

GENERAL REFEREE REPORTS

Committee on Drugs and Related Topics

Drugs and Related Topics

INES CEREIJO

Justesa Imagen Argentina S.A., Viamonte 1328, 9° piso,
Buenos Aires, (1053), Argentina, Tel: (5411)
15-4496-3425, Fax: (5411) 4206-4595, E-mail:
icereijo@ciudad.com.ar

Summary

Drugs is a topic that was certainly an issue of discussion at this year's annual meeting. This Committee had the responsibility of organizing a half day symposium on "Pharmaceutical Authenticity and Safety" that took place September 12, 2005. This symposium aims at improving the critical points in the analytical pharmaceutical field related to traceability assessment, use of certified reference materials (CRMs), and proficiency testing implementation to get the highest quality of the obtained results. Recognized experts presented these topics. Also, other complementary subjects, such as the application of advanced analytical technologies to reach the authenticity and safety of the pharmaceutical drugs and drug products, their microbiological quality assessment, without disregarding an important topic such as sampling, was presented and discussed.

The talks that were presented are the following: "Proficiency Testing as a Need in the Pharmaceutical Field," Arlene Fox (AOAC INTERNATIONAL, Gaithersburg, MD); "Implementation of Traceability in the Pharmaceutical Laboratory," Thomas Layloff, (Management Sciences for Health, Arlington, VA); "Harmonized Characteristics of Certified Reference Materials According to ISO Guides—Attractive also for Pharmaceutical Analysis," Hendrik Emons (Reference Materials, Unit Institute for Reference Materials and Measurements (IRMM), Joint Research Centre European Commission, (Geel, Belgium); "Importance of LC/MS/MS for the Fingerprinting of Pharmaceutical Drugs," Paul A. Steinberg, (Thermo Electron Corp., Woodstock, GA); "Process Analytical Technology (PAT) as a Way for Better Manufacturing and Quality Assurance," John F. Kauffman (Division of Pharmaceutical Analysis, U.S. Food and Drug Administration (St. Louis, MO); "Stability Testing for the Safety Assessment of Pharmaceuticals," Marta Vidal (Boehringer Ingelheim Argentina, Buenos Aires, Argentina); "Validation of Microbiological Methods for Sterile and Nonsterile Pharmaceutical Products," Michael Brodsky (Brodsky Consultants, Thornhill, ON, Canada); "The Relationship Between Pharmacopoeial Reference Standards and ISO REMCO Initiatives and Guides," Ronald G. Manning (United States Pharmacopoeia, Rockville, MD).

Clyde Carducci, Irma Ercolano, and Inés Cereijo co-chaired.

Pharmaceutical Task Force

There are no activities to report at this point of time.

Official Methods of Analysis Review

William Horwitz sent the General Referee Drugs chapters 18–22 of the *Official Methods of Analysis* for review. Several references were updated and others were corrected.

Interlaboratory Studies

The proficiency testing program organized by the Argentine group of AOAC INTERNATIONAL together with the National Institute of Medicines, Ministry of Health, Argentina (INAME; AOACI-INAME) is still in progress. At the moment new generic drugs (6 on the whole) are being identified to begin Round 4. This program is an interlaboratory study which is essential for the laboratory quality assurance and is also a requirement, together with the validation of analytical methods and the use of CRMs, of ISO/IEC 17025/Guide 25 (1) for laboratory accreditation (2). This program allows analytical laboratories to maintain the highest level of accuracy and reliability of results by comparing to other laboratories (3). Test materials distributed to participating laboratories must be homogeneous and one or more analytes in simple or complex matrixes may be analyzed. The laboratories may use pharmacopoeial methods or routine validated test methods, and they are given a deadline for the submission of their results. The returned data are then evaluated according to an internationally recognized protocol (4). To establish the assigned value to the test materials, the procedure of the consensus value from participant laboratories is used, using the average of the values found in the round, according to ISO 43-1 (5). During statistical analysis outliers are removed prior to calculation. Also a predetermined standard deviation, a standardized value, and a z-score is derived for each result submitted. Finally the results are sent to the participants in the form of a confidential report with identification codes.

In metrology, traceability, uncertainty, calibration and comparability of the results are primary requirements (6). Traceability according to the International Vocabulary of Basic Terms in Metrology (VIM) is defined as: "Property of the result of a measurement or the value of a standard whereby it can be related, with a stated uncertainty, to stated references, usually national or international standards, through an unbroken chain of comparisons" (7). Chemical measurements are traceable to a CRM or to reference methods. A reference material can be either a pure drug or a matrix reference material (8) in which the concentration of the analyte has been

certified and the uncertainty has been determined. Uncertainty of measurement (9) is a parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand; therefore it is applied for those measurements associated with CRMs (8). Although international pharmacopoeias use in their methods reference substances without certified values, it would be convenient that CRMs in the drug field were also available and used. Generally CRMs for the pharmaceutical industry are pure generic drugs.

These interlaboratory studies were intended to lead to the accreditation of the participant laboratories which met the international requirements by evaluating their performance by determining their *z*-score. It also aimed at assessing the consensus values and the uncertainties of the drugs obtaining their CRMs. The accessibility of these highly qualified materials will assure the traceability of the analytical results. Besides, the standardizing organizations (accreditation bodies) are looking forward to consider the same requirements for the pharmaceutical analytical laboratories regarding other areas (10).

