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Differences in the approval process for interventional devices in Europe and USA: IN MEDIO STAT VIRTUS

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Europe and USA: different answers to the same questions

The current process of approval of medical devices is profoundly different in Europe and in the United States. In Europe, a company manufacturing a new device is free to choose one of the 72 Notified Bodies, private organisations monitored by the National Health Authorities, to receive CE mark and seek subsequent approval by the National Health Authority which remains ultimately responsible for the surveillance of clinical application of the approved device. In the USA the process is centrally regulated by the Food and Drug Administration (FDA) following uniform schemes and starting from the very first, the identification of the intended use, the population of intended use, and the appropriate clinical trial design to ensure "reasonable assurance of safety and effectiveness." There are some similarities to the drug evaluation processes, including pilot safety/feasibility trials (on actual patients rather than normal volunteers), mechanistic Phase 2 trials compared to standard therapies (instead of dosing studies), pivotal Phase 3 trials generally randomised against controls, and post-approval Phase IV surveillance processes for additional undetected safety issues.

However, device evaluation must accommodate unique differences from drugs, including the rapid pace of device innovation and the interdependence of device performance with operator experience and skills. In all, the goals of evaluation include a hope to avoid widespread use of a therapy that is later found to have significant problems, leading to worldwide recalls, headline-oriented attention of the general media and shaking the stock market. If you have a chance to visit the beautiful gated citadel where several high rise building provide the new home of the FDA, just outside Washington, and compare it with the scattered offices of EMA in Canary Wharf, London, the device regulations agency still host in the Industry and Enterprises Department in Brussels, you can immediately understand the different breadth of scope of the US and European organisation, the first aiming at tight control of all steps of the approval process, the second offering more advice and orientation on the achievement of basic standards which will be supplemented by national approval.

A recent analysis of the value of the FDA

At the ESC 2006, data was presented regarding a worse long term prognosis following DES implantation compared with BMS[1]. This meta-analyse data triggered a media phenomenon casting doubt on the safety of DES with not only medical, but also financial consequences. This, in part, led the FDA to discover the on- and off- label use of DES. The response from the FDA was threefold:

– Firstly, the transfer of databases for evidence based medicine from the industry to academia;
– Secondly, the informal acceptance of the ARC definitions and,
– Finally, the FDA saw the need for the creation of "all-comers" trials, which is remarkable considering the selective restrictive indications in previous trials.[2]

Who provides the best care for patients is right

The European approach offers a relatively fast, if less stringent, pathway for new devices. US physicians attending live courses in Europe frequently blame the delays induced by the FDA's strict and centralised approval process for the paradox that European interventionalists have access much earlier to devices manufactured

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by US companies at much lower prices. It is very rare to hear among European interventional cardiologists and medical professionals in general the opposite comment, asking for a European Agency which, in fact, already exists, but has the authority to take over the process limited only to drugs (EMA, European Medicine Agency) .

Critics of the current European system argue that the system does not protect the consumer enough and leaves a wide margin of inconsistency due to the variable quality and competences across the many Notified Bodies and National Competent Authorities. In interventional cardiology, one may point out that, for instance, the number of approved drug eluting stents (DES) is much greater in Europe than in the US, including many DES offering no advantage over bare metal stents or with results much worse than other DES in restenosis prevention. Supporters of the current system reply that this empowers the physician to use this freedom to choose well proven devices for their patients. Unlike in the USA, in Europe an approved device does not automatically become reimbursed and then available for the majority of patients. The cost effectiveness criteria of the health economists are sometimes incomprehensible for practising physicians, but they imply outcome studies and compensate the more technical approach of the above described approval process. Medical societies, such as the European Society of Cardiology, are also somewhat involved in the selection process because Guidelines screen the approved devices recommending only the devices effective and well tested for clinical use. Table 7 of the recent Revascularisation Guidelines, a shared initiative of the European Society of Cardiology and EAPCI with the European Association of Cardiothoracic Surgery, specifically indicates the DES with sufficiently large trials with clinical or surrogate angiographic endpoints to warrant indication for clinical use.[3] There is no advantage, critics say, to take the process away from physicians, scientific societies and health economists who are well aware of trials, give a competent scrutiny of their results, and apply them to the very different economic possibilities of various European countries, centralising it in the hands of bureaucratic regulators.

European interventional cardiology can only be hampered by over regulation of the device industry

How should European interventionalists, and the EAPCI in particular, react to some proposals you hear of drastic changes in the current European regulation process, with a unified Medical Device Agency moving in the direction of requesting “Pharma” like mega-trials within the volatile market of medical devices which have a much shorter lifespan than drugs?

