NANOTECHNOLOGIES: WHAT MEANS A BENEFITS/RISKS APPROACH IN THE "IMPERATIVE OF PRECAUTION" CONTEXT?

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Abstract–This paper addresses issues raised by the development of nanotechnology. Although the expansion of the latter is not as fast as supposed, these new technologies have brought public controversies that are to be considered. In this research, we show that a condition for the development of medical nanotechnology is to revisit the concept of benefit-risk balance, too often considered from a technical point of view. To the extent that the risks are uncertain without any overall conclusions being drawn, it must be determined whether the applications offer benefits or not, in order to reduce the scope of nanomaterials and applications to be assessed. However, the determination of a benefit cannot be reduced to the physicochemical properties of the materials. It is a social process that combines efficiency and validity of applications. The determination of validity implies cooperation not only between the materials sciences and the social sciences, but also between academic research and public representations such as associations, be they environmental, patient or consumer ones, for example. This cooperation must take place upstream academic research, thus before any development of applications.

Index Terms - Nanotechnologies, precaution, medical device, benefits

I. INTRODUCTION

Nanotechnologies - and nanosciences - arethe results of the 2000s major "nanos" programs, such as the National Nanotechnology Initiative (NNI) in the United States[8], and others inAsia, Russia, USA or in the European Union.

The rationale for these sciences and technological programs has not been fully documented. Several hypotheses can be put forward, which relate to a tendency to re-articulate fundamental and applied research [6], the resumption of research funding by the materials sciences, or the reorganization of industrial policies, strained, not only towards the "massification" of activities ("economy of scale") but more and more towards gains in value added per unit of product [10].
However, the transformation of nanotechnologies, conceived as key enabling technologies, into marketed industrial products is unequally assured.
Put aside the use, dating back at least in the 1980s, of nanomaterials as "additives" (in food, cosmetics or paints, for example), the shift from nanotechnology to industrialized nanoproducts is more complex than announced and envisaged in the early 2000s.
Although, in the intensity of the controversies born immediately after the launching of the major programs, the reference to an omnipresence of the nanotechnologies was frequent, the examination of best controlled economic data tempers the idea of an unlimited expansion. While (private) firms of economic expertise report markets worth thousands of billions of dollars, for their part, public studies [4] or interviews with industry leaders lead to minimize the real expansion of nano-products. In fact, the NNI 2.0 program emphasizes the need to move to the commercialization phase of nanoproducts: "The Grand Challenges framework —a partnership between the public and private sectors— can drive scientific advances to revolutionary commercialized products", NNI 2.0, PCAST, October 2014.

In the same vein, a senior scientist in China considers that:"... the expectations of disruptive technologies have not been met. A breakthrough major in nanoelectronics is elusive as a result of a slowdown in the post-Moore era; Nanomaterials featuring nanotubes, bucky balls and graphene have not put their applications targets; nanomedicine is still in its infancy; nanomanufacturing faces insurmountable difficulties in efficiency."(Wei Yang, President of the National Natural Science Foundation of China, Nature Nano 2016).

The reasons for this gap between the "advertised promises" and the industrial reality deserve a thorough work that does not fall within the scope of this paper. Undoubtedly, the industrialization of nanotechnologies is less profitable than it was supposed to be, and it encounters technological difficulties that remain to be overcome. In addition, it comes up against questions from companies, about future regulations, questions fueled by the persistence of controversies.

In such a situation marked by unknowns about the evolution of nanoproducts, the present paper aims, not to constitute a balance sheet, but to look towards the future of nanotechnologies by helping to determine normative conditions of the "sustainable" nature of their development. For this, we will rely on the case of health products.
It is known that these products are considered through the determination of a benefit-risk balance as an evaluation criterion for obtaining a marketing

authorization (drug) or CE marking (medical device) for compliance with the rules of the European Union.
In this perspective, although the risks problems of nanotechnologies has been tackled but not solved, far from it, on the other hand the existence of the benefits is often taken for granted. Now, a benefit is a complex notion which cannot be reduced to that of the properties the efficacy) of materials. The validity of the projected products must be demonstrated, which implies a sociological process.

