Dream Biosensor
How to Create and Implement?

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Abstract: The idea to create a universal implantable medical device, cheap and effective (so called Dream biosensor) is proposed. We show that it should be a universal passive wireless device made of biodegradable polymers that have no direct impact on the body. It should be implanted during a simple outpatient procedure, and monitors the vital signs of a person's health. Main requirements for such a device are discussed, some existing technical solutions are performed. The perspectives of dream biosensor implementation in Russia are considered.

1 INTRODUCTION

High-tech implementation in medicine can be regarded now as a world-wide trend: for developed countries it is the way to sustain high life quality standards, for developing countries it is seen as a tool of modernization. Russia also strives to develop telemedicine and to implement high-tech achievements into practice. These efforts are likely to intensify especially due to sanctions and decrease in financing.

The need for telemedicine development is due to several reasons: first, improved monitoring and diagnostics lead to earlier detection and efficient treatment. Second, frequently the target measurement is most accurately obtained through internal detection. Third, gathered statistics allows the doctor to analyze the patient's data, and to determine if any lifestyle factors (such as diet) are affecting their condition. Forth, telemedicine helps the specialists to develop individualized treatment. Fifth, dealing with remote areas problems and exploration of northern poorly populated territories (especially future probable Arctic exploration should be mentioned).

Medical biosensors are supposed to be the most powerful tool for that purpose. Special attention is paid to the treatment and diagnosis of social diseases.

Previously we reported about the study of probable biosensors that could be implemented in Russia. The focus of our work was given to devices and approaches aimed at reducing mortality in the following areas: diseases of the cardiovascular system, control blood sugar levels, the disease of the gastrointestinal tract, and timely medication to the patient (drug delivery).

As a result of our study we formed a list of ready-to-produce devices that are in demand on the Russian market. By 01 August 2014 we have considered more than 200 companies, and found more than 80 devices worth to consider.

We also made a comparative analysis of health care financing in the United States, Russia and other countries, making the estimates of future biosensor market development. The Russian market of mobile biosensors by 2015 will be about 1.5-2% of the world (with the prospect of up to 3%), i.e. will be largely a niche market with no significant export prospects. The growth in the Russian biosensors market is expected to be rather high, (about 10% in 2014-2017), with gradual decreasing (down to 5% after 2017). Under certain conditions distant market medicine in Russia in 2020 could amount to 2 billion euros.

We also conducted risks and challenges analysis associated with biosensors implementation, particularly: technological issues, ethical problems, standardization issues, etc. We argue that main obstacle (at least in Russian Federation) to implement telemedicine into realty is connected with institutional aspects (managerial solutions).

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2 DREAM BIOSENSOR CONCEPT

However, the main question has not found its answer yet: what kind of biosensor exactly should be developed? If the country should implement a whole list of different devices (each for their own purpose), or there should be a universal one?

Within the framework of RFBR project we strove to find the answer for this question. We conducted the thorough study of available devices, organized an experts' survey, several scientific meetings, etc. This work was done in accordance with traditional foresight methods since the expected result should provide authorities with necessary measures to develop high-tech medicine.

As an outcome we formulate the idea of so called "dream biosensor" – an ideal implantable medical device aiming at cure of social diseases. Hereafter we discuss main traits of proposed device, and some arising problems.

The proposed idea is very close to the telemedicine development based on smartphones use. Since modern devices unite a variety of gadgets onto a smartphone one could almost get a complete physical treatment without visiting a doctor. This issue from technological viewpoint has been thoroughly studied in both Russia and abroad. All leading Russian mobile operators have tested the special software used for telemedicine.

The University of California, San Francisco, hopes to enrol a staggering 1 million people in its Health eHeart Study to see whether using mobile technology, including smartphone tracking of people's heart rate and blood pressure, could help treat and prevent cardiovascular disease. The FDA cites industry estimates that 500 million smartphone users worldwide will use some type of health app by 2015.

We stress however that telemedicine is more likely to focus on a smartphone as a transmitter/receiver and to operate only with a stable connection to the server. This on the other hand can be seen as a universal monitoring tool, not for an individual but for the whole society. The massive data could be used for better medical treatment or governmental policy.

The Dream biosensor in our viewpoint should work regardless of the mobile network coverage, and be reliable in remote areas. These devices would have an important role in developing countries, where full-size medical equipment is in short supply but smartphones are becoming common.

