed the established assay cutoff concentration. Quantitative results around the cutoff must be truncated, rather than rounded up to the nearest whole number, so that the statistical bias is toward a "negative" result.

Specimens directed for GC/MS retest analyses are not subject to cutoff concentrations and are reported as reconfirmed if the concentration is equal to or greater than the LOD of the method. The specimen retest must also meet all other criteria for designating a positive test result. Quantitative reports should be provided only upon written request of the Medical Review Officer.

If the specimen concentration exceeds the linearity limits of the assay and the specimen was not diluted accordingly, the report must state: "the concentration of '*analyte*' is greater than '*the established linearity limit*'." Also, all criteria for designating a positive test result must be satisfied including chromatographic performance, ion ratios, and retention time data.

VI. MISCELLANEOUS FACTORS

A. Data Presentation

Although presentation of GC/MS data is highly variable among laboratories, printouts for all specimens (calibrators, controls, and positive and negative specimens) must include specimen identification information, total ion chromatogram illustrating entire acquisition window, individual selected ion chromatograms drawn to an approximate 0.5-minute window, mass spectrum (if applicable), spectral data including abundance and ion ratios or spectral match, retention time data, and concentration of analyte. In addition, data file name, date and time of injection, and MS operator name are highly desirable. **Figures 2** and **3** illustrate typical GC/MS reports for confirmation of benzoylecgonine in urine using the Hewlett-Packard Mass Selective Detector and the Finnigan-MAT Ion Trap Mass Spectrometer, respectively. Further, a summary sheet presented in tabular format including injection sequence and specimen identification information, spectral data, and quantitative results should be prepared for ease of batch review (*see* **Figure 4**).

B. Dilution Protocols

Dilution protocols may be developed based upon the relationship of the immunoassay response and the quantitative result. Specimens may be diluted with GC/MS verified negative urine (or possibly purified water) prior to GC/MS confirmation in order to avoid carryover, prevent chromatographic overload, and to obtain acceptable chromatographic results. It is recommended that a quality control sample be diluted in the same manner as any routine specimen to assess the accuracy of the dilution.

A retest specimen may be tested by an immunoassay procedure in order to determine the need for dilution prior to GC/MS analysis. If dilution protocols are routinely applied by the laboratory, these procedures should be clearly described in the laboratory's SOP manual [72].

C. Reinjection of Extracts

Reinjection of specimen extracts may be necessary due to a failed injection or chromatographic overload. The laboratory must stipulate the number of acceptable reinjections (in regulated laboratories, more than one reinjection is generally considered unacceptable) and the maximum time after the end of the batch that reinjection is acceptable. If the reinjection is necessary due to column overload, the laboratory may elect to establish a policy whereby additional reconstitution solvent is added to the extraction vial prior to reinjection. However, such handling must be clearly recorded on laboratory documents, and the laboratory must establish minimum criteria for internal standard signal-to-noise and ion abundance to ensure that results continue to be reliable.

It is unacceptable to continue to reinject or reextract a specimen in order to "force" a negative or positive result. If a specimen fails acceptance criteria it can be reinjected one time and scheduled for re-extraction one time. However, if it continues to fail to meet criteria for the same reason, the specimen must be reported as negative. When reinjections are performed, it is necessary to reinject at least one standard and/or control in order to verify assay performance at the time of the reinjection. All initial and reinjection data, including failed or unacceptable data, must be maintained. Finally, retuning prior to reinjection is not permitted [72].

VII. REVIEW AND EVALUATION OF GC/MS DATA

All data must be thoroughly reviewed by a minimum of two individuals to verify compliance with the methods specified in the laboratory's procedure manual and to identify clerical and/or analytical errors. Batch acceptance criteria include within-range standards and controls and acceptable MS tune, chromatographic performance, ion abundance (adequate signal-to-noise ratio), and ion ratios or mass spectral match quality. Also, the laboratory may choose to monitor the consistency (reproducibility) of the ion abundance for the internal standard to ensure that it has been added appropriately, and at the correct concentration, to each calibrator, control, and unknown in confirmatory analyses. Furthermore, an acceptable calibration curve must be obtained, a lack of carryover must be demonstrated, and chain-of-custody documentation must be in order.