II. A Cooperative research

This paper is based on the so called NanoBrique research operation(Nanotechnologies, Benefits and Risks), which aims to better define the normative conditions in which a renewed approach to balancing the benefits and risks of nanotechnologies can be built. This research focused on the validity conditions of a nanotechnology application designed in an academic laboratory. The present work has thus been able to test an approach of benefits and risks by its coupling with a scientific operation (namely: Carboderm, operated by labs of materials sciences and social sciences (Cirimat, Certop, IMH, IPBS, 2015-2016, CNRS and U. of Toulouse.)
The idea was to design a medical nanotechnology: a device, a kind of transdermal delivery patch of insulin for diabetics, using the conductive properties of carbon nanotubes to electro-stimulate the skin in order to make it permeable to the insulin. The work of designing a medical nanotechnology has thus served as a basis for the work of the social scientists. Such an experimental approach remains (too) infrequent, not to say exceptional, in the field of materials, whereas it is more common in computer applications.
A first originality of this work is thus to contribute in an inter-scientific way to the conception of a medical nanotechnology. Academic applicative research operations in "Sciences" still rarely address the question of the social validation conditions of the (nano) technology considered. This research has thus generated, for the social scientists, a ground of a new kind of investigation and, for the chemistry and the biology scientists, a new way of working by integrating, upstream sociological and legal problems. Ethical problems [9] were not to be addressed in this case.
A second originality of this project is that it was conducted in close cooperation with the Diabetes Lab of the French Federation of Diabetics and in relation with the Association of Young Diabetics of Midi-Pyrénées. This has led, on the one hand, to benefit from the expertise of patients and their associations and, on the other hand, to open more easily and quickly doors in institutions of the health system.
The idea that prevailed in this research is to raiseproblems by working closely with patients and also with health professionals. This idea contrasts with the so-called "social acceptability", according to which application is first designed by the professional experts and then only submitted to users or consumers. The reasoning in terms of social acceptability suggests that the problems to be dealt with would only be adjustments to be application. However, any application has to face the well-known Collingridge dilemma [3]:
"When change is easy, the need for it cannot be foreseen; when the need for change is apparent,change has become expensive, difficult and time consuming'' (p. 11)
In total, this report is based on about fifteen interviews and two focus group meetings with young diabetics. The interviews were conducted with patients from Midi-Pyrénées), patient associations (FFD, Unaass, UFC-Que Choisir), members of health public evaluation institutions (ANSM, HAS) and diabetologists.

III. NANOS HEALTH PRODUCTS FACING THE BENEFIT-RISK BALANCE

The establishment of a "balance" implies, by hypothesis, that one can, on the one hand, identify the two terms in relation and, on the other hand, conclude. Regarding the risks, there is uncertainty about the toxic and ecotoxic effects of nanomaterials and of their combinations with other materials. Many reports draw attention to the impossibility of reaching a conclusion on nanotechnology in general, on nanomaterials in particular and, even, on a singular family of nanomaterials.
The multiplicity, a priori without visible limits, of possible cases, whether nanoparticles, agglomerates and aggregates, materials in which nanoparticles are included, renders inoperative a risk approach on a "case by case" basis. It is, however, the most justified approach because of the new but unresolved difficulties raised by the "nanos" risk assessment, which cannot rely on the dose-response relationship. This multiplicity implies reducing the scope of cases to be evaluated from the point of view of risks.
The determination of a benefit must frame, to reduce it, the spectrum of applications that are candidates for a risk assessment. However, the "obvious" nature of the benefits is not self-evident, because this notion may come from points of view that are not necessarily convergent. In this perspective, it is a question of clarifying what the "benefit" of medical nanotechnologies means in a context where the precautionary imperative, which applies to nanotechnologies, has become established.

