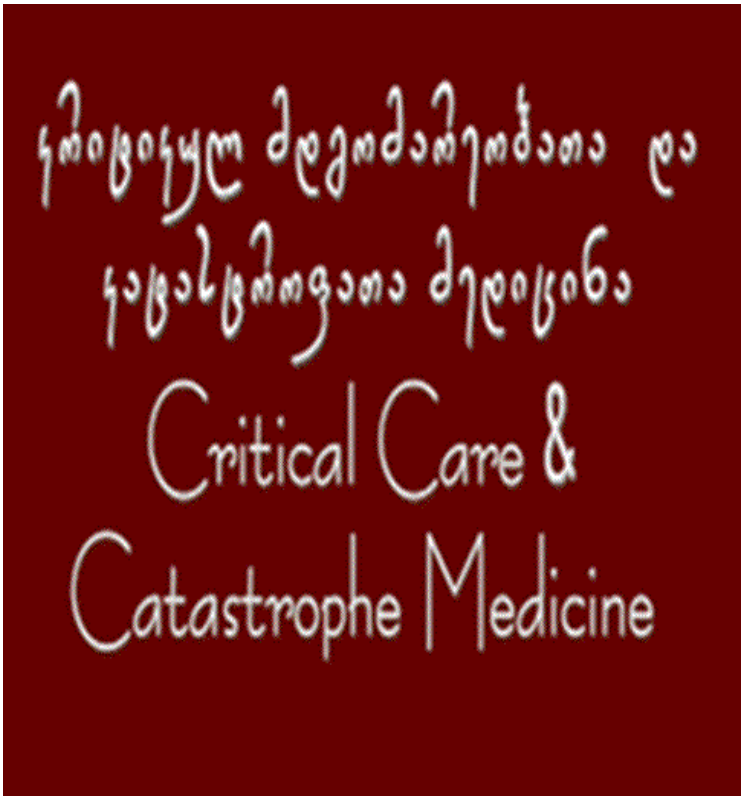
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NANOTECHNOLOGY IN A NEW DRUG DEVELOPMENT

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The revue presented bellow is an updated version of the open letter recently presented to USA Food & Drug Administration (FDA). The reason this open letter was written is that today there is a lot of misunderstanding and misconception about the role of Nanotechnology in Live Science Industries, specifically in its application in a new product/drug development.

Today, medico-biological scientific community standing on a verge. There was no breakthrough in new technology for drug development for almost last four decades. Modern pharmaceutical approach is based on usage of a 'singular active substance' (therapeutic agent) in a high concentration [1, 2]. Usually, a singular active ingredient acts on a specific pathway of biological information transfer [2]. To achieve a biological effect (biological information transmission) the usage amount of pharmaceutical substances very often exceeds physiological levels (maximum amount of biologically active substances, which naturally can be produced in a Living System) by thousands of times, thus creating new non-physiological pathways, causing multiple side effects. In addition, the physiological and biochemical responses from 'therapeutic' and 'physiological' dosages of bioactive substances are very different [2, 3]. Frequently, unusual and non-physiological effects are observed when the same bioactive substance is used in the amounts exceeding the physiological level.

Nanotechnological approach creates a lot of hope and expectation in a new drug development [4, 5, 6]. At the same time we should take in consideration that the new technology is only a tool that serves a purpose, but not the goal itself. That is why it is very important to set-up an appropriate goal in a new drug development strategy.

We truly believe that the future drug developments should be focused on a restoration of a genetically determined chain of biological information transfer, but not on an administering high dosage of a singular bioactive substance [1, 2, 3]. Taking in consideration that multiple approaches in medico-biological scientific community today are focusing their attention on a nanotechnology it is imperative that scientific community involved in Life Science Industries should have if not a unanimous understanding of how nanotechnology can be used in a new drug development, but at least should be able to differentiate themselves from industrial approach in nanotechnology. What we mean by differentiation? To look on a nanotechnology in medicine and biology from physiological point of view (in conjunction with self-regulation mechanisms and self-healing processes), instead of mechanistically adapting nano-particle approach from industrial and electro-engineering fields.

