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RECENT ADVANCES IN DOPING ANALYSIS (2)

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ANTIDOPING CONTROL LABORATORY AT THE GAMES OF THE XXV OLYMPIAD BARCELONA'92.
PART I. MANAGEMENT OF RESOURCES

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INTRODUCTION

The Antidoping Control at the Games of the XXV Olympiad was carried by a joint project developed between the Organizing Committee (COOB'92) and the Institut Municipal d'Investigació Mèdica (IMIM) of Barcelona. COOB'92 was responsible for the build up of a structure for collecting the samples at the competition venues. The preparation and development of a project in order to analyze the samples was assigned to the Department of Pharmacology and Toxicology of IMIM, its laboratory having been accredited by the International Olympic Committee (IOC) since November 1985.

Official agreement with COOB'92 was established on November 17th 1989, although Laboratory IMIM had already been unofficially involved with COOB'92 since the preparation of the candidacy project back in 1984. The compromise was signed by the Institut Municipal d'Assistència Sanitaria (IMAS) to which IMIM belongs to. Total responsibility for Laboratory IMIM in regards to the analysis of samples of the XXV Olympic Games was established. COOB'92 was responsible for providing economical resources for material, personnel and training, which was complemented by another minor contribution of IMAS. COOB'92 also developed two written agreements with the company Hewlett-Packard, USA, in order to buy the instrumentation needed for the training period and for the loan of additional equipment during the period of the Games. IMAS was responsible for providing additional existing instrumentation, for developing methods, procedures and training with the standards of quality established by IOC and to provide adequate laboratory facilities. The optimized facilities used

during the Games in the new building of IMIM were available after leaving the initial facilities in the area of Hospital del Mar that were used until march 1992.

This report presents details of the resources available and the way they were managed to prepare the set up of a suitable antidoping laboratory for the Barcelona'92 Olympic Games.

FACILITIES

IMIM is located in a Biomedical Research Area next to the Olympic Village and few minutes driving from the Olympic Ring. It is physically linked to the Hospital del Mar (the Olympic Hospital). The Department of Pharmacology and Toxicology is located in the second floor of the IMIM building in which a total surface of 1.100 m^2 was occupied. The whole space available was distributed in different areas according to their function:

- Sample preparation laboratory
- Screening analysis laboratories
- Confirmation analysis laboratory
- Clinical research area
- Other facilities: sample reception room, store rooms, washing room, freezers room, cold room containing a "compactus archive system" able to store all A and B samples, offices, meeting room, resting room and central documents archive.

