How to Cross the Border from R to D?
The Example of Conception of New Medical Devices

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Keywords: Translational Research, Medical Device, Innovation, R&D, Clinical Trials.

Abstract: The border between Research and Development for a new medical devices is often unclear since the process of development of a new medical device remains non linear, with the need of feedback from trials in clinical situation to new conception of the product. More importantly, the classification of the different steps of a project impacts on 1/the identification of right partners for the project, 2/ state aid intensities, generally lower for activities linked to development than for research related activities 3/impact factor of publication related to the phase of the project. Sometimes researchers under-estimate these studies because it is thought that, although essential to set-up new investigation tools, they do not lead to an increase of fundamental knowledge. However, and especially in the field of medical devices, users have to face specific difficulties due to the variability of the biological systems under study. Results obtained in translational research often depend on this variability and new questions or scientific obstacles arise from the confrontation to the real world. In order to address these new challenges, reverse translational research is required. Fundamental research is then fed from the results of translational research. In this position paper, we would like to present a useful model of medical device development through several examples of translational research to illustrate the adequacy of research to bridging fundamental research results to the closest to the patients.

1 INTRODUCTION

Basic research rarely knows what discovery will serve and disruptive innovations in health mostly come from basic research whose authors have not suspected the consequences (for instance, the discovery of electron spin in 1922 to the MRI in 70's). At the opposite, applied research is primarily directed towards a specific practical objective (for instance the long story to capture and preserve images began with the Egyptians some ten thousand years ago when they noted the ability of light to transmit images). Between these both enemies' brothers, experimental development is a systematic work, using knowledge gained from basic research and/or practical experience, which is directed to produce new products or to improve substantially those already existing. To transform basic research results into a practical innovation, translational research needs big efforts to conceive future application, and requires thinking differently and changing our mind. Research and Development for a new medical devices is often unclear since the process of development of a new medical device remains non linear, with the need of feedback from trials in clinical situation to new conception of the product. Sometimes basic researchers neglect these further studies because it is thought that, although essential to set-up innovative technologies, they do not lead to an increase of scientific knowledge. However, and especially in the field of medical devices, users have to face specific difficulties due to the variability of the biological systems under study. Variability is easily understood from one patient to another one. But there is also the variability of a single patient whose metabolism evolves naturally by the time and additionally with the therapeutic actions. Translational research has to understand these variability and new basic research questions arise from the confrontation to the real world. In order to address these new challenges, reverse translational research is required. Fundamental research is then fed from the results of translational research.

In this overview, we would like to present a useful model of translational research for medical

Pazart L.
How to Cross the Border from R to D? - The Example of Conception of New Medical Devices.
DOI: 10.5220/0006803100010001
In *Proceedings of the International Conference on Biomedical Electronics and Devices (BIOSTEC 2015)*, pages 7-12
ISBN: 978-989-758-071-0

device development through several examples to illustrate the adequacy of research to bridging fundamental research results to the closest to the patients.

2 CLASSIFICATION OF RESEARCH ACTIVITIES

The Frascati Manual[1] defines R&D as *"creative work undertaken on a systematic basis in order to increase the stock of knowledge"*. The term R&D covers in fact three activities: basic research, applied research and experimental development.

Basic research is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundation of phenomena and observable facts, without any particular application or use in view.

Applied research is also original investigation directed primarily towards a specific practical aim. In technical fields, applied research could be associated with the '*industrial research'* for developing new products or processes.

Experimental development is systematic work, drawing on existing knowledge gained from research and/or practical experience, which is directed to producing new materials, products or devices, to installing new processes, systems and services, or to improving substantially those already produced.

For example, the determination of the amino acid sequence of an antibody molecule would be basic research. Investigations undertaken to identify the right antibody for a specific membrane protein of a virus would be applied research. Experimental development would then consist of designing a biochip functionalized with the right antibody for the disease on the basis of knowledge of its structure and clinically testing with biological liquid of interest (blood, urine, etc.) in order to make the right diagnosis.

