

The Role of the ISS in the Italian Health Service, and the Need for Medical Device Market Surveillance

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After the First World War, attempts were made to improve both health administration and research policies, worldwide. Thanks to the financial support of the Rockefeller Foundation and the role of the League of Nations, national health institutes were created in many countries, Italy included. The Istituto Superiore di Sanità (ISS) was thus created (in 1934) for the safeguard of public health. The decree establishing the Institute envisaged the creation of a number of scientific laboratories, operating in the different sectors of public health (1,2).

In 1935, Domenico Marotta was appointed as Director of the ISS. He acted as a catalyst and organizer of research in different fields, and shaped the ISS into one of the most up-to-date scientific centers. During Dr. Marotta's direction, two Nobel Prize winners worked at ISS. Daniel Bovet (Nobel Prize for Medicine in 1957) was the Director of the Laboratory of Therapeutical Chemistry from 1948 to 1964, and Ernst Chain (who investigated with Howard Florey and Alexander Fleming the activity of natural antibacterial agents, including penicillin) directed the International Centre for Microbiological Chemistry of the Institute in 1948. He produced semi-synthetic derivatives of great therapeutic as well as commercial value, and thus Italy entered the 'club of antibiotics'. From the very beginning, the management of ISS was aware of the need to equip laboratories with the most modern research instruments. Hence, an electron microscope for the Physics Laboratory was ordered from Siemens in 1939 and operating in spring 1943. On October 8, 1943 - one month after the armistice of Italy - the microscope was withdrawn by order of the German military command "...to be put in safe keeping with

the promise to give it back after the undeniable victory". In the same way, ISS realized a linear accelerator Cockcroft Walton in 1938, following a project promoted by Enrico Fermi, just before his leaving for the USA, in order to guarantee the highest levels of nuclear research performed in Italy by "I Ragazzi di Via Panisperna" (Fermi's boys). In the thoughts of Domenico Marotta was a program for the production of artificial radioactive substances for therapeutic use in oncology. Finally, the governmental production of penicillin led to the realization for new patents, both in Italy and abroad.

The same tasks of research, control and training as activities for the safeguard of health will continue to characterize all the efforts of ISS researchers and technical personnel in the spirit of a service to patients. Under the direction of Francesco Pocchiari (1971-89), the research orientation of the ISS was focused on major themes of biomedical research by developing links with the leading organizations of the sector, notably the World Health Organization.

The Engineering Laboratory was instituted in 1941, and several new laboratories were subsequently added to the ISS structure. The structure of the Laboratory of Biomedical Engineering was defined by a Decree of the Minister of Health, 29 April 1982, with four operative units: Biomaterials, Diagnostics and functional monitoring, Technology of the biomedical imaging, and Technologies for Therapy and Rehabilitation. Initially, the laboratory activities were devoted to the use of electronics in the design and development of new instrumentation for internal needs or for patient monitoring, after which tasks for the control of devices on the market, ruled by national decrees as in the case of pacemaker, were developed.

Since 1988, one operative unit at the ISS has been devoted to the in-vitro testing of implantable cardiovascular devices, including artificial heart valves, grafts and stents (3-13). In this respect, several techniques have been set up to investigate the biomechanical and fluid dynamic performance of these devices, such as steady and pulsatile flow in-vitro testing tools,

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and investigations into the comparability of data produced by different centers. In addition, valve fatigue life using long-term durability testers was studied by using high-speed videography and by producing mechanical models of prosthetic valves in order to investigate valve occluder kinematics. Perhaps the most relevant investigation was that into the role of shear stresses on blood trauma (e.g. hemolysis), which was achieved by the development of an LDA apparatus and, more recently, with two- and three-dimensional PIV systems using principal stress analysis.

When investigating the in-vivo performance of passive implantable devices, a variety of methods and algorithms were developed, including ultrasound for investigating native valve regurgitation, and both stenting and grafting compliance and downstream perfusion, using one-dimensional real-time determination of velocity profiles in the arteries. Today, the numerical simulation of fluid dynamics in cardiovascular devices is used to compare results obtained from simulations and in-vitro experiments. The result of these studies has led to the development of a new model for assessing the mechanical load on red blood cells, by using Reynolds stress values.

Today, a new organizational structure has been introduced to the ISS whereby three laboratories form the Department of Technologies and Health, with a role in the research, control and evaluation of several new technologies. The aim of this unit is to promote healthcare, in collaboration with the Ministry of Health, and to achieve goals laid down by the National Health Program. The assigned tasks include research into medical devices (both active and non-active implantable), the training of national health service personnel, market control of medical devices (via Certification and CE marking of medical devices), inspecting the medical device market and its surveillance, and a consultatory role for judicial authorities and the Ministry of Health, mainly following the withdrawal of medical devices from the market by the NAS that are the Italian anti-alteration, anti-counterfeiting operatives, because of accidents and Higher Council of Health for decision making.

