Theranostics – Ethical, Legal and Social Aspects

3rd Horizon Scanning Workshop

6th – 8th June 2007, SCHLOSS WILKINGHEGE Münster

This joint interdisciplinary workshop of **Nano2Life** and **NanoBio-RAISE**, organized by the Centre of Bioethics (University of Muenster) and bioanalytik-muenster, took place from 6th – 8th June at Schloss Wilkinghege, Muenster (Germany). Nineteen international experts met (see list at the end of the text), sharing their knowledge to map out the field of *theranostics* and to discuss its future prospects and especially its ethical, legal and social implications.

minutes

Lecture: *Prof. Dr. Ingolf Cascorbi*

Impact of Pharmogenetics to Individualized Medicine

The extremely variable, patient-dependant efficacy of medicinal treatment and the frequently severe side effects of drugs should be seen not only as an important challenge to recent medical science, combating these defects may also be one of the key elements in overcoming the crisis of Western public healthcare systems. For example, 7% of all patients in US-hospitals are suffering from adverse drug events, in departments of psychiatry the proportion of patients hospitalized due to adverse drug events is even higher (ca. 16%). Besides this, the efficacy of drug treatment is, in general, rather low, particularly in the (cost-intensive) field of oncology (25%).

The identification of hereditary polymorphisms in genes of drug metabolizing enzymes and membrane drug transporters contributed considerably to the explanation and prognosis of inter-individual differences in susceptibility to side effects and in the efficacy of a number of drugs. Along with these pharmacokinetics-related factors, there is a large progress in clarifying the role of polymorphisms in receptors or signal transduction proteins modulating drug efficacy. Thus, pharmacogenomics may facilitate also the identification of novel drug targets and improve the drug development process.

Especially for *oncology* the application of pharmacogenomics has been shown to improve significantly the therapeutic outcome. E.g. in breast cancer therapy the consideration of the her2/neu-receptor status has been implemented in routine therapy decision (Herceptin®-indication). Paying attention to the polymorphic character of the thiopurine-S-

methyltransferase in the azathioprine treatment of acute leucemia or inflammatory bowel disease makes possible the prediction of severe life threatening adverse events in cases of TPMT poor metabolizers. In the field of *cardiovascular diseases* first prospective studies clearly have demonstrated that the early use of pharmacogenetic knowledge in the anticoagulation regiments improves significantly the clinical outcome. Pharmacogenetical procedures of distinguishing different metabolism-genotypes could also play a crucial role in improving *pain therapy*, as recent studies have been shown convincingly.

Although even regulatory authorities like the U.S. Food and Drug Administration (FDA) have recognized pharmacogenetics as an important tool in drug development processes and in advancing drug safety, it is not yet fully accepted in medical guidelines and is applied only in selected medical centres. However, in contrast to rigid guidelines, individualized medical treatment offers many therapeutic and economic benefits. From a technical point of view efficient genotyping technologies enable already today a fast and reliable pharmacogenetic diagnosis. Of course, further more standardized prospective clinical studies are required to secure and extend the role of pharmacogenetics in medical treatment.

Discussion:

1) (Limited) Scope of pharmacogenetics

In spite of the impressive success of pharmacogenetics in special fields, like breast cancer, there are large areas, where little or no pharmacogenetic support for therapeutic fine-tuning is to be expected. Often the correlation between genotype and phenotype is rather loose. But even more important: in most cases no single gene at all can be identified as responsible for the patient's proneness to a particular drug or her susceptibility to side effects (*Korenstein, Cascorbi*).

2) Therapeutical divide?

With regard to diseases, which allow for only one kind of (sensible) drug treatment, identifying poor metabolizers may amount to a death sentence for these patients.