A third round was organized with the following drugs: amiodarone hydrochloride, amlodipine besylate, salbutamol sulfate, ciprofloxacin hydrochloride, neomycin sulfate, and polymixin B sulfate. For Round 3A (amiodarone hydrochloride, salbutamol sulfate) of the 21 participants, only 6 (28.6%) reported one or more unsatisfactory results. Of the 134 analyses reported in duplicates by the laboratories, a total of 8 (6.0%) were identified as unsatisfactory and 22 (16.4%) had a high variability between replicates (unsatisfactory within-laboratories *z*-scores). For Round 3B (ciprofloxacin hydrochloride, amlodipine besylate) of the 20 participants, only 2 (10.0%) reported an unsatisfactory result. Of the 116 assays reported in duplicates by the laboratories, a total of 2 (1.7%) were identified as unsatisfactory and 12 (10.3%) had a great variability between the 2 replicates (unsatisfactory within-laboratories *z*-scores). For Round 3C (neomycin sulfate, polymixin B sulfate), of the 13 participants, only 3 (23.1%) reported an unsatisfactory result. Of the 54 assays reported in duplicates by the laboratories, a total of 3 (5.5%) were identified as unsatisfactory and another 3 (5.5%) had a great variability between the 2 replicates (unsatisfactory within-laboratories *z*-scores).

Certified Reference Materials

As a result of Round 3, 6 new CRMs were obtained and their assigned value was as follows:

Amiodarone hydrochloride.—Quantitation = $100.16 \pm 0.22\%$ (calculated on dry basis); loss on drying = $0.08 \pm 0.03\%$; pH = 3.51 ± 0.07 ; sulfated ashes = $0.019 \pm 0.009\%$.

Salbutamol sulfate.—Quantitation = $99.89 \pm 0.18\%$ (calculated on dry basis); loss on drying: $0.16 \pm 0.04\%$; sulfated ashes = $0.018 \pm 0.011\%$.

Amlodipine besylate.—Quantitation = $99.70 \pm 0.36\%$ (calculated on dry basis); water = $0.26 \pm 0.05\%$; sulfated ashes = $0.046 \pm 0.017\%$.

Ciprofloxacin hydrochloride.—Quantitation = $100.81 \pm 1.25\%$ (calculated on dry basis); water = $5.09 \pm 0.14\%$; sulfated ashes = $0.024 \pm 0.015\%$; pH = 3.78 ± 0.05 .

Neomycin sulfate.—Quantitation = 737.78 ± 19.7 mcg/mg (calculated on dry basis); loss on drying = $4.91 \pm 1.24\%$; pH = 6.49 ± 0.08 .

Polymixin B sulfate.—Quantitation = 8267.53 ± 351.13 I.U. (calculated on dry basis); loss on drying = $3.95 \pm 1.09\%$; pH = 5.94 ± 0.23 .

Other determinations specified in the pharmacopoeias for each drug were carried out by 2 reference laboratories and the values were included in the certificate as noncertified values.

Collaborative Study

As a result of the second round of the proficiency testing, in which enalapril maleate was assessed quantitatively, a collaborative study has arisen, in order to improve the quantification method, and will be organized. The topic to consider is "Determination of Enalapril Maleate by HPLC," Study Director, Clyde Carducci, e-mail: ccardu@interlink.com.ar. The proposed method is a modification of a USP compendial method for enalapril maleate bulk drug. The European Pharmacopoeia uses a titrimetric method to determine enalapril maleate as a bulk drug substance and an HPLC method for the related substances while the United States Pharmacopoeia (10) only utilizes liquid chromatography. Both official methods employ a styrene divinyl benzene column, which has poor versatility and is expensive. The chromatographic conditions are a gradient system and 70°C temperature. The proposed method utilizes a C₈ column and an isocratic system at a lower temperature with lower time of analysis. The resulting method is simpler, quicker, and cheaper. The method is suitable for the quantification of the maleate enalapril bulk drug allowing also assessment of its impurity profile.

Although absolute methods do not need standard reference material, sometimes, according to the nature of the drug, it is necessary to have complementary chromatographic methods where all the impurities can be separated.

Recommendations

Determination of Enalapril Maleate by HPLC.—Study Director, Clyde Carducci, Junin 956, Facultad De Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina, ccardu@interlink.com.ar. The precollaborative study has been evaluated by the Study Director who recommends it for a collaborative study. Continue study. Collaborators are sought.

References

- (1) ISO/IEC Guide 17025 (2005) General Requirements for the Competence of Testing and Calibration Laboratories, ISO, Geneva, Switzerland
- (2) EURACHEM GUIDE EA-03/04 (2001) Use of Proficiency Testing as a Tool for Accreditation in Testing, 1st Ed.

- (3) EURACHEM GUIDE on Proficiency Testing (2000) Guide on Selection, Use, and Interpretation of PT Schemes, Ed. 1.0
- (4) ISO/IEC Guide 43 (1997) Proficiency Testing by Interlaboratory Comparisons, Part 1: Development and Operation of Proficiency Testing Schemes
- (5) Thompson, M., & Wood, R. (1993) *J. AOAC Int.* **76**, 926–940
- (6) EURACHEM/CITAC Guide (2000) Quantifying Uncertainty in Analytical Measurement, QUAM: 2000. P-1, 2nd Ed.
- (7) International Vocabulary of Basic Terms in Metrology (VIM) (1993) 2nd Ed., ISBN 92-67-012075-1, ISO, Geneva, Switzerland
- (8) ISO/IEC Guide 35-Certification of Reference Materials (1989) General and Statistical Principles, 2nd Ed.
- (9) Guide to the Expression of Uncertainty in Measurement (GUM) (1993) BIPM, IEC, IFCC, ISO, IUPAC, IUPAP, and OIML, Corrected and reprinted 1995
- (10) EURACHEM Guidance Document 1 (1993) WELAC Guidance Document No. WGD 2, Accreditation for Chemical Laboratories
- (11) The United States Pharmacopoeia USP 27 (2002) The United States Pharmacopoeial Convention, Inc.