PERSONNEL

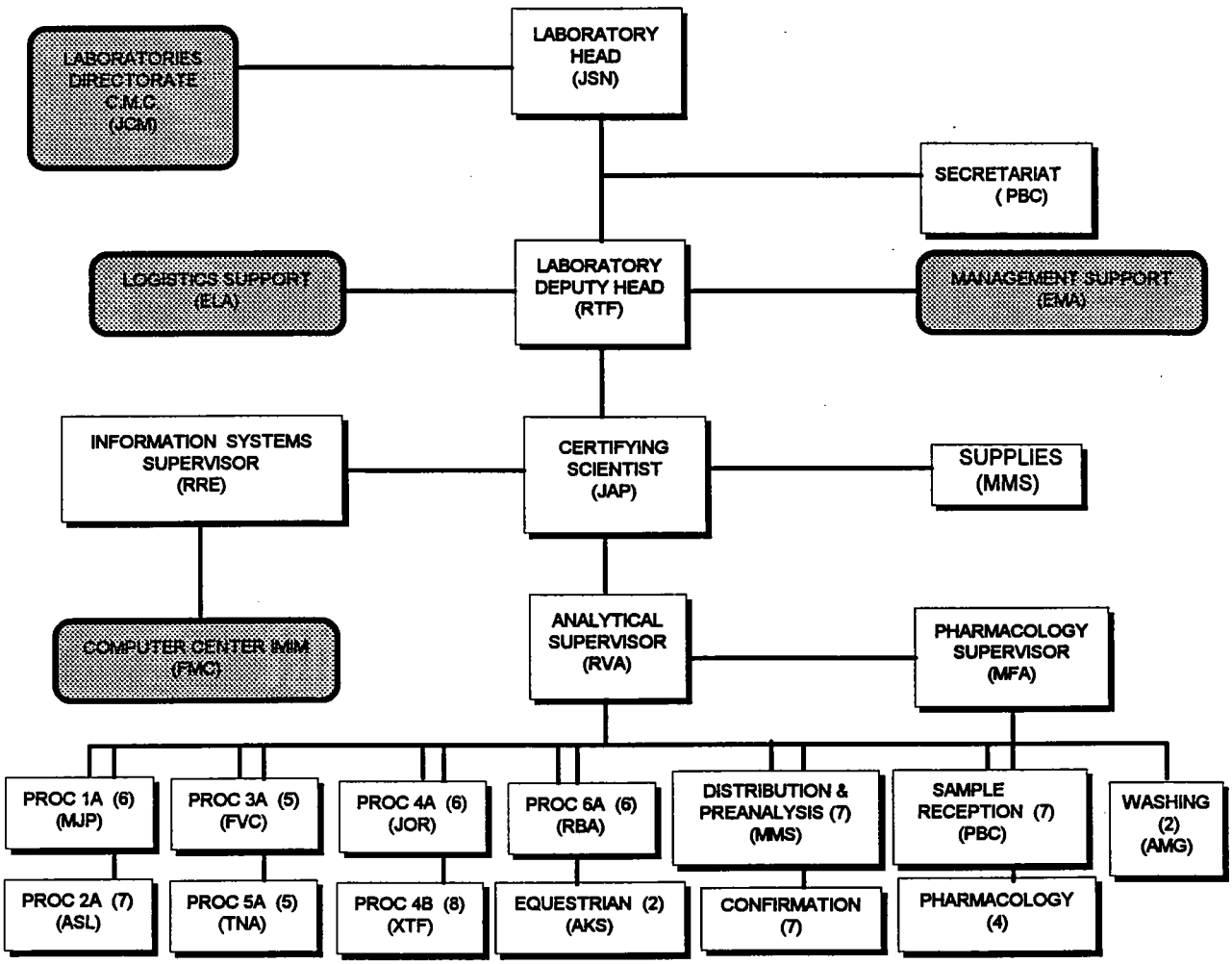
During the Olympic Games, the laboratory was run by staff from the Department of Pharmacology and Toxicology of the IMIM. The staff included 7 scientist at a management level (1 PhD, 1 PharmD, 2 MD, 1 Chemist, 1 Pharmacist and 1 Engineer in Computer Sciences), 19 scientists, heads and deputy heads of the different procedures (12 pharmacists, 3 chemists, 3 biologists and 2 physicians), 8 highly qualified technicians and 3 administratives. Two months before the Games, as many as 45 volunteers were recruited and included in the team involved in the doping control as additional collaborators. Most of them were students having finished the last period of their curriculum in chemistry or pharmacy.

In addition to these staff members and collaborators, three engineers and two visiting specialists (computer sciences and mass spectrometry) from the company Hewlett Packard provided support to the laboratory on a 24 hours basis distributed in two shifts. Concerning technical support from Abbott Laboratories, a convention between the IMIM Laboratory and this company made possible rapid intervention in the case of technical problems. One engineer from Central de Procesos Informáticos (CPI) was also available when needed. The Laboratory benefited too from the intramural support given by IMIM for the local area network (LAN) of personal computers and general maintenance services. The daily maintenance of the facilities, entrusted to a cleaning private company by IMIM, was carried out each night under the surveillance of the laboratory personnel. A Security Company hired by the COOB'92 assured the control of the access to the Laboratory. During the Olympic Games period, only the laboratory accredited personnel and the members of the Medical Commission of IOC were authorized normal access to the laboratory.

Personnel was hierarchially organized following the structure described in Figure I. They worked in two shifts covering 24 hours per day. Nevertheless, they were not distributed homogeneously during the day. The main constraint for the distribution of personnel was to have a sufficient number of samples available for analysis, at least 20 that constituted an analytical batch. Accordingly most of the personnel worked at night. A typical shift started at 10 p.m. and finished at 6 a.m.. The morning, was dedicated to the evaluation of analytical results and if necessary to the confirmation of presumptive positive cases. All the B sample analysis were scheduled and carried out also during the morning.