3. Who is interested/not interested in advancing pharmacogenetics?

Pharmacogenetical research is almost exclusively restricted to academic science. Big pharmaceutical companies show very little interest in funding research programmes that are aimed at an individualized medical treatment, which will have no positive impact on the company's turnover, while complicating mass production and marketing. The better adaptation of drug dosage to individual patient's needs will presumably lower the sales

figures. (*Korenstein, Hayhurst, Zajicek*) The industry is definitely interested in the results of pharmacogenetical research, but reluctant to push the process (*Cascorbi*).

On the other hand, public health insurance systems would very probably profit from the application of pharmacogenetic methods, e.g. via reducing the number of rehospitalized patients and optimizing drug dosages. (In some fields beneficial effects even can be reached by very simple means, e.g. by just keeping into account the different weight of patients or by introducing different pill sizes, which allow drug measuring in a more simple and precise way.) Regulatory institutions like FDA have (and should have) a vivid interest in driving the pharmacogenetical research process forward (*Bruce, Khushf, Cascorbi*). Nevertheless, it remains doubtful, whether pharmacogenetics can contribute significantly to a change in public healthcare without any realistic prospects of adequate industrial support (*Korenstein, Hayhurst*).

Lecture: Prof. Dr. *Ruth Chadwick*

Ethical Issues of Pharmacogenetics

The postgenome era of medicine arouses big hopes as well as deep scepticism. On the one hand an extensively personalized medication and prophylaxis, fine-tuned to individual genetic dispositions, may lead to a renewal of healthcare, analogous to the changes the world underwent during the Renaissance period (J. Brock). On the other hand, besides scientific obstacles like the, in general, very complicated uncovering of the functions of particular genes, there are huge ethical, societal and economic concerns, e.g. with regard to data protection and health inequalities.

The main *moral argument for* the application of pharmacogenomics consists in the principle of nonmaleficience ('Above all, do no harm'). Avoiding severe adverse drug events by genotyping patients is obviously in accord with this principle (cf. prediction of Abacavir (Ziagen®) hypersensitivity in HIV treatment). In the future this principle may also justify or even demand a routine genetic profiling of children, which is followed, if necessary, by a life-long medication of young risk patients.

Pharmacogenomics has the potential either to increase or decrease *health inequalities*. From a global perspective we have reason to change the paradigm from 'race' to human genome variation and to shift from individual differences to interpopulation differences, which do not necessitate the testing of each individual (cf. Bidil® indication for African Americans with

heart disease). If we are to reduce global health inequities, we must continue to support efforts to define the nature of human variation across the world, focused primarily on medical goals (P. Singer/ A. Daar). However, the different medical treatment of different ethnic groups will presumably evoke protest. Another precarious effect of pharmacogenetical testing could be the formation of 'orphan patient' groups, for which, due to genetical dispositions, no successful therapy is available (patient stratification).

In many cases pharmacogenomic research does not aim at the development of new products, but at the refinement of already existing drugs. An important obstacle to scientific progress in this field could be the fact that once medicines are *no longer protected by patents*, there is little financial incentive to refine their use, especially if this refinement means that fewer patients are advised to take the medicine. Manufacturers of generic medicines have only limited funds for investing in research and development (cf. report of Nuffield Council on Bioethics). Another sometimes delicate effect could be the resuscitation of certain drugs which have been banned due to their extremely severe side effects in some patients, who now can be singled out by genotyping.

There are most notably two prerequisites which have to precede the introduction of pharmacogenetic tools on a large scale: first, the implementation of a reliable quality control. Here, for example, we must pay attention to consequences of the vast increase in the volume of tests; secondly the establishing of public and professional acceptability. The more the promises are individualised, the more collective action is required.

In the *implementation* process various things have to be settled: the foundation and role of new regulatory associations and institutions, the access to genetic tests, the possibly extended role of pharmacists and the control of genetic information and databases.