IV. TOWARDS A DYNAMIC PRACTICE OF PRECAUTION

Any approach of precaution, far from being reduced to the only institutional principle, can be represented through three dimensions.
The first dimension refers to the precautionary

principle itself, constitutionalized in France and admitted, under another formula, by the European Union. Within this framework (Article 5 of the French Environmental Charter), the implementation of the precautionary principle is the responsibility of the public authorities to adopt measures proportionate to the uncertainties and suspicions of the risks and to carry out the necessary risk assessments.
If the constitutional principle is used as a reference, we can also consider a second dimension of precaution. This is precautionary prevention, which consists in implementing, in the field of the manufacture and use of nanomaterials (companies or laboratories), a hardened prevention, which falls within the obligations of the employers, adapted to the specificities nanomaterials. As it stands, this precautionary prevention is very unevenly established, whether by the companies or organizations responsible for risk monitoring, medicine or labor administration [1].
The reflection carried out in this report has drawn a third dimension that can be called “dynamic practice of precaution”, which does not come under any particular regulatory constraint or institutionalized principle.
A modality of this dynamic practice of precaution is to integrate a reflection on the benefit at the stage of the application research, thus even before the application is operational. Since risk assessment is particularly complex, precaution with the identified benefit is likely to limit the number and range of applications to be evaluated.
However, the notion of benefit applicable to health products is increasingly the subject of an interrogation falling within the principles of "health democracy" (see Touraine Act of January 2016). Because the benefit is not only definable by its technical and clinical dimensions and because the patient associations claim to have their say, the conditions of validity of a balancing of the benefits and risks of nanoproducts should be (re) examined by focusing on the "benefit" dimension.

A. Lessonsfroma Nanotechnology Experimentation

The experiment concerning our device of delivery of insulin is based on the properties of the carbon nanotubes. These nanotubes have been emblematic of the controversies on nanotechnology since the launch of the major research programs "nanos". In France in particular, their rapprochement, for reasons that are often more physical (the fiber effect) than physico-chemical, with asbestos fibers has provoked tensions over the possibility of a new health scandal. This comparison weighed heavily in the debates, which were sometimes fed by publications or expertise alerting, without definitively concluding, on the potential problems of toxicity of nanotubes.
However, the possibility of designing a medical device with nanotubes is not, in principle, the object of a refusal of patients or doctors, because of their permanent expectation of solutions.
Therefore, the attention given to people with diabetes: "You are interested in us ...", as well as the guarantee, at least theoretical but provided as soon as the design, that will be ensured the control of the nanos risks of the device, meet the requirements of patients and professionals. It should be noted here that the possibility of "promising" this guarantee is based on knowledge and control of the toxicity of carbon nanotubes by the laboratory (Cirimat, chemistry) that manufactures them and is the source of the application, a knowledge established by several academic publications. This guarantee must be further reinforced by demonstrating the non-penetration of the nanotubes into the body but also by taking into consideration the conditions of treatment of the device at the end of the cycle, that is to say,when the device becomea waste materials.
However, the commitment to control - ultimately - the risks is not sufficient to demonstrate the existence of a potential benefit provided by the device. While the suppression of the injections appeared, for the project, as an "obvious" progress, this hypothesis was discussed not so much by the professionals as by some patients.

B. A medical device and so?

In the case of diabetes, medical devices, more than the evolution of the quality of insulin, have been the lever for a transformation, considered positive by patients, of the treatment of diabetes. The glucose meter, replacing the intake by the urine and his delayed knowledge of blood glucose levels, or the small disposable needles replacing "the stake that had to be sinking", are experienced as undeniable technological advances. The suppression of injections, which would be made possible by the application of a patch on the skin, is however not uniformlyconsidered as a progress. For some patients, the idea of a patch looks attractive if linked electronically to a blood glucose sensor automating the delivery of insulin, to spend an overnight, especially for parents of young people diabetics obliged, if necessary, to wake their children in the middle of the night.
For other patients, particularly adolescents, the issue of medical devices is to ensure that: "between two injections, they are no longer diabetic". In other words, the benefit of life occurs when the pathology can be “forgot” for as long as possible. However, medical devices that must be worn over the long term can remind patients of their pathology and thus represent a burden. Therefore, having "something that exceeds" to use the expression of a health professional, can be unbearable to the point of getting rid of it, in a context marked by the play of adolescents with the limits of the tolerable, a game of "jumping" injections. Even though wearing a medical device for continuous insulin delivery could avoid this gambling with the pathology, the risk is that it will be

rejected because of its psychological remanence effect in some patients' lives. We can see, if not a tension, at least a gap between the required medical effectiveness and the theoretical comfort of a medical device, as it is really appreciated by the patients. Therefore, the notion of benefit, represented here by the suppression of injections, appears to be less universal than supposed and confronts the daily reality of the disease. This approach forces us to revisit the technical approaches to health products, approaches that are still often in effect.