Translational Research involves, for the National Institutes of Health (NIH), "*the extensive body of work required to move a discovery from bench to bedside*" and Wikipedia definition insists on the capacity of translational research to shorten the time-frame to reach the market. Accordingly to these definitions, translational research covers applied research and experimental development till the market launch of the product. Some others add in healthcare fields the feedback loop "*from the bed to the bench*"

3 CHALLENGES OF R&D ON MEDICAL DEVICES

With the great diversity of the medical devices from crutches to programmable pacemakers it is not feasible to subject all medical devices to the same development scheme. Much specificity of MDs vs drugs should be taken into account[2], and methodological adaptation could be performed to try to exercise discretion to propose a feasible methodology:

• Clinical investigation is particularly needed to get CE mark for class IIb and III MDs[3]. First tests in human need to answer to essential requirements and to assume the safety of the device by in vitro, on bench and in vivo (animals) tests. For the other ones (ex: glove, eyes occlusion plasters, conductive gels, non-invasive electrodes, image intensifying screens) predictability of performance could be a useful manner to answer the question.

• The interest of product may concerns either therapeutic, diagnostic, or compensation of disability area and the methodology of clinical assessment should therefore be adapted classically to the main objective of the study. For instance, clinical trials of diagnostic tests are sometimes divided into exploratory phases, challenge phases and advanced phases to see how effective and how accurate the tests are[4]. In all cases, a distinction should be made between the clinical proof of efficacy and safety in order to get the market approval and the place in the diagnostic or therapeutic armamentarium in order to define the price or the reimbursement of a MD. In the latest intent, randomized controlled trials are generally conducted to compare a new intervention or strategy to the classical one.

• The level of innovation; should the new MD be considered as an incremental evolution or an evolution of rupture ? Minor or incremental changes on an existing medical device are the most frequent type of innovation activity in companies. Activities leading to minor, incremental changes or adaptations should in principle not be counted as R&D activities,

unless they are part of, or result from, a formal R&D project in the firm.

• The equivalence with a predicate; substantial equivalence means that the new device is at least as safe and effective as the predicate[5]. This concept can be applied to many products including high-risk products, such as coronary stent or hip prosthesis. To prove the equivalence, technical bench tests and preclinical study could be done. Production of specific clinical data could be limited to a cohort study in order to retrieve the similar results of predicate. However, this applies only if the equivalence criteria are not affected claim, clinical and technical data and environment.

• The operator/MD interaction; the clinical benefit may depend not only on MD itself but also the performance of the medical team (operator dependent nature, learning curve) and the technical platform, this organizational dimension is an element which must be taken into account in the early investigations of a new MD; trials should incorporate this learning curve by providing a first acquisition phase, in the number of subjects required for example, and / or any interim analyzes. Another possibility is to use a sequential adaptative Two stages design (i.e Fleming methods)

• The diversity of use; one or more studies are needed to develop the implementation of a new MD and describe different operator (medical staff or the patient himself), operating times, the technical facilities and personnel skill to the success of the procedure.

• The reduced life cycle. The clinical assessment should be realized in short-term monitoring, on technical and clinical intermediate parameters. Nevertheless, a long term monitoring should be performed till failure occurrence for all patients who were implanted with an old version of MD (particularly for implantable devices like cardiac prosthesis, breast implants, cochlear implants etc.).

• The small size of target population. Of particular methodological solutions can be proposed: conducting multicentre clinical trials in Europe (within ECRIN network for instance), or exhaustive survey of patients through national or international register.

• The short track of development; a lot of MDs could be developed with few technical experimental tests to get the Proof of Concept without clinical test, like for instance dental impression materials, tubes used for pumping the stomach, urinary catheters intended for transient use etc. For other MDs category, the absence of an animal model to test preclinical MD and the futility to test it on healthy volunteers contribute to go quickly to the patient, for instance for hip prosthesis or implantable analgesic pump.