Wherein lies the impact of values? The HUGO Ethics Committee's new Statement on Pharmacogenomics (2007) emphasizes that because of shared vulnerabilities people have common interests and moral responsibilities to each other. Willingness to share information and to participate in research is a praiseworthy contribution to society. To reduce health inequalities between different populations, and to work towards equal access to care is an important prerequisite for implementing genomic knowledge for the benefit of society. In order to reduce health inequalities, there is a need both to develop new drugs for people with certain genetic variants, especially in the case of neglected and orphan diseases, and to consider the possibility of resuscitation of abandoned drugs for particular population groups. The unit of care with respect to drug treatment may include the family as well as the

individual, e.g., physicians should be alert to the implications for the relatives of a patient who suffers a serious adverse drug reaction, and should initiate genetic counselling.

Discussion:

1. Science or Science Fiction?

It has to be emphasized that, even if the hopes of genome-related biotechnology will come true some day, many of the developments outlined in Chadwick's talk lie in the distant future. It is at best dubious, whether ethical reflection on hypothetical future scenarios which will take place under totally different and widely unforeseeable social conditions, make much sense at all. (*Rip*) On the other hand, we have to choose as our starting point the concerns people actually have, because these concerns will willy-nilly have an impact on the present development of pharmacogenomics. Ethical reflection should offer an answer to these fears. (*Bruce*)

2. Unlicensed Generalisations?

In trying to anticipate future ethical conflicts we have to take into account a wider social and political context. We should be reluctant to give a prognosis on the basis of our recent social situation. Unforeseeable mayor cultural shifts in the future could make an important difference, e.g. they might defuse the potential powder keg of different medication for different racial groups. (*Bruce, Khushf, Chadwick*)

3. Biobanking

One of the most important ethical issues concerning (pharmaco)genetics consists in regulating the collection and storage of genetic data. Of even greater importance are the access rules for genetic databases (Human Genom Diversity Project etc.).

There might be bad intentions behind pushing these projects. One major concern with this kind of research has been the potential for racism in certain countries. Governments could arm themselves with genetic data linked to certain racial groups, using them as arguments in the process of depriving people of their civil rights. Another concern has been the threat of genetically targeted biological weapons.

4. Beyond patents?

Installing regulations which secure the protection of intellectual property in new ways, thereby assuring investments and innovations, will be a mayor task for the future.

5. Economic issues

On the one hand, big pharmaceutical companies are very much interested in gathering genetic information and in getting access to genetic databases. In the past they even tried to buy their way into these databases. However, in general, they do not promote pharmacogenetic research.

Only some new and relatively small companies specialized in diagnostic technologies would profit from advancing pharmacogenetics. But new diagnostics, of course, only make sense in connection with adjusting therapeutic tools, the latter remaining in the hand of the big companies.

If pharmacogenetics involves a general genotyping of young children and/or possible risk patients, thereby in many cases initiating life-long prophylactic medication, immense new costs will emerge, which presumably cannot be balanced by the (financial) benefits. A change in our system of reimbursement and the concentration on selected fields seems unavoidable. "We can't do everything" (*Khushf*).

Lecture: Prof. Dr. *Rafi Korenstein*

Challenges of nano-mediated drug-delivery

Three factors are crucial for successful nano-mediated drug delivery: overcoming the biological barriers (1), efficient nano-carriers (2) and improved targeting (3). With a multifunctional targeted drug delivery system that meets all three constraints in an optimal way we would have found Paul Ehrlich's "magic bullet".

(1) Four important *biological barriers*, which are relevant for drug delivery, can be distinguished: skin, intestine, air-blood barrier of the human lung, and blood-brain-barrier. With regard to transdermal drug delivery, in order to evaluate the different possible delivery methods, like the common hypodermic needle, chemical enhancers or still unusual methods like electroporation or microneedles, we have to compare their efficacy in various categories (speed of transport, sustained delivery, pain and other side effects, financial costs, complexity of treatment).

The main obstacles for the pulmonary administration route lie in the particular constraints of airway geometry and in endogenous clearance mechanisms (mucociliary clearance, alveolar macrophages, metabolic activities of enzymes), which defend the lung against invaders.