As mentioned previously, the opinion bellow is based on more than two decades of the fundamental scientific research in study of Human Physiology and Pathogeneses of Post-Aggressive Reactions of Organisms [pathogenetical mechanisms and thanatogeneses of post-aggressive reactions of the Living Organisms] and more than a decade of experience in a new product development based on new technological processes associated to Bioactive Substances Modeling [4].

1. INTRODUCTION

Multiple regulatory organizations (ISO, FDA, OSHA, EPA, UNESCO, etc.) are trying to come up with unified definition and create a policy for nanomaterials [7, 8, 9]. However, premature or not fully and correctly covered definition of nanotechnology causes more confusion in this rapidly emerging technology. Correct definition / terminology / nomenclature are not only fundamentals for any growing industry, but also a guideline for long-term future scientific developments.

Nanotechnological approach in Life Science fields is able to dramatically change the quality and effectiveness of new product development [and as a result, longevity] by enhancing/supporting physiological processes naturally existing in a Living Organism.

Nanotechnology is at crossroads. Today, high-tech companies and government officials are focusing their attention on terminology and definitions for such nano-objects as nanoparticles, nanofibers, nanotubes, nanoplates, etc., which reflect the size range related to the length of the matter from approximately 1nm to 100nm. If such descriptions of Nanotechnology [10, 11] more or less applies to the industrial fields it has very little to do with the Life Science Industries and their objects, specifically in area related to a new drug development. This is not about the semantics, but about more fundamental differences between Industrial (electrochemical, electro-engineering, physicochemical, computer science, etc.) and Live Science Nanotechnologies (Pharmaceutical, Nutritional, Cosmetic, and Bio-Defense). Any living system is a very complex auto-regulated system, with multi-stage feedback mechanisms. In order to sustain genetically determined physiological processes, we have to be very careful in mechanical transform of achievements from Industrial Sciences to the Life Science objects. Unfortunately, today, nano-particles concept from the Industrial Nanotechnology has been mechanistically transformed and adapted by Life Science Industries [Life Objects]. This tendency can have long-term negative consequences, which is imperceptible today, but will have negative effect in a long term [6]

It is important for academicians and regulatory organization to define what Nanotechnology means in Life Science Industries, particularly in a new products/drug development [11, 12]. This does not mean absolute separatism from Industrial academicians and regulatory organizations, but a careful systemic approach in such emerging area as Life Science Nanotechnology is. Benefits from the right positioning can be tremendous, while the failure can slow down or drive the new developments towards wrong direction, which can cause a waist of billions of dollars.

Today, the chances of progress in area of Life Science Nanotechnology and its failure are 50:50. In addition, the important question is which country can take a leadership in this rapidly emerging and transformative technology which can affect virtually every product produced by Pharmaceutical, Bio-Defense, Cosmetic and Nutritional industries.

Nanotechnological approach in Life Science Industries could help in creation of new generation of biologically active products, which will significantly prevent and/or more effectively treat multiple diseases/dysfunctions, thus increasing human longevity with quality of life [13, 14].

2. BARRIERS OF ENTRY INTO LIFE SCIENCE NANOTECHOLOGY

Nanotechnology in Life Science Industries has a high barrier of entry and requires following objectives:

- Deep fundamental scientific requisite knowledge base
- Strong intellectual property platforms
- Correct and accurate set-up of the objectives for a new product/drug development
- High equipment cost

If we accept above mentioned criteria' than a reasonable question should be raised - how it is possible that in a very short period of time in such new scientific discipline over 300 manufacturers identify their [consumer] products as Nanotechnologically developed? Either something is wrong with the definition, as well as with understanding of what the real Life Science Nanotechnology, or if it's so easy to develop a new Nanotech product that what is so unique in this discipline?