4 PRACTICAL SITUATIONS OF TRANSLATIONAL RESEARCH

4.1 “Optical Biopsy”

Invasive biopsy is still today the reference diagnostic technique of a lot of skin or mucosa pathologies (inflammation, tumours). Nevertheless, several situations of diagnosis should be kept as conservative as possible. Consequently, non-invasive imaging methods (ultrasounds, computed tomography, magnetic resonance imaging) have been developed for clinical use. Based on the principle of white-light interferometry and developed initially in 1991 for in-vivo imaging of the human eye[6], OCT was investigated by a large number of groups worldwide. With regards to penetration depth and resolution, OCT could be a perfect trade-off between ultrasound and confocal microscopy. The use of optically pumped based on specific swept sources for OCT was first demonstrated in 2011 but since that time, the threshold towards the use of low-cost electrically-pumped devices is still not crossed.

How to translate the basic knowledge to a practical application in healthcare?

A first way could be to fix the possible application fields (for instance skin biopsy) and ask the specialists (here university dermatologists) about the possible clinical use with the technical characteristics of the future device concerning the spatial resolution of the system, the field of view and imaging magnification. The design parameters will be selected according to the system specifications and technological constraints, for instance a miniature (< 15cm3), low cost OCT imager providing cross-sectional 3-D tomograms with a depth around 0.5 mm, axial and transverse resolutions of 5 µm and imaging field of 5x5 mm2. Of course, specialists could imagine possible clinical applications[7] such as superficial baso-cellular cancer, follow up healing after an injury or surgery, assessment of new wound dressing or graft,

determination of the degrees of skin burns, the local efficacy and tolerance of topical treatment etc. But the usefulness of such an OCT imager remains questionable, and clinicians are doubtful of pictures interpretation since they have no experience feedback about such imaging. The learning curve is for the moment very slow with those new technics (new images, new colors, new field of view…), which is currently a real limiting factor for the diffusion of those technologies.

A second approach could be clinical use based specifications. First of all, dermatologists are invited to express their will. In this way, they claim for a new device able to provide detection of early skin cancer by discerning diseased and healthy skin, and helping the practitioner to accurately determine the margins for resection, which is usually affordable by the examination of the overall architecture of epidermis and identifying the number of atypical cells per unit of area.

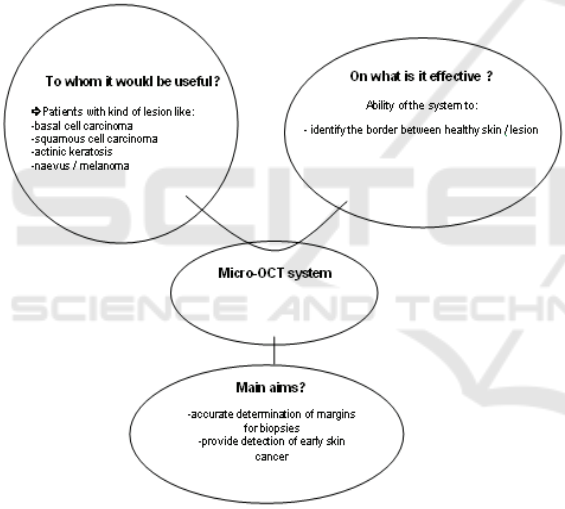

Figure 1.

Thus, the parameters of new OCT microsystem design have to be determined by examining the biomedical application requirements as well as the instrumental characteristics of selected interferometric architecture including array-type as well as high-speed camera requirements. The Medical ISO13485 methodology requires also a Risk Analysis of the final product. It must be initiated with every participant and especially the future users. A Functional Analysis can then describe what we expect from the MD and split it in building blocks.

Current works are trying to improve the accuracy, resolution, penetration depth of these devices. Manufacturers and researchers should focus their insights on the easiness of recording, measuring and analyzing, the daily practice in doctor office, their reliability, and the prize.