These tasks are also carried out on the basis of three fundamental European Directives which regulate the marketing and introduction into clinical practice of medical devices: Directive 90/385/EEC for Active Implantable Medical Devices (AIMDD), (MDD) Directive 93/42/EEC for passive Medical Devices, and (IVDD) Directive 98/79/EC for In Vitro Diagnostics. Other instruments include examination of the standards and guidelines, and the use of risk analysis (EN1441), which is generally employed by manufacturers to determine the corrective action to be taken in case of adverse events.

One particular issue required under the EC directives is that of post-market surveillance, and this is an area where the ISS is especially active. In fact, a project has recently been started involving studies on the marketing of medical devices, termed SO.VI.DI.ME. This role has been added to the ISS list of activities, such that the Institution provides technical advice to the Competent Authority in Italy (Ministry of Health), with regard to:

Adverse events (serious or non-serious; according to ISO14155).

Advising about supposed non-conformity to the essential requirements of marketed medical devices, starting from a trigger sent by operators in the NHS. Issues regarding the withdrawal of medical devices, as directed by the judicial authority.

The 'chain' of vigilance exerted by the ISS can be described typically as follows. Based on EC directive 93/42, any adverse events are notified to the CA, from both health operators or/and the manufacturer (see Med Dev guidelines). Thus, in Italy the NAS withdraws the device, along with several samples from the same lot, if available. The CA then asks for a technical report from the ISS, sending the withdrawn sample of a device (unless it has been sequestered by the judicial authority). The ISS then requests new samples of the same model from the manufacturer (or mandate holder), or requests that the NAS acquire a sample from the market.

A technical examination is then conducted of the medical device and of its documentation, technical instructions for use, and commercial details. Details of adverse events are not always available for a given device, in which case at least samples from the same batch are collected for the in vitro study of the event.

For a state-of-the-art device, a sample from another manufacturer may be used as a reference if its safety and efficacy issues have been previously published over a sufficient period of time for them. This is especially important when the device's performance cannot be determined in an absolute sense. If needed, more information or/and technical documents are required from the manufacturer, as well as their own final reports, as required by EC guidelines. An analysis of published data and of any international alerts (FDA, MDA, etc.) is also made to determine if the device has been the subject of any other assessment procedures. Simulation or specific tests may also be carried out, based on the available skills and resources developed by the laboratory.

All information is then evaluated by using specific standards (harmonized or not) if applicable. The information reported in the service manual, together with any operator's instructions, are then examined to

answer the following question: has the operator followed the intended use as defined by the manufacturer, for ensure safe operation?

The technical documents are then assessed to determine if the manufacturer has followed the EC directive to mitigate risks for correct and incorrect use.

Finally, the failure and its mode are identified or hypothesized; an hypothesis is then created as to why the adverse event occurred, and a final report with the ISS advice is provided to the CA, indicating the corrective action (if any), and then to the healthcare personnel (ASL, IRCCS, clinics, universities, etc.) and the manufacturer.

Despite huge advances in knowledge having been made in the hemodynamic and material properties of cardiovascular implants, and in their biocompatibility and biostability, many problems remain in terms of product surveillance. For new technologies - which are often used in medical devices - the process of certification does not conclude a device's assessment due to the continuous and rapid evolution of these devices and the need to develop investigational methods that are appropriate in interpreting data obtained as a result of adverse events.

Whilst the failure of devices is the first issue, thrombosis represents a common threat to the use of mechanical and biological artificial valves, in particular with regard to the hemodynamics of the device or its surface properties. Similar attention must be paid to risk analysis and intended use. In fact, all cardiovascular devices (valves, graft, stents, pacemakers, defibrillators, etc.) must be correctly implanted in relation to their intended use, and instructions for their use; thus procedural problems must be correctly addressed following the risk analysis made for the specific device.

On account of the complexity of implantable devices, it is necessary to improve surveillance systems in order to monitor possible clinical problems that might occur, even after careful pre-market assessment. An example is the Medtronic Parallel valve and the growth of anemometric set-ups to study the thrombogenicity of cardiac valve prostheses (14).

The provision of databases on alerts (e.g. CDRH of the FDA or MDD) are used by the ISS to identify any possible repetition of an adverse event, or to determine whether a medical device has been approved (or not) in other countries. In general, a spontaneous user report can be taken into account, but this does not have the same value as a scientific report as they are not appropriately designed (in statistical terms) as clinical trials. Moreover, it is the responsibility of the manufacturer to maintain a systematic procedure to review information on the medical device's post-production phase, such as previously unrecognized hazards, or any risk which is no longer acceptable.

The use of implant registers could be highly relevant in this situation, especially if the information is of high quality, and may guarantee a more systematic approach.

It is supposed in the EC that reporting on adverse event is affected by under-reporting and biased by incorrect information. Post-market clinical evaluation must be considered as a relevant tool to address problems that are either not known or are inappropriately evaluated in the risk analysis, at the time of the authorization to the marketing, for several reasons such as the technological development (innovation) or the ability to maintain constant the production characteristics of a medical device quality system.

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