On the one hand, nanocarriers have to be aggregated or loaded into larger (but *not too large*) porous microcarriers (1-5 μm, dependent on whether they are used for the treatment of local diseases or for systemic delivery) to meet the so called *Mass Median Aerodynamic Diameter* (MMAD) requirements. On the other hand, particles with geometric diameters 1-5 μm are engulfed by macrophages, which means that aggregates and microcarriers should have geometric diameters *larger than* 5μm to avoid phagocytosis before the release of drug-loaded nanocarriers. These two opposite constraints illustrate how difficult overcoming biological barriers can be. [Analogous considerations for the intestine omitted for brevity's sake]

(2) There are a couple of possible kinds of *nanocarriers*: polymeric nanoparticles, ceramic nanoparticles, polymeric micelles, dendrimer and liposomes could be used for drug delivery; magnetic nanoparticles and especially so called quantum dots (nanocrystals) for imaging.

The most prospective candidates for drug delivery are perhaps dendrimers: Drug molecules can be loaded both in the interior of the dendrimer as well as attached to surface groups. Water-soluble dendrimers are capable of binding and dissolving small molecules and can be used as coating agents to protect or deliver drugs to specific sites in the body or as time-release vehicles. Other exploitable properties of dendrimers are their polyvalency, monodispersity and low toxicity.

(3) In general, two different *targeting strategies* are conceivable. First, nanocarriers may find their target by chemical recognition, cf. antibodies or ligands; secondly, external physical forces (magnetic, electric, mechanical) may be applied locally, thereby forcing drug release at the target.

Extracellular targeting in cancer could be improved in the following ways: by enhancing permeability and retention by large carriers in the cancerous tissue (e.g. EPR-effect); by developing new types of targeting agents by rational design that uses structural knowledge of a docking; by multi-target approaches dealing with the target's cell heterogeneity; by methodologies for in-situ activation of prodrugs and smart agents; by designing nanostructures with stealth properties (e.g. pegilation, adsorption of natural serum proteins) and finally by aiming at specific intracellular targets (compartment).

Intracellular targeting can be enhanced, roughly, in two ways: via induction of *artificial pathways* in the cell membrane or via the stimulation of *natural cellular processes* which lead to the incorporation of macromolecules in the cells. An example for the latter strategy is the electric-field stimulated endocytosis (electroendocytosis) which is characterized by the following two features: First, the exposure of cells to pulsed low electric fields in the presence

of nanoparticles or macromolecules stimulates the adsorption and uptake of these entities, secondly the nanoparticles/macromolecules are released into the cytosol where they can interact with their appropriate molecular targets.

Experiments with mice suggest that electroendocytotic chemotherapy (=EECT; Taxol®) of metastatic cancer can significantly improve the clinical outcome in comparison to standard treatment like surgery or isolated chemotherapy. Mice already cured of melanoma by EECT also show a remarkable resistance to subsequent inoculation with tumour cells of the same kind.

Discussion:

1. Questions concerning EECT-experiment

Why are mice used instead of an in vitro set-up? Immunological systems can only simulated in vivo. Is there any safe explanation for the partial immunization against cancer cells in the cured mice? No. What about the accumulation of toxins in the animal (human) body and other side effects? Electroendocytosis generally causes an increase in the body's temperature, but this effect is negligible. With regard to (local) toxic residues, it should be noticed, besides other things, that in the human case the ratio between body weight, tumour size and mass of the chemical agent would be much more favourable than in the mice case; so this effect is negligible, too. In fact, methods for improved targeting like EECT are aimed precisely at the reduction of drug dosages and the alleviation of adverse side effects.