The SOP must also address the handling and reporting of results when duplicate extracts are assayed, or diluted and undiluted extracts are analyzed. Acceptance criteria for duplicates must specify minimum correlation of quan-

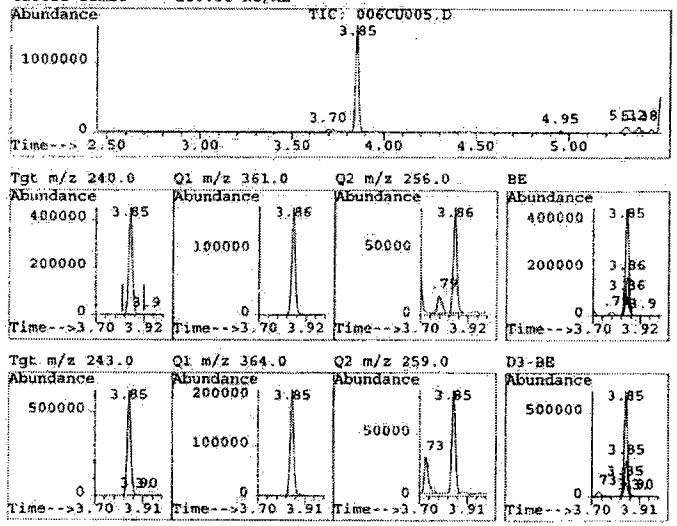

```
QUANTITATION REPORT FOR BE ON : 5972 - MS
Data File              : C:\HPCHEM\1\DATA\05AUG96A.10A\006CU005.D
Tune File Name         : C:\HPCHEM\1\5972\ATUNE.U
Tune Date              : 5 Aug 96 9:42 am
Acq Method Name        : BEDRL.M Calib date : 05 Aug 96 1:24 pm
Sample Name/Barcode    : 150 NG/ML
Acq date/Exp Barcode   :  5 Aug 96  11:43 am /

Retention Time   3.85 BE              +/- 1.00% =  3.81 -  3.89 min
Retention Time   3.85 D3-BE           +/- 1.00% =  3.81 -  3.89 min
R.R.T. =  1.001  Unknown target ion / ISTD target ion =   0.75

BE          => 240.0 =   528009  361.0 =   183619  256.0 =    89775
D3-BE       => 243.0 =   707972  364.0 =   244509  259.0 =    95708

BE          => 361.0/240.0 =    34.8 +/-  20.0% rel =   27.8 -   41.8
BE          => 256.0/240.0 =    17.0 +/-  20.0% rel =   13.6 -   20.4
D3-BE       => 364.0/243.0 =    34.5 +/-  20.0% rel =   27.6 -   41.4
D3-BE       => 259.0/243.0 =    13.5 +/-  20.0% rel =   10.8 -   16.2

Concentration =  144.84 ** CUTOFF CALIBRATOR **
Cutoff limit  =  150.00 NG/ML
```




```
BE                  : RT extraction window from   3.70 to   4.00 min
D3-BE               : RT extraction window from   3.70 to   4.00 min

Page 11                                  Printed on : 05 Aug 96 1:24 pm
```

Figure 2. GC/MS report for confirmation of benzoylecgonine in urine using the Hewlett-Packard Mass Selective Detector.