In summary, the best way could be analyzing the constraints of available techniques, defining the needs from the end-user (medical) point of view and adapting research program to conciliate both requirements. The following scheme tries to represent this approach:

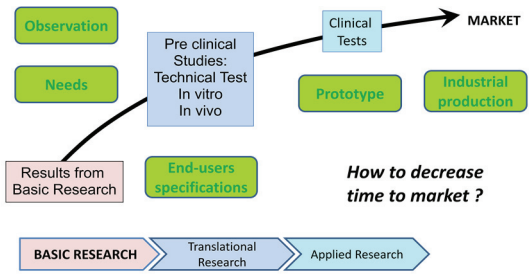

Figure 2.

4.2 Screening at Birth

Routine screening by capillary blood sample at birth concerns several diseases in France. The lateral edge of the feet was chosen as sampling area by scientific societies, on an anatomical removal of the main neurovascular bundles and to avoid the risk of osteomyelitis of the calcaneus, previously found with bites to the posterior heel. The method is painful for the newborn and quantitative failure often leads to sample a second time.

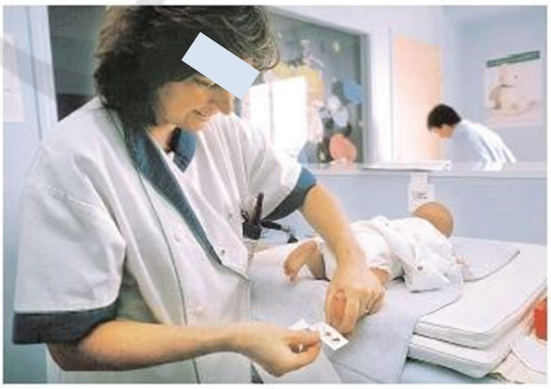

Figure 3.

How to improve the quality and the capacity of screening at birth, particularly to reduce newborns' pain?

The first way consists to search available techniques on the shelves, then to try to adapt them to the need.

Micro-needles array appears to be a good solution to replace the lancet (see picture). This matrix would be applied on the heel as a patch, the multitude of micro-needle (deemed not painful) replacing the wide blade of the lancet.

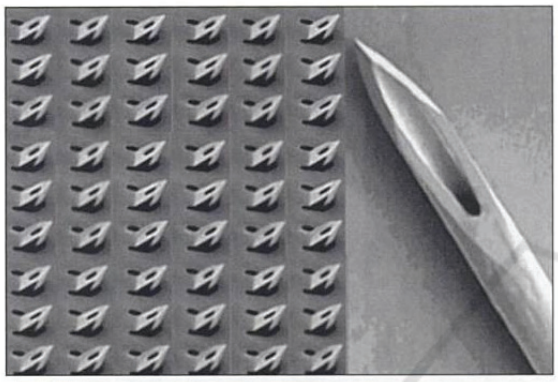

Figure 4.

But a lot of questions emerge to adapt this technology to the heel of newborns:

- How deep to prick ?
- Which density of needle should be compose the network?
- Which size for the channel, if any ?

A better understanding of the distribution of capillary networks could improve the specifications for a new device based on micro-needles array. To acquire these data, we conducted a clinical study using ultrasound (device Dermacup Atys) and videocapillaroscopy (device Moritex, MS-500C Micro-Scopeman) on both sides (lateral and medial edges) of the heel of 62 newborns according to gestational age at birth. The parameters of the microcirculation were obtained by ultrasonography (depth of dermis) and capillaroscopy: capillary density and distribution, inter-capillary distance and average diameter of the capillaries. The results show that on average, the density of the capillary network is 60 capillaries / mm2, the inter-capillary distance of 155 microns and a diameter of 22 microns. Another result shows that the capillary network is oriented mainly parallel to the lateral edge of the foot and less on the medial edge.

From our study, the results of capillaroscopy and skin ultrasound will help determine the right micro-needles array configuration as follows:

- The area provided for the needle plane is 25 mm^2, and the number of micro-needles depend on the density of capillaries and of the inter-capillary distance
- The depth of the dermis specified the maximum depth of the micro-needles.