2. Angiogenesis, prodrugs etc.

Another very promising strategy in cancer therapy consists in attacking the nutrition (angiogenesis) of the tumour. Here exact targeting is of great importance, too. Much progress has also been made with prodrugs, which are metabolised in vivo into the pharmacologically efficient compound (*Hayhurst*). For example, drugs used to target hypoxic cancer cells, utilise the large quantities of reductase enzyme present in the hypoxic cell to convert the drug into its cytotoxic form, essentially activating it. As the prodrug has low cytotoxity prior to this activation, there is a much lower probability of it attacking healthy cells, which reduces severe side-effects.

3. "Second generation" drugs?

It seems at least conceivable that some day there will be (pro)drugs, which remain inside the human body for years, "waiting" for their activation by certain disease markers. The existence

of such pharmacological "sleeper spies" would presumably revolutionise our understanding of disease and medication (*Khushf, Weltring*). Unfortunately such ideas amount to mere science fiction. It is even dubious, whether, in principle, such latent drugs can be produced at all; in each case they will not be available for decades to come (*Korenstein*).

Lecture: Dr. *Hans H. Riese*

Ethical and Societal Implications of Nanotechnology-Based Diagnostic Procedures

Nano-based diagnostics promises a number of advantages in comparison with conventional methods. Besides its greater efficacy, results will be much more readily available and can be achieved more easily, even by a more or less trained layperson. Especially the latter fact will have an huge impact on everyday life (monitoring chronic diseases, telemedicine, training support for athletes, watching professional driver's vital signs; cf. also MyHeart project by Philips). The *relationship between physician and patient* will undergo a radical change. A shift towards a much greater personal responsibility of the patient in interpreting data and making therapeutic decisions is to be expected. Therefore, present ethical and legal principles which govern the doctor-patient relationship have to be reviewed carefully.

Every time a new technology emerges, there are several dangers lurking in the neighbourhood. Above all, premature enthusiasm for nano-medicine may lead to counterproductive effects. The predictive value of nano-based diagnostics is still controversial, expected features still have to be assessed. We also should be aware, that a mere snapshot of a body's functional status without doing any anamnesis, that is without taking into account the patients' history, could be misleading. The extreme acceleration of diagnoses, which in many cases might follow almost immediately after the first symptoms occurred, is in danger of provoking rash and emotional decisions.

Besides this, citizens have to be protected against data misuse by insurances, employers, politicians etc. for discriminatory actions. (Think of the detection of genetic dispositions to Alzheimer or cancer).

The development and establishment of a new ethical and legal framework for nano-based diagnostics and its control is a multidisciplinary task, involving clinicians, scientists, private companies, health insurance companies, public administration as well as patients' associations, politicians, journalists and intellectuals. Each of these groups should reflect on

its particular task or duty in the process; for example, scientists as well as journalists should confine themselves to the facts, restraining hype; insurance companies may promote general screening in order to assess health risk levels of individuals, but should avoid unfair procedures that lead to discrimination; politicians should promote a wide-ranging ethical debate, install control measures and tools in order to avoid misuse, fight against global nanodivide etc.

Roughly, the main future task will be the promotion of trust in nanotechnology-based diagnosis inside the society, based on objective facts, informative actions and a public debate led by scientific and intellectual authorities. This process will necessarily include mayor educative activities. Although the challenge nanotechnology poses to us, is a very complex one, there is no reason for knee-jerk decisions or for hysteria.

Discussion:

1. Shift in the physician's role

The close connection between computer sciences and nanodiagnostics has to be emphasized. This connection may lead to a 'dehumanization' of decision-making – a process which is of course not particular for nanotechnology. Informational overload is not only a problem for patients, but for physicians as well, who often are not able to see the wood for the trees. (*Zajicek*). Recent studies have shown, for example, that often nurses are superior to physicians in assessing the complex risks of a treatment, due to their better knowledge of the patient's life context (*Bruce*). Nevertheless this shouldn't divert our attention from the fact that it would be the height of irresponsibility to leave patients alone with complex data, for example with the diagnosis of a genetic risk. (*Cascorbi*)