2.1 Dream Biosensor. Main Requirements

Implantable medical devices are likely to be personalized oriented, with both active and passive exposure to the symptoms of patient chronic diseases. Hence, a priori, they are not supposed to be produced in large series. Contrarily, mass production enables to greatly reduce prices and make the biosensor available for a large number of people. Since solving social issues is the main priority for both developing and highly industrialized countries, we could draw the **first requirement**: "dream biosensor" should be rather cheap and produced in a large numbers (mass production).

Second requirements – safety. Mostly this issue concerns biocompatibility.

Since it is assumed that the implantable device is to monitor during limited time (the goal is to collect and analyze information, to prevent), then at the end it must be safely removed from the patient's body. The best option is to create a biosensor of biodegradable polymers. These materials possess a number of exceptional chemical and mechanical properties: can be completely resorbed (bioresorbable), unlike traditional materials such as metals, ceramics, and composites; have the opportunity to actively use in the device for 1-6 months; their usage significantly reduces the cost of medical care of the patient (for example, do not need special surgical procedures to remove the devices from the body); there is no risk of infection; they are non-toxic; all degradation products can be completely metabolized. Biodegradable polymers are synthesized from various monomers, including lactide, glycolide, dioxanone, trimethylene carbonate and caprolactone. The polymer properties and the degradation rate can be tailored to meet the most stringent requirements, due to changes in the composition of the polymer and its molecular weight. To date there has been accumulated considerable experience in the use of biodegradable polymers as integral part of many commercial medical devices and pharmaceutical products.

Additional characteristics of biosensor include technical properties: size, weight, radiation. As a result of available papers analysis, the device should be rather small (approximately 10 mm), not heavy (less than 10 gr.). System must not exceed recommended electromagnetic radiation or tissue heating levels, thus electromagnetic radiation should be less that 10 mW/cm. It also should not produce tissue heating more than 1°C increase in tissue temperature.

Also before mass production the device should undergo testing for cytotoxicity, sensitization, irritation, system toxicity, subacute and subchronic toxicity, genotoxicity, implantation, hemocompatibility, chronic toxicity, and carcinogenicity.

Third Requirement is easy to use, easy to implant. It should be injected in patient's body by simple outpatient, minimally invasive procedures (eg, by special syringe). While operating, it should be easy to navigate, to control, and/or to halt it if necessary. This issue is often neglected, but friendly interface greatly increase the effectiveness of such a device and allows its vast usage. The last one is especially important, since those are elderly people (not ready to learn difficult rules) who are the aim of the device.

Fourth Requirement is the maximally full list of monitored parameters; it should not be too long, but enough to make clear statement and prediction about patient's health. We asked specialists, what should be included, and form the following list: body temperature; blood pressure; blood analysis; glucose level; oxygen, proteins and enzymes; ECG.

Also many producers (e.g., Biotronik with their heart failure monitoring system) propose to combine in one device collecting some "additional" data, not directly referring to studied conditions, previously to be neglected. Those parameters may include body positioning, body temperature, speed of the movement, etc. They provide doctors with additional information, and could improve the diagnosis.

Fifth Requirement deals with data transmitting and analyzing. Monitoring and data transfer should go all day and night, in the dynamics of ordinary routine of life. Information about physiological condition of an organism should be transmitted from the mobile device to a personal computer of the treating physician in real time and with a predetermined periodicity.

Note we do not take into account such issues as data protection or preciseness of models used to make the forecast.

The Sixth and most important requirement is battery issue. Because at the moment this problem (re-charging the device) has not been resolved, it seems the best solution would be to apply a biosensor as a passive device that is independent of external charging. This, in turn, imposes a limit on the lifetime of the device (average 1 month, and up to 6 months).

Thus, in our view, the massive demand could benefit from a universal passive wireless device made of biodegradable polymers which has no direct impact on the patient body. It should be implanted as a result of a simple outpatient procedure, and after monitor the vital personal characteristics. Collected information about physiological condition is transferred to a remote server for further analysis.

The list of requirements could be widened by geo-positioning. This implies especially in case of remote and poorly populated areas.