After some prototypes adaptation, we performed several tests on animals. The results show that a network of 8 micro-needles could be acceptable, and avoid any "fakir effect" of the skin. But these micro-needles must penetrate about 1 mm in the heel of the newborn and three applications of the matrix are needed to achieve a 96% probability of blood collection. Under these conditions, it is difficult to talk about withdrawal without pain.

A second way to solve the problem of pain consists firstly to understand the mechanisms of this painful process to provide input for improvement in terms of medical devices and also to explore new avenues for screening at birth.

A systematic clinical observation of blood collection steps at the 72 th hour of life was conducted on a sample of 50 newborns (PREVMAL study). The purpose of this observation was to get confirmation of the frequency of pain and when it appears and on another hand to understand the factors behind its occurrence on which further action could be taken. The anatomical data from videocapillaroscopy and ultrasound were also collected to be correlated with results of observation of the act of screening in terms of pain (DAN scale) and quantity of blood obtained.

89% of newborns have expressed a pain[8]. It appeared that the pain is mainly observed when pressure is applied on the newborn's heel to collect the blood on the blotter paper and secondarily at the heel prick with the lancet. So, the most painful is not the bite but the pressure of the foot ($p = 0.0005$). The pain at the sting of the lateral edge appears less important than the sting of the medial edge, but this result should be confirmed by a more powerful study with more cases. No correlation was found between pain and deep dermis, or density, or the diameter of the capillary.

Considering these results, we were committed to finding new methods of blood collection, particularly to avoid pressure on the heel and the proliferation of bites to get the blood in sufficient quantity on the blotter paper. We have therefore developed a system provided with a micro-machined nozzle. This tip is applied to the heel, after bite of

the lancet. The blood viscosity properties and the geometry of the tip make possible to maintain the blood captive inside a reservoir. This tip is then stamped on the blotter paper. Tests have shown that a volume of less than 800 µl of blood sufficient to properly soak the spaces provided on the blotter paper.

From clinical needs to fundamental research, this approach could be summarized as follow:

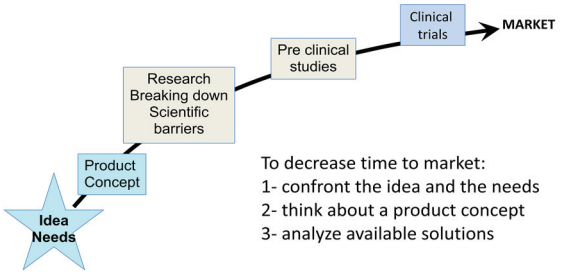

Figure 5.

To go on with the development of the new device, it is planned to conduct clinical trials on parallel groups for ethical reasons, with prototypes and classic screening methods.

5 CONCLUSION

To conclude, in this position paper we considered examples of the conception of MD either based on technology availability or clinical use requirements. In both approaches, identification of clinical useful technical characteristics are critical issues to faster the development of new medical device. As mentioned in the introduction of the paper, translational research activities are sometimes under-estimated and postponed because they do not lead to an increase of "scientific" knowledge.

However, translational research covers applied research and experimental development and it is essential to set-up new tools especially in the field of medical devices. It isn't only a question of semantic as illustrated few years ago in a similar congress, but a way of thinking.

If we design a clinical study to describe the capillary network of newborn, without any objective other than knowledge, this study should be qualified of basic research. If the same study is intended to complete technical specifications for a new screening device, it becomes applied research. The translation is there, behind the aims of the study protocol: what might be the usefulness of study results? Basic Researchers should be aware of this new paradigm, even if they haven't to focus their attention on application anymore. Louis Pasteur perfectly summarized this necessary connection: "*There is not basic research on a side and applied research on the other. There are research and applications thereof, united to each other as the fruit of the tree is joined to the branch that has worn.*"

ACKNOWLEDGEMENTS

The studies presented in this paper are funded by public grants, under the European Commission's 7th Framework Program, or French Health Ministry and French National Agency for Research.

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