V. FROM HEALTH DEMOCRACY TO THE BENEFITS OF MEDICAL NANOTECHNOLOGY

In the area of health products, the weight of the benefit on the benefit-risk balance was mainly measured in terms of technical-medical effectiveness, without systematically taking into account the approach that a patient can take.

However, the benefit of a health product may differ not only according to whether one is professional or patient, according to the patients, as we have just seen, but also according to professionals. A neurologist and a neurosurgeon may have different points of view, respectively interrogation or trivialization, facing the operation of implantation of carbon nanotubes in the brain to reconnect failed neurons.

These problems are known, but they ultimately come down to a personal choice, in principle informed, and not a process associating industrial issues, state policy and participation of patient associations.

As far as nanotechnology-based health products are concerned, a reflection on the notion of benefit is therefore all the more necessary as the development of products (from their conception to their placing on the market) is in the context of health democracy.

Since the risks are difficult to apprehend, the profit thus becomes themain stake. On the one hand, this leads, with regard to medical nanotechnologies, to invalidate a strategy known as "me too", consisting, for a company, of placing itself in a market that has already been occupied, but without proposing technical progress or improving the technical and medical benefits. This possibility is also ruled out by the French ANSM (National Agency for the Safety of Medicines and Health Products), when it considers that: "... the use of nanoparticle properties in medical devices is justified only if it brings a significant benefit compared to a more traditional approach."

However, experience shows that the definition of the significance of a benefit is itself variable. For example, patients can claim to maintain the reimbursement of a drug whose effectiveness is challenged by professionals, "because there is nothing else, and families are happy that there have that. ", A kind of a placebo effect claim, so to speak.

Consequently, this uncertainty on what is "significance" implies that an application research on nanotechnology-based medical devicessubmits to the "cooperative" determination of benefit.

In the context of health democracy, the precautionary condition formalized by the distinction of a benefit supposes a rise of the participation of the patients up to the design of the products likely to be authorized to be put on the market as envisaged by the law. However, in France, the effective participation of patients' associations still primarily concerns the evaluation of products during their assessmentto be reimbursed or not, by the High Authority for Health (HAS).

VI DETERMINING A BENEFIT IN A COOPERATIVE WAY

Various works, such as those carried out in the context of the "Constructive Technology Assessment" [7] have focused, sometimes specifically on nanotechnologies, on the implementation of procedures involving stakeholders in order to evaluate nanotechnology applications and their implications [5] before any industrialization.

Although this approach leads to a balance between benefit and risk, it focuses only on defining procedural conditions for a constructive assessment of technologies. The considered procedures: writing "questionable" development scenarios,appear to be more formal than substantive. This leads to placing the notion of benefit at a relatively general level, even though another approach, of substantial consolidation, is possible.

The thesis of our research, which makes it possible to further discussions on the expansion of nanotechnologies, considers that the question of the benefit must be asked before anything else since it conditions the interest to carry out a risk evaluation of the application whose complication has been described.

In this context, we will define the benefit of an application (nanotechnology) as the combination of (technical) efficiency and validity. This combination is problematic since its two components do not belong to the same approach.

The determination of the medico-technical effectiveness and efficiency of nanotechnology is not the responsibility of the Human and Social Sciences: The ability of a medical device to deliver insulin given medical (and environmental) requirements is a laboratory work. It is unavoidable; otherwise the application lacks reason to be considered, at least as such.

The determination of validity, which belongs to the Humanities and Social Sciences, supposes the consideration of universalizable requirements (protection of the environment for example) or more restricted when it comes to answering requests of patients.

At this stage, it can be seen that the industry, or even the academic research laboratories, do not ask for, if ever, patient representatives in the design of drugs or medical devices. Academic laboratories generally favor links with industry, which, in the main, has tended to look for relationships with institutions and prescribers (doctors), especially for marketing purposes. To some extent, responsible research [2] is not prevalent yet.

