Regulatory Science: the Application of Scientific Principles for the Regulation of Medical Devices

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REGULATORY SCIENCE CONTRACT

Under the sponsorship of Dr. Jesse Goodman, Chief Scientist of the FDA, the Fischell Department of Bioengineering at the University of Maryland has received a $3M, 3 year contract from the FDA to work with the University of Maryland Baltimore to create

REGULATORY SCIENCE

with the goal of improving the regulation of pharmaceuticals and medical devices

DEFINING REGULATORY SCIENCE

AS APPLIED FOR MEDICAL DEVICES

REGULATORY SCIENCE CAN BE DEFINED AS APPLYING SCIENTIFIC PRINCIPALS TO ESTABLISH WHETHER A MEDICAL DEVICE IS SUFFICIENTLY SAFE AND EFFICACIOUS TO WARRANT PMA APPROVAL OR 510(k) CLEARANCE FROM THE FDA FOR USE IN THE USA

A TWO-FOLD PROBLEM

- **#1. MANY USEFUL MEDICAL DEVICES ARE NOT BEING MADE AVAILABLE IN THE USA TO PROVIDE IMPROVED MEDICAL TREATMENTS**

- **#2. A FEW MEDICAL DEVICES CAUSE SOME SERIOUS MEDICAL SIDE EFFECTS FOR THOSE PATIENTS IN WHOM THOSE DEVICES ARE IMPLANTED**

CREATING REGULATORY SCIENCE

THE GOAL:

Create an improved system for the regulation of medical devices that will approve safe and efficacious devices for improved health care in a reasonable time and prevent potentially risky devices that have not undergone a scientific clinical trial from being made available for patients in the USA.

SOLUTION TO THE PROBLEMS

A PLAN FOR USING THREE DIFFERENT MEANS TO OBTAIN FDA APPROVAL OR CLEARANCE FOR A MEDICAL DEVICE:

1. If the device can be approved or cleared with a PMA supplement or 510(k), without a clinical trial, then that modality should be applied by the FDA.
2. If the medical device company considers that the FDA review process is reasonable, then that company can agree that the existing FDA review process should be utilized.
3. If the medical device company is dissatisfied with the FDA review process, that company should have the right to apply REGULATORY SCIENCE as defined herein to obtain approval or clearance for a medical device.

THE ESSENCE OF REGULATORY SCIENCE

- DISALLOW FDA REVIEWERS FROM BEING THE ONLY POSSIBLE JUDGE FOR APPROVAL OR CLEARANCE OF A NEW MEDICAL DEVICE

- CREATE A SMALL BUT HIGHLY COMPETENT TEAM OF REVIEWERS TO DETERMINE WHAT IS NEEDED TO OBTAIN APPROVAL OR CLEARANCE FOR A MEDICAL DEVICE

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There is a great tendency for FDA reviewers to deny approval of a medical device or to require a clinical trial that is unduly long and expensive because such reviewers feel that being "conservative" will make that reviewer look good and prolong his/her employment at the FDA.

SOME REAL EXAMPLES

A device implanted like a pacemaker that indicates a heart attack has started typically before the patient receives any symptoms of that heart attack. The FDA has required a PMA clinical trial with about 900 patients in which the device is turned off for 6 months in half the patients thereby probably causing the death or significant damage to the heart muscle for approximately 30 of those 450 patients in whom the device is not turned on.

An implanted heart defibrillator that includes the early detection of a heart attack, the FDA PMA trial requiring 5,500 patients. That totally safe device being approved in essentially all countries (including China, Japan, India, etc.) but not the USA and saving 1,000s of lives, but no lives being saved in the USA.

SOME MORE EXAMPLES

An external device that applies a magnetic pulse onto the brain that eliminates most migraine headaches with no adverse effects and eliminates pain, photophobia and phonophobia but because too few patents in the *de novo* clinical trial had nausea, the device was not cleared for use to treat migraine headaches in the USA. 72% of patients in the UK have stated that the device works really well in relieving their migraine pain, with none of the serious side effects experienced with the use of migraine drugs.

CE Mark for a drug eluting stent with a conventional balloon, stent metal and eluting drug requires 100 patients with 6 month follow up. The FDA requires 1,500 patients and 1 year follow up, very expensive and inordinate delay in getting new stents for Americans.

CREATING THE RSVP

- To apply scientific concepts to the process for the approval or clearance of medical devices requires that the formulation of the clinical trial and the evaluation of the results of that trial be carried out by a limited group of people who are truly expert in that specific field of medicine, device engineering and medical statistics.
- A ***REGULATORY SCIENCE VERIFICATION PANEL*** (RSVP) could optimally consist of five experts who have no bias either for or against the approval or clearance of the medical device.
- The RSVP might optimally consist of 3 MDs, 1 biomedical engineer and 1 statistician. The MDs should be 1 to 5 years after completing specialized training in that field of medicine.