2. Patients' new self-confidence

It cannot be denied that more and more patients are using new sources of information, putting the capacity (and patience) of their physicians to a hard test. Although sometimes naive trust in the doctor just has been replaced by naive trust in the internet, this trend can in general be seen as part of an antipaternalistic emancipation movement. More and more patients are sick of being treated like a child. This may give us a new vision of our healthcare system, whose consequences may have an impact on many other parts of society as well. Even if some patients will never be able to go without the advice of experts, we shouldn't take it for granted that information is to be channelled through the physician. For example, there may be more

reason to trust a carefully constructed computer programme, which is never tired, never overworked, free of human errors or emotionally biased decisions, than a physician (*Khushf*)

In any case there is an urgent need for better educated patients. This is true even for more conventional kinds of medical treatment (insuline administration etc.). New control mechanisms and access rules to databases and genetic tests have to be discussed.

3. 'Theranostics' and automation

If we think of theranostics in its narrowest sense, that is of the combination of diagnosis and therapy in one device, the following problem looms large: patients have to make their therapeutic decisions *before* they know any diagnosis. Such an automatic procedure clearly goes hand in hand with a loss of autonomy. (*Bennett*)

4. Healthcare system

A general genetic screening would put too great a strain on the present health system. Alternative models have to be considered.

Lecture: Prof. Dr. *Sjef Gevers*

Legal Aspects of Nanotechnology-Based Medicine

Although legal and ethical aspects, both normative in character, are entwined in multifarious ways, and although the law incorporates certain moral convictions, it has a distinctive approach, special problems and solutions. It is not up to law to settle controversial issues of value, but to ensure peaceful coexistence in a pluralistic society. Of course, there are also many connections to the third ELSA-compound. Laws can be tools for social conservation or for the promotion of social change.

We also should keep in mind the different levels and forms of law. For example, inside the E.U. *national* law only plays a marginal role in product-related pharmaceutical law. At the same time court decisions and judicial *precedents* have become more important in comparison to classical legislation. Often we have to choose between *substantive* rules (e.g. prohibiting a certain practice) and *procedural* ones (like ethical review or licensing). Procedural laws are more flexible in dealing with issues that are not clear-cut (cf. embryo research).

How may the law respond to the introduction of new technologies? A key issue is whether such a response can or should be technology-specific. One should beware of elaborating specific legislation, unless there is a overriding need to do so. This applies also to

nanotechnology, all the more because it is basically rather an enabling technology than anything else.

Our societies do have complex legal orders that include different types of rules, ranging from general principles (e.g. human rights) to detailed regulations in fields like protection of health and safety, patent law etc.; in between are the general rules of e.g. contract law, product liability. The complexity – but also the flexibility and the range of alternatives when it comes to some form of regulation – is further increased by the coexistence of *statutory rules* ('hard law') and *voluntary* ones ('soft law`). In particular in new, rapidly developing fields, self regulation by means of soft law may be a useful alternative to premature attempts at legislation.

There are some legal issues of immediate and practical concern, related to the existing regulations in the field of clinical research, introduction of new devices on the market, product liability etc. In general, the area of drugs and medical devices is well regulated inside the E.U., there seems to be little need for additional legislation (See European Technology Platform (ETP 2006) and European Group on Ethics (EGE 2007) reports). However, due to the fact that the limits between drug and medical device typically become blurred in nano-medicine, further clarification may be desirable. It is also necessary to monitor existing regulations (Have they sufficient scope? Do they provide adequate risk evaluation for all new nanomedicine products? Are there ambiguities that may create uncertainty or hinder development?) Usually, it takes time to identify the needs and to elaborate the adequate response.

As to product liability the precautionary principle may conflict with the so called "development defense". If we interpret the precautionary principle in a strict way, considering extensive product liability as a deterrent, we may create insurmountable obstacles to the development of new technologies, whose consequences, in principle, cannot be infallibly foreseen.