ANALYTICAL INSTRUMENTS

The laboratory equipment used for chromatographic and immunological analyses is described in Table I. Three types of immunological techniques were used: fluorescence polarization immunoassay (FPIA), microparticle enzime immunoassay (MEIA) and enzime linked immunosorbent assay (ELISA). FPIA and MEIA were performed automatically using the instruments described in Table I. ELISAs were performed manually, except for the final absorbance reading.



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TNA: Teresa Nadal Aquilué
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Figure 1. Organization of the staff of the Olympic Laboratory Barcelona'92.

Technique	Instrument Type	Manufacturer	Operating System	Nmb. Inst.	Analytical Procedures(*) (nmb. inst.)
GC/NPD	hp 5890 GC/NPD	Hewlett-Packard	MS-DOS	5	1A scr (3) 1B scr (1) 1 conf (1)
GC/MSD	hp 5971 GC/MSD	Hewlett-Packard	Unix	10	2A scr (3) 4B scr (4) 1 prec (1) 1 conf, 5 conf (1) 2 conf, 3 conf (1)
	hp 5970 GC/MSD	Hewlett-Packard	Unix	3	4A scr (2) 4 conf (1)
HPLC/DAD	hp 1090	Hewlett-Packard	Pascal	6	3A scr (2) 5A scr (3) 3 conf, 5 conf (1)
HPLC/MSD	hp 5989	Hewlett-Packard	Unix	2	3 conf (1) 5 conf (1)
FPIA	MTDx(**)	Abbott Laboratories	--	1	6A (1)
	TDx	Abbott Laboratories	--	1	6A (1)
MEIA	IMx	Abbott Laboratories	--	2	6A (2)
ELISA	Miniscan	Labsystems	--	1	6A (1)

(*) scr, screening; conf, confirmation; prec, preconfirmation. For specific procedures description, see Part II.
(**) equivalent to 4 TDx plus data track software.

Table I. Main laboratory equipment used for the different procedures during the Barcelona Olympic Games.

INFORMATION PROCESSING

One of the major features of the Barcelona'92 Antidoping Laboratory was the extensive use of computer technology. This is evident by the number of analytical instruments under computer control, the extensive use of network connectivity between instruments, and the development and installation of a number of advanced software systems.

- Hardware

Computing equipment can be identified in three categories: control of analytical instruments, centralized information management, and document and data post-processing. In addition to the systems included in Table I, other computing equipment purchases include a medium sized HP 9000/832 Unix system (900 mb disk; 64 mb memory), and the loan of a 9000/425 Unix workstation (1200 mb disk; 16 mb memory). The 9000/832 was used to support the LABiX (Central de Procesos Informáticos (CPI), Valladolid, Spain) Laboratory Information Management System and Oracle data base, and the 9000/425 for file management and additional storage during the Games. Document and data post-processing was carried out using IBM compatible 286, 386 and 486 PC personal computers.

- Network configuration

All computing equipment was connected via a Local Area Network (LAN) based on Ethernet (IEEE 802.3) protocols. This LAN consisted of an Ethernet Multiport Repeater (Allied Telesis CentreCOM 3008) with five thin wire branches linking the various sections of the laboratory. In addition, an Ethernet Bridge (Xyplex Maxserver 3010) connected the Antidoping Laboratory to the LAN of the remaining departments of I.M.I.M.

- Software

The inventory of software used by the laboratory was quite extensive, and can be categorized in a number of ways: by supplier, by function or by operating system. Major suppliers of software were Hewlett-Packard and CPI, the remaining products being locally developed or purchased from software distributors. Functionally, software was used either for analysis, information management, network control, reporting or document and data post-processing. Two operating systems and one pseudo operating system were used: Unix for sample analysis, information management and network control; MS-DOS for sample analysis, document and data post-processing; Pascal for sample analysis.

The major Hewlett-Packard software products used by the laboratory were the various operating systems (Unix, MS-DOS and Pascal), the ChemSystem analytical system with versions for each operating system, and the ChemLAN networking utility, also for each operating system.

The most significant non Hewlett-Packard software product used by the laboratory was the Laboratory Information Management System LABiX supplied by Central de Procesos Informáticos (CPI). This product contains a core system which was configured to the needs of the laboratory, but was also enhanced by the addition of modules designed as a joint project between IMIM and CPI. LABiX is based upon an ORACLE relational data base for which a run time license is required by each LABiX installation.