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If the company elects to apply the principles of REGULATORY SCIENCE, then the process for device approval or clearance could efficiently be carried out as follows:

1. The company submits a plan for a clinical trial for a medical device to a reviewer that the FDA has selected from their staff.
2. The reviewer has a list of MDs, biomedical engineers and statisticians that have competence in the field of medicine where the device would be used and each committee member would sign a sworn statement that they have no conflict of interest.
3. This RSVP would meet within 45 days after the request for approval of the clinical trial has been received by the FDA.

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4. The RSVP would meet for 3 days: the first day would be to study the plan for the clinical trial; the second day the RSVP would meet with the company that has developed the device to try to reach an agreement on the terms of the clinical trial; and on the third day the RSVP would decide on the features of the clinical trial that would prove that the device is sufficiently safe and efficacious.

5. While the clinical trial is underway, the FDA would inspect the company's manufacturing facility to ascertain that the level of quality assurance is sufficient to allow approval or clearance for the medical device under review.

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6. After the clinical trial is essentially completed, the company will provide 60 days warning to the FDA prior to submitting the results of the clinical trial to the reviewer at the FDA.

7. The reviewer at the FDA will notify the five members of the RSVP that they must agree on the 3 successive days to have a meeting during the time period from 70 to 100 days after the FDA has been notified that the results of the clinical trial will be submitted to the FDA. Therefore, the actual 3 day meeting of the RSVP to review the results of the clinical trial will take place between 10 and 40 days after the results of that trial are sent to the FDA. A great time saving for the review process.

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8. The discussions on those 3 days will be as follows: day one will be devoted to a study by the members of the RSVP as to the results of the clinical trial; day 2 will be a day to meet with the principal investigator of that trial, the principal biomedical engineer and the principal statistician who worked on that trial to answer questions that the RSVP would have as to the safety and efficacy of the device as revealed from the clinical trial data, and the third day will be devoted to discussion by the RSVP whether or not to allow approval of a PMA or clearance for a 510(k) for that device or to require additional data from the company.

9. Any requirement for additional data and another meeting would be negotiated between the company and the RSVP.

THE RSVP COMMITTEE

10. The members of the RSVP, the name of the device and the disease that it is intended to treat, and the date of the meetings would all be in the public domain. Anyone can attend the meetings except when proprietary information is to be discussed.

11. It would be considered an honor to be selected to be a member of an FDA sponsored RSVP.

12. Each member of the RSVP would be paid $3,000 per day if the company had less than $100,000 profit for the 12 months prior to a RSVP meeting and they would receive $6,000 per day if the company made more than $100,000 dollars in profit during that prior 12 month period. All funds to be provided by the company, not the FDA.

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13. Approval or clearance for the device would be granted if 4 of the 5 members of the RSVP voted for approval or clearance.

14. If the RSVP did not vote in favor of approval or clearance but recommended obtaining additional clinical trial data, then the company could accept that recommendation and there would follow a third meeting of the RSVP to review that additional data.

15. If the company elected to appeal the decision of the RSVP, then an Appeals RSVP would be formed consisting of a second group of 5 MDs, two biomedical engineers and one statistician who would again review the clinical trial data and the report of the original RSVP. Approval by 6 of the 8 members would constitute approval. Rejection by the Appeals RSVP would be final.

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16. Each and every member of the RSVP would be held harmless for any matter pertaining to product liability.

17. Any and all post-market surveillance would be the responsibility of the FDA.

EXPECTED RESULTS

THE APPLICATION OF REGULATORY SCIENCE AS DESCRIBED IN THIS PRESENTATION WOULD HAVE THE FOLLOWING EFFECTS:

1. PROVIDE SIGNIFICANTLY IMPROVED HEALTH CARE FOR AMERICANS

2. DECREASE THE COST FOR MAINTAINING THE FDA

3. DECREASE THE NUMBER OF UNSAFE DEVICES THAT HAVE SOMETIMES BEEN CLEARED FOR HUMAN USE BY THE FDA

4. CREATE MANY NEW JOBS IN THE USA

5. DECREASE THE COST FOR MEDICAL DEVICES IN THE USA

6. PREVENT AMERICAN COMPANIES FROM FORMING FOREIGN CORPORATIONS TO MARKET THEIR PRODUCTS OUTSIDE THE USA

7. ALLOW MEDICAL DEVICE COMPANIES IN THE USA TO HAVE A REASONABLE CHANCE TO OBTAIN VENTURE CAPITAL FUNDING

Dr. Jeffrey Shuren Quotation
Wall Street Journal
(June 25, 2012)

"The FDA is moving forward to help keep the American medical device industry the world's most productive and innovative while giving our patients timely access to products that are safe and improve their health. It is time that our critics move beyond pointing fingers and toward working constructively with us."

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QUESTIONS AND DISCUSSION