2.2 Existing Technical Solutions

To date we have identified following implantable devices ready to produce: body temperature - smart pill by Ohio State University, USA; arterial pressure - EndoSure® Wireless AAA by CardioMEMS Inc, USA; glucose level - GlucoChip™ by PositiveID Corporation Headquarters, USA; blood analysis (enzymes and ferments) - Chip EPFL by EPFL, Switzerland; oxygen level in blood - B-Care5 Blood temperature and SpO2 monitor by SORIN GROUP, Italy; EKG - Reveal™ and Reveal Plus™ by Medtronic, Inc, USA.

Necessary materials and parts of the device: biodegradable polymers - RESOMER® by Evonik Industries AG, Germany; battery charging Nyxoah system by Nyxoah, Belgium (used adhesive patch).

We conclude that right now there is a number of devices that can gather and transform information about patient's health, but they all deal mostly with 1 or 2 important characteristics, not taking into account others. Proposed project ("dream biosensor") can combine them all together, using all advantages in one device.

From the list above mostly the universality can be attributed to following devices: 'smart' pill by Ohio State University, USA and Chip EPFL by EPFL, Switzerland.

The first one ('smart' pill) monitors drugs reception: time, dose, heart rhythm, body temperature. It is constructed as a microscopic chip the size of a matchstick recording all the details of the program of medication through a patch receiver, attached to the arm or shoulder of the patient. It transmits medical information to patient's or doctor's smartphone/computer. It has been on sale in Great Britain since September 2012 (£ 50).

Chip EPFL is an implantable device for blood analyzing (proteins and enzymes) equipped with wireless transmission system. It is designed to monitor the treatment effectiveness (such as chemotherapy, also applicable in anesthesia). It possesses the option to simultaneously monitor several diseases, and can detect up to 5 organic acids and proteins at a time. The apparatus can be also used to monitor the overall health status (e.g. for sportsmen). It is small and light (Length-14 mm; weight-7g). These studies were the part of the Swiss Nano-Tera program, some preliminary results were first presented at 13/03/13 Europe's largest electronics conference.

Another promising trend is connected with creating smart devices playing several functions. In this case the monitoring is regarded as an additional property of the device. Mostly it is a stent that also collects data and servers as an emitter (so called, smart stent). Or it can be an additional attached device only for short post-operational period.

Geopositioning could be another important issue. For instance, chip (RFID) of Xega - a chip the size of a rice grain inserted in the adipose tissue arm between the shoulder and the elbow by a syringe is widely used in Mexico to determine the location of people online.

Another pressing issue concerns battery charging/recharging. The original solution was proposed in implantable devices Nyxoah system by Nyxoah, Belgium. They apply an adhesive patch to patient's body. The device is intended for the treatment of obstructive sleep apnea and snoring. It includes the actual implantable device, a portable battery and a charger. Implantable device is mounted close to the nerves of the tongue muscles as a result of a small incision. The implant is powered and controlled via external disposable batteries, which are fastened under the chin with adhesive pad (like a patch). Every evening, the patient uses new disposable sheet, which was powered previously by a battery charger. Pad size is of 55 x 90 mm, and is attached to the skin under the chin. It has enough energy to activate the wireless implantable device for full session during the calculated average duration of a night sleep.

There is a new trend in medical biosensor development connected with 3-D bio-printing. As a substrate the living cells (often belonging to the patient) are used. Previously those devices were motionless or dependant on blood flow, but now they are equipped with a strip of skeletal muscle cells that can be triggered by an electric pulse thus serving as a pusher. The size of such bio-bot is now about 1 sm. with prospects to decrease. Experts estimate these devices to be in use in about 3-5 years.

We note that there is no such Russian device that could correspond to all requirements listed above. They all lack in quality and/or performance. This inevitably raises the demand to attract foreign investors and/or developers to Russian market, or require buying corresponding licenses by the government.

2.3 Perspectives of Dream Biosensor Implementation

In our previous work we studied risks and challenges of biosensor implementation using Russian Federation as an example of a country with strong governmental support for health care system. We listed technological issues, data handling problems, ethical aspects of biosensor implementation, and institutional problems. We stressed that for the biosensor market (that has not formed yet) the last ones are the most crucial. However for dream biosensor to implement we consider social obstacles to play main role, since a person will be the ultimate consumer of innovative services/products, his/her opinion will determine if the device is successful or not.

Social risks of accepting the device could be divided into 2 large groups: cognitive and behaviour stereotypes.