However, the associations have long shown their willingness to be heard as such, which has in particular gone, for some of them, to be independent vis-à-vis the medical experts. Consequently, prescribers are no more than an intermediary among others to reach patients and, for their part, health institutions (ANSM and HAS) are now gradually calling on the expertise of patient representatives, in various forms: some activity presentations (ANSM), some participation in expertise and consultation (HAS).

As a result, the industry is increasingly tied to the perspectives and expertise of patients who are more than just laypersons. The patient-expertise is exercised, at this stage, in the "reimbursement procedure” but also in the feedback of information to the ANSM, on the negative effects of a device or a drug. It may that manufacturers seek the support of patients in the event of a product being dispensed with, or to obtain alignment, in terms of reimbursement, of their product on equivalent products.

The conditions are thus ripe for the development of cooperation between manufacturers and associations, upstream of technological innovations. This cooperation is all the more relevant as the patients themselves depend for their health on products supplied by manufacturers and research projects. In this sense, the field of health products is not comparable to that of the environment, which is marked by a challenge of risks (chronic, accidental) by associations (environmentalists or residents). Most environmental associations do not have any direct relationship with the industry, which they question as a source of risk. This differentiation between ecological democracy, largely focused on power relations, and health democracy, more likely to foster cooperation, deserves to be deepened in the continuation of this research.

VII. OPENING THE FILES

However, our work identifies a "lock" in the process of extending patient expertise: the confidentiality of files submitted for reimbursement but also for marketing authorization.

Access to information is known to be an environmental issue because of the pressure on businesses (or other organizations, as the case may be). The associative demand for an opening of the industrial files on the risks gradually built up and was gradually heard by the public authorities, in particular atthe European scale (Aarhus Convention in 1998, for example).

In the field of health, the information delivered by the producer is, as we have seen, the counterpart of risk taking by the consumer. However, while a process tends to integrate a patient perspective into the reimbursement of drugs or medical devices, this integration may be limited.

The role of the HAS is to render an opinion on the degree and improvement of the actual benefit (drugs) or the expected service (medical devices) for setting a monetary level of reimbursement (product price x reimbursement rate) by the State. This role includes expert-patients in the appropriate bodies. However, these experts are, like all other experts, subject to a confidentiality clause on the files filed. Thus, although an experimental consultation of the associations by the HAS was launched in 2017, in addition to the multi-expert evaluation of the products, the associations do not have a right of access to the files deposited by the industrialists. As a result, because of this confidentiality regime, the expertise capacity of user representatives in HAS commissions cannot feed on the practical expertise of patients, because patients often know more than their doctor about their illness.

Thus, there is a tension between the requirements of specialized expertise by the representatives of patients and the difficulty for these representatives to address a file without soliciting the patients themselves. The normative conditions for the lifting of this clause imply a work of specific reflection, legal and sociological.

By going back through the course of the health product cycle, a query equivalent to the previous one can be raised about the marketing authorization (MA). To date, patients do not intervene in the procedure of MA or CE marking and do not ask to intervene systematically (except on clinical trials), which is different from the demands made by environmental associations vis-à-vis companies. The reasons for this absence are largely due to the extreme technicality of the very large files (sometimes: thousands of pages), which could be partially overcome by the provision of a technical summary. In the environmental field, the evolution of the consultation has led the associations to acquire recognized expertise. In addition, even if the technical nature of the files hinders the involvement of patient associations, the pressure exerted by an even limited access to authorization or marking application files can only increase the level of security for patient products.

CONCLUSION

If the expansion of nanotechnology is to take place, it supposes overcoming obstacles.

The first way is to adopt a "benefit by design" approach that involves going beyond the sole

effectiveness of nanoproducts of health. This approach assumes the participation of associations in the academic design of products, which would be a paradigmatic change. But for this, the question of confidentiality must be addressed, given the tension between business secrecy and determination of a "benefit by design". These conditions are necessary but probably not sufficient. However, if they are not fulfilled, it is necessary to question the raison d'être of the development of nanotechnologies.

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