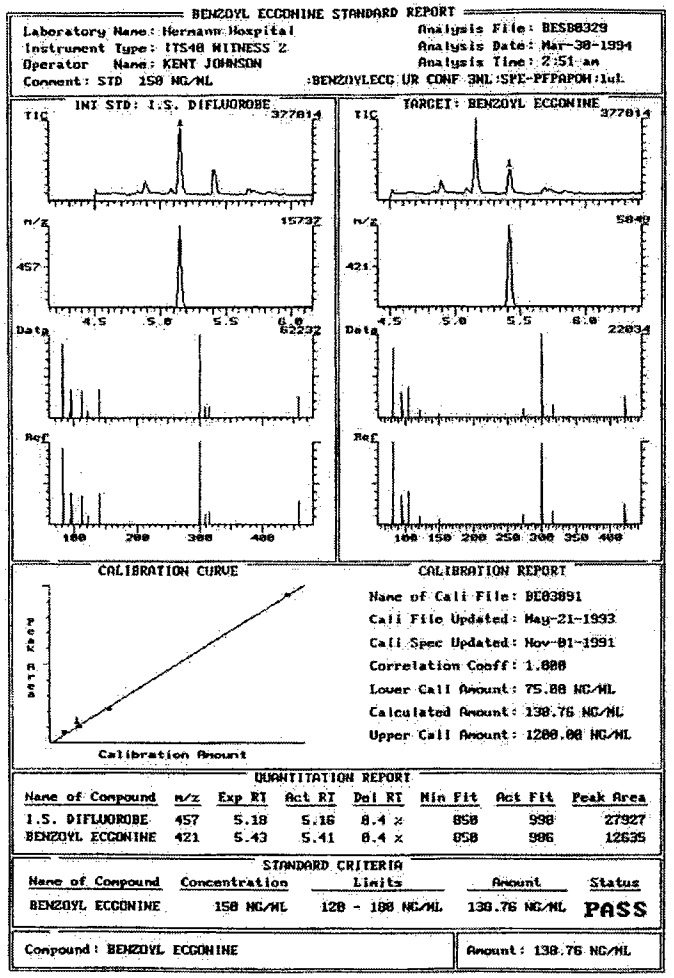


Figure 3. GC/MS report for confirmation of benzoylecgonine in urine using the Finnigan-MAT Ion Trap Mass Spectrometer. (Courtesy of Kent Johnson of Hermann Hospital: Houston, TX.)

Batch Summary Report
TOXICOLOGY LAB

Batch Dir.: 05AUG96A.10A

Acquisition Date: 8/5/96 10:46 AM
Drug Class: BENZOYLECGONINE
Batch Name: 05AUG96A.10A
Original Method File: C:\HPCHEM1\METHODS\BEDRL.M
Data Path: C:\HPCHEM1\DATA\05AUG96A.10A

Instrument Name: 5972 - MSD2
Operator: B. GOLDBERGER

Ion Ratio Range: +/-20%
Retention Time Range: +/-1%

Cutoff File Information					Quantitation Database					
	Compound Name	Cutoff Conc.	File Name	Calc. Conc.	Sample Name	RT	Ratio 1	Ratio 2	ISTD Ratio 1	ISTD Ratio 2
	BE	150	006CU005.D	144.84	150 NG/ML	3.85	34.78	16.98	34.54	13.52
Run No.	Compound Name	Result	File Name	Calc. Conc.	Sample Name	Target RT	Target Ratio1	Target Ratio2	ISTD Ratio1	ISTD Ratio2
1	BE	POSITIVE	001SP001.D	155.98	UNEXTRACTED STD	3.85	34.94	16.60	33.97	13.24
2	BE	Blank	002BL000.D	0.00	SOLVENT BLANK	0.00	0.00	0.00	0.00	0.00
3	BE	No ISTD	003NE002.D	0.00	BLANK	3.85	0.00	0.00	0.00	0.00
4	BE	Good Neg.	004NE003.D	0.00	BLANK + IS	3.85	0.00	0.00	33.45	13.41
5	BE	Calibrator	005CA004.D	74.45	75 NG/ML STD	3.85	33.89	16.59	33.62	13.39
6	BE	Cutoff	006CU005.D	144.84	150 NG/ML STD	3.85	34.78	16.98	34.54	13.52
7	BE	Calibrator	007CA006.D	1000.12	1000 NG/ML STD	3.85	35.43	17.03	34.87	13.65
8	BE	Blank	008BL000.D	0.00	SOLVENT BLANK	0.00	0.00	0.00	0.00	0.00
9	BE	POSITIVE	009SP007.D	270.22	R96-00001*5	3.86	35.82	17.05	35.34	13.49
10	BE	Blank	010BL000.D	0.00	SOLVENT BLANK	0.00	0.00	0.00	0.00	0.00
11	BE	Negative	011SP008.D	135.59	R96-00002*5	3.86	35.25	16.91	35.34	13.73
12	BE	Blank	012BL000.D	0.00	SOLVENT BLANK	0.00	0.00	0.00	0.00	0.00
13	BE	Negative	013SP009.D	0.00	QC NEGATIVE	3.85	0.00	0.00	35.81	13.60
14	BE	POSITIVE	014SP010.D	188.58	QC POSITIVE	3.85	36.11	17.40	34.66	13.98
End of Batch										

Figure 4. GC/MS Batch Summary Review form.

titative results, usually ±20% if both results fall within the assay's linear range. In addition, both of the results must be equal to or greater than the mandated cutoff concentration, although use of the lowest value is recommended. The averaged results or a single value, diluted or undiluted, may be reported if both results meet acceptance criteria, and SOP requirements are consistently applied.

Review of specimen data should include comparison of the initial immunoassay response with the GC/MS result, an evaluation of chromatographic performance including presence of interfering or extraneous peaks, retention time, minimum ion abundance, ion ratios or mass spectral match quality, quantitation, extraction efficiency, potential for carryover, and chain-of-custody documentation.

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