This is not a rhetorical question. This is a question of the society to trust scientists and industrial professionals. We have to be concerned about the future of this high-tech scientific field, which has the ability to transform the way we are developing new products in Pharmaceutical, Bio-Defense, Cosmetic, and Nutritional industries.

Realistically speaking only big companies and government-funded institutions can afford long-term R&D in such a new area of science as Life Science Nanotechnology.

3. WHAT IS THE LIFE SCIENCE NANOTECHNOLOGY?

Life Science Industries related to new drug development have nothing to do, or at least very little with nano-particles. A simple reduction of particle sizes of biologically inactive substances, like Titanium Dioxide, or Zink Oxide has nothing to do with nanotechnology itself. This reduction of the matter into nano-particles happens purely on a machinery level. It means that manufacturers, who have relatively high shear homogenizer, or high quality grinder, can claim that they are in nanotechnology business. By allowing these products to be called 'nanotechnology based products', we simply not only diminish, but also mislead ourselves with real power of nanotechnology.

On another note, for example, pharmaceutical ointments or cosmetic/skincare products contains nanoparticles in their emulsion for many decades. Any good quality, long time stable emulsion should contain nano-size droplets [particles] – this technique was achieved thirty-forty years ago. By then, it was not viewed as Nanotechnologically developed products.

At the same time, simple reduction of particle sizes of Organic and/or Non-Organic substances raises several important concerns, which should be taken into careful consideration:

- reduction of particle sizes of biologically active substances into nano-sizes increases the possibility of significant reduction of biological activity of the matter, due to the changes which can occur in their [bioactive substances] tertian conformation [structure]. How can we imagine reducing particle sizes of the large peptides or proteins (for example, insulin, growth hormone, collagen, etc.) without affecting their biological effects? What is the purpose? Better delivery into targeted places, or better biological effects? A simple reduction of a particle size of the biologically active substances cannot deliver expectation. It is another attempt to change the matter and as a result transform naturally occurring physiological regulations.
- after reduction of particle sizes, most of non-organic [as well as organic] molecules have the tendency to coalescence, thus creating larger size matters than originally created [before their reduction into nano sizes].

Manipulation with a matter on an atomic level is an important aspect for the industrial nanotechnology, including researches related to a creation of a new diagnostic tools, but the real challenge and benefits of Life Science Nanotechnology relates to a new product/drug development based on a construction of substances [or biologically active complexes - NANO-COMPLEXES] **with previously unavailable biological effects and at the same time with absolute predictable treatment results**. Today, It is becoming imperative to develop methods of 'copying' nature, actually developing the methods of how to 'put together' multiple biologically active informational substances in physiological concentration (nano-and pico quantities) - the amount that living system needs to repair malfunctioning lines of information communication. Minute quantities of carefully selected and balanced biologically active substances that naturally occur in the human body were sufficient to restore initial healthy regulation of the cells and its functionality.

Let's one more time remind ourselves that the prefix "nano" denotes to a fraction of one-billionths of … size, weight, volume, etc. measurement units. While Industrial Nanotechnology is focused on a nano-sizes (nano-particles) manipulation, Bio-Medical researches related to new drug development should focus their attention not so much on particle sizes of the matter, but on more important physiological element – quantity of biologically active substances [and their combination] used in products for specific biological effects.

Nanotechnology in a Bio-Medical field (Life Science Nanotechnology) is not so much about the science of manipulating a matter on a nano-particles level, but most importantly is the science of assembling of targeted Biologically Active Complexes (NANO-COMPLEXES) with previously unavailable biological effects by using nano-quantities of biologically active substances in a very precise way to imitate/model physiological processes occurring in a living organism. The outcome of such approach has a physiological impact to the normal biological information transfer, with strong and predictable results, without side effects.

What do we mean by nano-quantities of biologically active substances? Is it a simple mixture of small quantities of biologically active substances? ABSOLUTELY NOT. Simple usage of small quantities of biologically active substances has zero effects by multiple reasons, which is a different subject of discussion.