You can have a “defensive” approach and oppose any interference of Europe in national or professional prerogatives. This attitude is, by definition, in conflict with the statute of our Association which calls for greater integration of training and practice in all European countries. Furthermore, we take the risk that this position might be felt as protective of the interests of the industry against the patient due to perceived conflicts of influential members of the interventional community. The midway point I suggest to follow is different and calls for a re-evaluation through intellectual partnering across regulators, industry and professionals of the basic principles informing the approval of medical devices, with appropriate adjustments and corrections, but without revolutionary changes that may paralyse a system that currently works. We can guide such changes based on the knowledge accumulated in three decades of clinical application and research. One of the strengths of interventional cardiology is the vast amount of clinical trials conducted in the field informing and supporting the progress of new techniques, from balloons to stents and DES, rigorously testing various iterations of these devices in a wide range of patient populations.

Diversification in the approval pathway

The big challenge to fight against is the development of unnecessary increases in the complexity and cost of the European regulatory process leading to delays in approval which are only due to a formal increase in “red tape” with no real improvement in patient safety, and benefiting only a new layer of bureaucrats, lawyers and lobbyists involved in the preparation and control of plethoric files. Similarly, flexibility of the approval process should acknowledge the diversity, and therefore the very different needs, of devices that induce a transient mechanical effect on the vessel (wires, balloons, thrombectomy catheters, filters) as compared to permanent “inert” implants (stents), compared to hybrid devices with a long-term pharmacological effect such as drug-eluting stents.

The second point of diversity is in the magnitude of device modifications over time. You cannot have the same regulatory requirement for a new iteration of a wire expected to confer minor additional increments in steerability and that of a stent using drugs never before applied in the clinical arena and eluted by a novel fully biodegradable polymer. The regulatory path should also remain flexible to reflect the great difference in potential beneficial impact for patient treatment of a device targeting a new clinical need (for instance stents with large drug reservoirs to reduce reperfusion damage and non-embolic no reflow observed after primary angioplasty) versus yet another iteration of a drug eluting stent using known drugs and polymers and unlikely to lead to major improvements in clinical outcome. Grading the complexity of the approval path according to the response to true clinical needs is in the interest of doctors, patients and regulators. Minor incremental improvements in a mythical “workhorse” guidewire able to cope with all needs should have an approval path potentially less stringent than the path reserved to wires using truly innovative technology to address still unmet needs such as the recanalisation of chronic total occlusions, within a more limited market of expert operators in the field of CTOs.

When the new device offers truly new and unique applications (a super deliverable covered stent for coronary perforations and aneurysms, new DES outside the current range [<2.25 mm or >5.5 mm diameter] or a conformable self expanding DES with low restenosis rates in long occlusions of the superficial femoral artery) the regulatory pathway should offer an expedited approach considering the limitations of the current techniques and the urgency to offer alternatives.

Non-implantable inert mechanical devices

For the first class (non-implantable devices), the current pattern of approval is probably adequate with focus on consistency of the manufacturing process. The only advisable changes involve greater standardisation of the process and proper input by expert unbiased professionals during pilot clinical testing. I am always asking myself how much credit I should give experiments run in the R&D of the manufacturing company, or how much attention I should pay to the statistics generated by putting together standard forms quickly filled by company reps asking your opinion at the end of the first tests of free samples of a new wire or new balloon. Regulatory bodies should give no credit or attention to data acquired outside a rigorous controlled environment, and with no guarantee of independence of analysis and consecutive, well documented clinical use. The approval pattern must go through a serious scrutiny of the results of controlled in vitro tests using standardised adequate models. In many cases, a small clinical comparison study with standard devices may also be reasonable. Animal experiments are of no use since the behaviour of a device in non-calcific unobstructed arteries cannot discriminate the quality of performance in the more challenging clinical arena. Companies may lose the incentive to come up with a new family of balloons and wires every year, but we all know that often these changes have only a commercial drive and sometimes "new" wires and balloons perform not as well as the old ones because insufficient attention is paid to critical features such as visibility of markers or re-wrapping capacity. If a proper series of consecutive cases shows worse results for the new versus the old balloon generation, doctors and patients will only benefit from not being forced to downgrade their material to a lower standard. Companies will also learn the lesson and spend greater attention to license new devices for testing only when true incremental benefit is expected, concentrating their resources on more valuable projects.