Other commercial software included the VMS operating system and associated utilities (Digital Equipment Corporation, USA) available on the IMIM VAX systems, as well as MS-DOS and supported utilities available centrally on the VAX systems, or locally on individual PC's.

- Locally developed software

The two most significant local software developments were modifications to the LABiX system, and a suite of programs known as NeoMacros. They were designed to improve the quality of data analysis, specifically as applied to antidoping screening procedures. The basic features of this system are: vastly improved reporting quality, better peak detection and integration, and centralized data management and storage. NeoMacros are explained in more detail in the paper by J.A. Pascual, R.R. Ewin and J. Segura, *Automated Control of Doping Samples and Their Analysis, Preparing for Barcelona'92: Part II*, Proceedings 10th Cologne Workshop on Dope Analysis, M.Donike, H.Geyer, A.Gotzmann, U.Mareck-Engelke, S.Rauth, editors, Sport und Buch Straub, Edition Sport, Koln 1993.

- Data Management

During the sample analysis phase, data files were generated locally for each sample. These files were transferred to a central server system for subsequent report generation, and for inclusion in the Laboratory Information Management System (LIMS) data base. Hard copy

reports (NeoMacros developed in the central server) were always redirected and printed beside the instrument which performed the analysis.

The number and type of instruments installed in the laboratory was a function of the number of samples expected daily, the time required to process each sample, and the average size of data and report files generated by screening procedures. Table II shows the actual number of batches, and the amount of data generated during the 15 days of competition.

Procedure	Batches	Size
1A	97	28 mb
1B	100	15 mb
2A	100	3685 mb
3A	94	147 mb
4A	100	139 mb
4B	101	504 mb
5A	99	220 mb

Table II. Data Files Archived.

- Laboratory Information Management Sustem (LIMS)

A description of features of the LIMS can be found in the publication by J.A. Pascual, R.R. Ewin and J. Segura, *Automated Control of Doping Samples and Their Analysis, Preparing for Barcelona'92: Part I*, Proceedings 10th Cologne Workshop on Dope Analysis, M.Donike, H.Geyer, A.Gotzmann, U.Mareck-Engelke, S.Rauth editors, Sport und Buch Straub, Edition Sport, Koln 1993.

REAGENTS AND MATERIAL

Water used in the liquid chromatographic eluents was of Milli-Q grade (Millipore Ibérica, Barcelona, Spain). Methanol, acetonitrile and ethyl acetate were of HPLC gradient grade. Diethylether was of reagent grade quality and freshly distilled over calcium hydride. Other reagents were of reagent-grade quality. ß-Glucuronidase from *Escherichia coli* (Boehringer Mannheim, Mannheim, Germany) and ß-glucuronidase-arylsulfatase from *Helix pomatia* (Sigma Chemicals, St. Louis, MO) were used for enzymatic hydrolysis. For solid-phase extractions, Detect Abuse™ (Biochemical Diagnostics, Edgewood, NY, USA) and Bond-Elut Certify (Analytichem International, Harbor City, CA, USA) columns were used.

Dimethylchlorosilane (DMCS), N-methyl-bis-heptafluorobutiramide (MBHFB), N-methyl-bis-trifluoroacetamide (MBTFA), N-methyl-N-trimethylsilyl-heptafluorobutiramide (MSHFB), N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA), and trimethylsilylimidazole (TMSI) were obtained from Macherey-Nagel (Düren, Germany). Ammonium iodide, methyl iodide and 1,1,1,3,3,3-hexafluor-2-propanol were supplied by Merck (Darmstadt, Germany). Dithioerythritol and trimethylboroxine were purchased from Aldrich Química (Alcobendas, Madrid, Spain). Pentafluoropropionic anhydride was supplied by Supelco (Bellefonte, PA).

Reagents for immunological analyses were purchased from WTT Inc., Lexington, USA (ELISA tests); Abbott Laboratories, Chicago, Ill, USA (FPIA and MeIA tests) and Pharmacia, Uppsala, Sweden (DELFIA test).

Cross linked methylsilicone or 5% phenylmethyl silicone fused silica capillary columns (Ultra 1 or Ultra-2, respectively) (Hewlett-Packard, Palo Alto, CA) were used for gas chromatography. Reversed phase Ultrasphere ODS columns, 7.5 x 0.46 cm, 3 μm (Beckman Instruments, Fullerton, CA) were used for liquid chromatography.