To make our position clear, we have to go to the fundamentals of Human Physiology and its Homeostasis taking into consideration the following well-known facts:

- What is the primary function of the Living Organism? Adaptation and survival from variety of extreme conditions and than the reproduction, and other vital functions.
- What is the best way to help the Living Organism to achieve its primary [as well as all other] functions? To activate self-healing processes that naturally exist in the Living Organism by normalizing/correcting genetically determined chain of Biological Information Transfer.

If we agree with these basic postulates than the goal of Life Science Industries should be the imitation of PHYSIOLOGICAL PROCESSES existing in the Living Organisms but not the interference with them [physiological processes]. Achievement of this goal is only possible by creating/imitating Biologically Active Substances Complexes naturally existing in a Living Organisms. Such a simulation (imitation) requires several guiding principles:

- Developments of targeted Biologically Active Complexes [NANO-COMPLEXES] with previously unavailable biological effects necessary for protection / prevention / treatment of multiple dysfunctions/diseases. For example, in case of a specific ailment/disease, the new drug should act on a pathogenetical level of the disease, while skincare field products should perform on an epidermal level to help to improve skin protective function and visual appearance, providing true long-term age-protective [but not short term cover-up] benefits.
- Biologically Active Complexes with new targeted biological effects preferably to be composed of bioactive substances naturally existing in a Living Organism.
- By all means, the usage amount of each of Biologically Active Substance in a developed/assembled NANO-COMPLEX should be in the same quantities, naturally found in a Living Organisms, particularly in nano (10^{-9}) and pico (10^{-12}) quantities.
- Complex of Biologically Active Substances [used in nano and pico quantities] requires the development of new generation of the Delivery System, which should have the ability for proper Stabilization of unstable biologically active substances and their Delivery to the targeted places.

To achieve the primary function of the Living Organism as well as its well-being it is necessary to develop absolutely new, not-existed before technologies. New product/drug development should be oriented toward enhancement of self-healing processes with specific curative effects to repair malfunctioning biological information transfer, targeting the problem-specific biochemical pathway. Life Science Nanotechnological approach for new product/drug development can be indispensable, thus allowing to re-establish naturally existing self-healing processes from within.

It is a real challenge but this new innovative approach is where the Life Science Nanotechnology should be focused. That is what we mean by nano-quantities [complex of substances in nano-quantities stabilized and delivered into the targeted places with previously unavailable biological effects] of Biologically Active Substances, but not simple nano-sizes of substances.

- **NANOTECHNOLOGY in Life Science is the science of using nano-quantities [complex of substances in nano-quantities stabilized and delivered to targeted places] of biologically active substances with previously unavailable biological effects that imitate physiological processes occurring in a living organism.**
- **The outcome of nano-quantities modus operandi in Life Science Nanotechnology should have a physiological impact on the normal biological information transfer, with strong and predictable results, without side effects.**
- **The usage amount [10^{-9} & 10^{-12}] of biologically active substances should be in the absolute range of buffering mechanism within normal function of the Living System.**

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ნანოტექნოლოგია ახალი წამლების წარმოების საქმეში.

მ.დანიელოვი

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მოტანილია ცოდნა ნანოტექნოლოგიის საფუძვლების შესახებ. განმარტებულია გადამტანი სისტემების და ბიოაქტიური კომპლექსების არსი. მითითებულია, რომ ნანოტექნოლოგიურ პრინციპებზე შესაძლოა მრავალი სხავადასხვა მიმართულების წამლის მომზადება. ეს მნიშვნელოვნად შეამცირებს წამლების მომზადებისათვის საჭირო ხარჯებს: ნანოტექნოლოგიის გამოიყენებით საგრძნობლად შემცირდება აგრეთვე წამლების უარყოფითი მოქმედების შემთხვევებიც და რაც მთავარია გაიზრდება წამლის მიზანმიმართული მოქმედების ხარისხი.