Among the most significant risks one should mention cognitive ones. The main reason for them derives from the low level of awareness and understanding of high-tech medicine among people, rating it as something inaccessible and "distant". The attitude towards innovation as a whole has similar nature. Based on diffusion theory from sociology one can estimate a group of high degree of innovations loyalty (attracted to high-tech) in the amount of 15% of the general population. In countries such as Russia this number is also narrowed by great difference between large cities (Moscow and St. Petersburg) and other country. Thus the main task for the promotion of dream biosensor would be to inform people about the innovation.

Behavior risks are also important. They were formed by consumers' stereotypes. Concerning medicine in Russia, only 6% of the population is ready to use the services of private medical institutions, the vast majority (55%) prefer to go in for free municipal/state medical institutions. This means that people treat as unacceptable the practice to pay for the medical treatment regardless of its pros and cons, what is worse one third of population is devoted to self-cure, and monitoring and prevention seem to be useless (only 18% regularly check their health).

These factors greatly threaten the perspectives of biosensors implementation. There is no desire to pay for better living, or the readiness to monitor one's health. There is a contradiction: they who need the device do not know about it or do not will to implement it. We stress that this situation is typical for developing countries with strong paternal ideas. This makes the role of the government and the experts' community very important.

To identify the most effective way of biosensors introduction two-component model of population was proposed, assuming different dynamics within two social groups conventionally called a "city" (services) and "village" (production). The most important term is the flow between the 2 phases. Practically, we are talking about the so-called "binary structures", stratifying socio-economic space.

A numerical simulation of the system was carried out, characteristic regimes were studied. It is shown that in some cases there can be observed unstable solutions. Special attention was paid to the opportunity to control system dynamics by changing governing parameters (corresponding to some managerial solutions).

Two most important results should be mentioned: first, innovation within the conditional "city" is not only economically feasible, but also has a positive effect on the whole system. Given the strong connection between "city" and "village", the increase of living standards in the first region (biosensors are implemented in a big city where infrastructure is available and costs are low) inevitably leads to improvements in the second area.

In our simulations a 2-percent increase in the "city" accounts for 1 percent growth in the "village". The second important finding was the conclusion that changes in lifestyle (whether to use biosensor in a habitual life or not) can be compensated by appropriate outer management (regulation of the flow of the population between the city and village), and their depth can be relatively small (2-3 times less than desired changes in lifestyle).

These results show that telemedicine implementation should not be conducted in the whole country or for the whole population, its impact is transferred from one group to another, and the purpose of the authorities is to correctly determine the target group that is not necessarily the very unhealthy or poor people.

3 CONCLUSIONS

Biosensors to our viewpoint have an important peculiarity: their usage aims at preventing rather than curing. Thus we note that the proposed device (dream biosensor) is not long-lived and only involves assisting a patient under special conditions or monitoring his health. In case of serious problems the use of more expensive and specialized devices would be necessary. The last ones despite their importance are niche product in contrary to "Dream biosensor" that should involve mass production. In this regard "Dream biosensor" can be an effective tool for high-tech distant personalized medicine.

We have also examined the economic aspects of the "Dream biosensor" implementation: we conducted market analysis and evaluation of the factors influencing the pricing of medical implantable devices. The most challenge in biosensor market is its small-scale production. The expected price (affordable for the majority of population in Russia) is approximately $3000 a year for the whole cycle (biosensor itself, operation, post-operation treatment).

The project to create "Dream biosensor" may require significant investment. Therefore, the implementation of such a project is possible only in the form of the federal program.

In our opinion the need to implement "Dream biosensor" is vital. We stress that on the one hand, there is a direct interest from the main customer – from the state (in particular, the work of the Technology Platform "Medicine of the Future") and on the other hand – there are already existing both technical solutions that could be implemented and scientific research creating the background for future development. It will not solve all problems though, but can greatly improve quality of living.

In upcoming future the telemedicine biosensors are supposed to become smaller in size, and greater in numbers, all connected together. Thus, there could be established a smart grid. First, it would be a "nervous system" at the level of the organism (within next 10 years according to forecasts). The National Nanotechnology Initiative has organized in 2013 a special roundtable dispute about probable application of nanobots for medical purposes; some first standards, methods and approaches were discussed. Next discussions are to come soon.

In future medical sensors will become the part of the Internet of things, and would play crucial role in organizing comfortable life. The construction of world-wide distributed systems of biosensors is expected to occur by 2050.

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