Stents and DES: not all changes require thousand patient trials

As recommended in a previous document issued by the ESC and EAPCI after the DES storm of Barcelona 2006[4], the approval process for a new DES must be more rigorous and include controlled trials, but a logical gradient of complexity must be followed according to the expected biological relevance of the changes performed. In principle, changes in stent design may also modify the elution pattern, but this fear is not supported by the experience acquired so far. The revolution of nanotechnology has the potential to offer purified stronger materials to build super thin, highly compatible struts, and possibly reduce the need of strong antiproliferative coatings. There is no need to unnecessarily delay or prevent the development of stents with thinner struts, better mechanical scaffolding, dedicated designs to avoid strut malapposition across bifurcations by requiring large randomised trials of thousands of patients with clinical endpoints. If their key biological features (drug and polymer) are already approved and in clinical use, the wealth of data obtainable with sophisticated intracoronary imaging techniques post-deployment and at follow-up in a small scale trial, ranging from neointimal thickness to percent of strut coverage and malapposition, may offer valid surrogate endpoints. The long-term effect on clinical outcome of these changes is still unclear, but once the safety of deployment and presence of favourable changes or comparable results in surrogate endpoints are documented, subtler differences can be detected in the surveillance period monitoring large clinical application or through smaller clinical outcome trials using Bayesian analysis plans which leverage well informed prior data and thus may also be useful.

For truly new devices, when clinical outcome measures are required, the number of patients is never the only qualifying aspect of a trial. We cannot expect that a trial in type A lesions and large vessels in patients with stable syndromes answers questions applicable to the majority of the patients currently treated with angioplasty, which are more often unstable and with complex lesions. All comers studies should not be the initiative of few enlightened investigators, but become a strict requirement for proper phase 3 trials preliminary to the approval of truly new stents. On the other side of the Atlantic, similar initiatives have tried to move away from purely mechanistic endpoints in patients with simple lesions to again embrace clinical endpoints in high risk populations. The success obtained in convincing their regulatory authorities that "enriched" populations of "more-comers" (acute myocardial infarction, SVGs and occlusions are still excluded) bring closer the research practice in this field and facilitate comparison of US and European regulatory trials.[5,6]

Post-marketing surveillance: a neglected aspect of the regulatory process worldwide

If a stringent scrutiny is applied to pre-registration mechanical evaluation and clinical studies, unforeseen surprises are unlikely with wider clinical applications. Still doctors and regulators have a commitment to their patients to ensure that a sufficiently large and prolonged follow-up is available in sufficiently complex patients to be generalisable to clinical practice. This should be collected and analysed independently from the industry with the same rigorous quality and statistical methodology of pre-market trials. Forcing the industry to provide "some" data is probably the most ineffective approach. Very few of the many e-Registries set up by companies for new devices made their way to reputable peer-reviewed journals. Professionals should ally with policy regulators and the industry for the common goal of acquiring high quality individual data including follow-up in the post-market environment. Interventional cardiologists and professional societies who determine guidelines have an interest to monitor results of coronary, peripheral and valvular interventions for many other reasons. Retrieving data of post-marketing surveillance can provide funding to run large registries and the ESC and EAPCI should not lose the opportunity to lead this process for cardiology in Europe. Some European countries like Sweden are at the forefront of research in this field, with the ability to obtain near universal entries of patients in their country, with access to follow-up data on mortality and hospitalisation from their National Institute of Statistics.[7]

Working together to create a better regulatory pathway

The few points above are far from an exhaustive examination of the many possible uncertainties that require discussion and creative

agreements. Which approval pathway should we use for drug eluting balloons (no permanent implant, but huge biological effects with drug doses higher than DES)? How to test the durability of a new transcatheter valve? Other treatments, such as cell therapy, require answers going beyond the field of expertise of cardiology, and we must be humble and involve other specialties in medicine and biology. We must ensure transparent and collaborative relationships between interventional device companies and our Association are maintained. It is in nobody's interest to make our subspecialty lose credibility, or be accused of unhealthy links with the device industry. Disclosures must be complete and verified. The level of conflict of interest among physicians with vested interests in specific areas because of consultancies, grants, PI roles in sponsored trials which should be the basis for exclusion from evaluative decision making should be well thought out and publicly accessible. There is space to make the regulatory process in Europe better without hampering the historical advantage of a fast approval process, following transparent rules and with the rapid turnover private companies can ensure. Our goal as a profession and professional society is to not interfere in individual cases, but to help the regulatory agencies set the rules of the game and adapt them to the fast pace of technological development.

They should listen to us because we have the same primary goal they have, defending patients.

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