

Orphan Devices for the Surgical Treatment of Patients with Rare Diseases: Present Status and Recommendations for the Future

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Text

Orphan devices are medical devices intended for the treatment of a very rare life-threatening or chronically debilitating condition. Several institutions (United States Food and Drug Administration (FDA), European Medicines Agency (EMA), Australian Therapeutic Goods Administration (TGA),...) have put in place regulatory and economic frameworks to facilitate the development of orphan drugs (134 authorized by EMA today), but much needs to be done for these medical devices especially in Europe. The core EU legal framework consists of three directives (90/385/EEC on active implantable medical devices, 93/42/EEC on medical devices and 98/79/EEC on *in-vitro* diagnostic medical devices) without measures for surgical procedures with devices in patients with rare disorders.

During the twentieth century, several breakthroughs in surgery were achieved¹. For example, Alfred Blalock (1899-1964) developed a surgical procedure in 1944 to relieve the cyanosis from Blue Baby Syndrome, a kidney was transplanted between identical twins in 1954 and a liver transplantation was performed in 1963 by Thomas Starzl (°1926). Numerous new techniques were developed such as direct blood transfusion by George Washington Crile (1864-1943) in 1905, amniocentesis in 1952 by Douglas Bevis (1919-1994) and diagnostic ultrasound by Ian Donald (1910-1987) in 1958.

Today operating theaters have a large collection of sterile medical material to be implanted during surgical interventions such as neuro-stimulators, prostheses, heart valves, stents, osteosynthesis material and pacemakers. All this material is evaluated by so-called “notified bodies” in every EU-Member State (Regulation 93/42/EEC from 14 JUNE 1993 concerning medical devices and Regulation 90/385/EEC concerning implantable active medical devices) and assigned a CE marking when conform. Also different systems have been implemented to evaluate post-marketing the efficacy and safety (“materio-vigilance”) of such devices. The use of a medical device outside the population or purpose for which the safety and effectiveness profile has been evaluated (off-label use) is quite common with low-prevalence diseases (mainly in children). But do we need initiatives to stimulate research and development of medical material (“orphan devices”) intended for the *in-vivo* diagnosis, prevention and treatment of rare diseases with incentives such as a centralized European procedure and protocol assistance? Especially because the marketing period for devices is shorter than for medicinal products, the risk on obtaining no return on investment for R & D on devices is real and clinical studies with

devices are totally different than randomized clinical trials with medicinal products. In some EU Member States such as Belgium medical devices are dispensed by the hospital pharmacists.

A general public consultation of the European Commission (2007) has been launched to find out if the EU should have an orphan regulation on medical devices and diagnostics² (Question 9). Hundreds of responders (patients and their families, national and international (patient) organizations, national authorities, commercial organizations and companies, universities and experts, reference centers and researchers) were in favor of such a regulation except the following six:

- * The Association Internationale de la Mutualité thought there was not enough information nor evidence.
- * The European Social Insurance Platform mentioned that medical devices already on the market were not “rare disease”-specific.
- * The UK National Health Service stated that they did not believe that there were sufficient problems in the development and commercial marketing of devices to justify the administrative effort and special privileges for orphan regulations.
- * The Ministry of Health, The Elderly and Community Care in Malta felt that such a regulation would neither be necessary nor beneficial and that the current legal framework already catered for rare diseases.
- * The Dutch Ministry of Public Health, Welfare and Sports, Drugs and Medical Technology considered a EU regulation in this matter not the right way forward as there are different reimbursement systems within the different EU Member States.
- * Baxter Healthcare did not see any justification to introduce such a legislation.

Of all the overwhelming positive reactions I cite a few here:

*The Finnish Rare Disease patient organization replied to this question of the consultation that developing equipment and determining norms in the EU would help those countries who still have challenges to improve their national standard. Possibilities to improve the national standard were considered poor in many EU countries and the markets too small.

*The Swedish government agreed that there was a need to better investigate the required conditions for developing incentive measures and legislation for orphan devices similar to orphan drugs. But they suggest first a thorough analysis of the financial impact and possible rules.

*The UK Genetic Interest Group (patients) suggested

that the burden of regulation should be kept to a minimum with a single European application.

But an “orphan-device” legislation has not (yet?) been introduced in Europe today as we have for orphan medicinal products since 2000. Only some EU-Member States have national rules (for Belgium: Royal Decrees 15 JULY 1997 and 18 MARCH 1999) for medical devices (“dispositif à usage unique”).

In the United States of America a Humanitarian Use Device (HUD)³ is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4000 individuals in the United States per year. The application (since 1990) must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Up to the present, 68 HUD’s have been approved by FDA, mostly implantable (programmable) therapeutic devices in pediatrics (pediatric devices)⁴, cardiology (ventricular assist devices in congestive heart failure)⁵, neurology (microelectrodes for neurostimulation), hematology (cryofilter for cryofiltration apheresis)⁶, otorhinolaryngology (auditory brain stem implants) and orthopedics (craniosynostosis).

Custom made (active implantable) medical devices are medical devices that are made by special request (eventually 3D-printed) of a health professional intended to be used for a particular patient. Printing can be outsourced (<http://www.materialise.com>) or performed in the hospital based on beam computed tomography. Even stem cells can be grown around the 3D-print. Several agencies (UK, TGA, FDA)⁷ have regulations in place to allow the use of these unique one-time devices. But a regulatory framework with economic incentives to stimulate the research and development of orphan devices similar to the legislation around orphan drugs is still lacking in Europe⁸. Reimbursement will always remain a decision of the different Member States as for orphan drugs which will result in inequalities in access to health care.

Recommendations

A regulatory European framework with economic incentives needs to be installed to stimulate the research and development of orphan devices similar to the legislation around orphan drugs. Incentives are needed (as for orphan drugs) to enable useful medical devices to reach the patients and clinicians in a timely fashion. Collection and analysis of publicly accessible safety/efficacy data (EUDAMED: European Databank on Medical Devices) needs to be centralized between all EU Member

States to reach a sufficient number of patients to perform comparative-(cost)effectiveness and –safety studies.

Illustrations

1. Saving a Newborn with the Support of 3D Printing: <http://www.materialise.com/cases/saving-a-newborn-with-the-support-of-3d-printing>
2. Groundbreaking 3D Printed Splint Restores a Baby's Breathing: <http://www.materialise.com/cases/baby-s-life-saved-with-groundbreaking-3d-printed-device>

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