Attention has to be paid to issues that would seem to lay more in the future, as they are linked to specific applications. An important point is that, basically, what (further) safeguards are needed with regard to a new technology depends mainly on the way it will be used. For instance, it makes a lot of difference whether it is applied in the private sphere, or in a situation of external constraints (e.g. employment relationship, military, prisons etc.). This again underlines how difficult it is to regulate a technology 'per se'

Much of the discussion about future uses is directed at the potential of nanotechnology for 'enhancement' purposes. Although not linked to 'theranostics', it is important to consider how we should look at this issue, not so much from a point of view of individual/private ethics, but from a point of public policy (and law). As a society we should not try to assess every single application in terms of good or bad, but rather try to define and put in place the conditions under which decisions whether or not to use 'enhancement' procedures can be left to 'the market'.

Discussion:

1. The market as panacea?

Belief in the self healing powers of the free market should not be overdone. Leaving technologies like nuclear power completely to the market would have disastrous effects (*Siep*). Surely, some considerations may trump individual freedom. However, as a general rule, we should not interfere with individual freedom, as long as there is not very strong justification to do so. (*Gevers*) The extent, to which one approves of legal intervention, is of course to a large degree dependent on whether one favours a more liberal or more communitarian resp. paternalistic approach to the government's responsibilities (*Bruce, Siep, Gevers*; cf. discussion about sex selection by parents)

2. Law necessarily one step behind

It's a truism: *First* new technologies emerge, *then* regulation crystallizes. We have learned from the IT-case, that, if a technology develops in a disruptive way, there will always appear uncertainties in the law. Although the revolution in biology is less rapidly, traditional models of (substantive) regulation may no longer be appropriate here (Khushf)

Lecture: Dr. *David D. Rickerby*

Implications of Nanomedicine for the EU Regulatory Framework

Current developments in biomedical nanotechnology are expected to lead to significant advances in medical treatment and healthcare. Public acceptance is likely to be strongly

influenced by the perceived risks versus the potential benefits and the correct balance has to be found between allowing technological innovation and guaranteeing safety and quality. Effective regulatory procedures for the approval and certification of products are a fundamental part of this process, particularly where there is a high degree of concern regarding the potential health and environmental impacts.

The application of nanotechnology in the medical field must conform to requirements for public health, safety and environmental protection laid out in the relevant EU Directives. This legislation make no distinction between nanotechnological medical devices and pharmaceuticals and those based on conventional technologies. Nanotechnology will pose some particular problems by generating hybrid products incorporating diagnostic and therapeutic functions. The regulations have, however, been recently amended specifically to take account of 'borderline' drug-device products.

The environmental impact of pharmaceuticals must be assessed and specific arrangements made to limit it. Safety measures for storage, administration to patients and disposal of waste products, together with an indication of potential risks to the environment. The environmental impact assessment should not however constitute a reason for refusal of a marketing authorization.

Risk-benefit assessment of medicinal products is carried out, when they are placed on the market and there exist formal vigilance procedures for reporting adverse incidents for both medical devices and pharmaceuticals.

The existing regulatory framework can be considered sufficiently flexible to deal with nanotechnology at its current stage of development (cf. the 'recommendations' of the Royal Society, DG Sanco and DG RTD workshops, ESF Forward Look, EMEA, EGE). Continual review by the regulatory authorities will be necessary to determine whether it is adequate to safeguard human health and the environment. Modification of the legislation may be required in the light of new scientific data regarding the effects of nanoparticles in the environment and on living organisms. Research is therefore essential to support the regulation of medical nanotechnologies. The following key areas can be identified: a) technology assessment, including the evaluation of the economic, social, health and environmental impacts; b) international agreement on standards, terminology, metrology and harmonized methods of risk assessment; c) methods for the detection and monitoring of nanoparticles, determination of their persistence in the environment and identifying exposure pathways; d) investigation of

the toxicological properties of nanoparticles in relation to their chemistry, size and surface area.

In a communication from the year 2000 the E.U. commission has emphasized the importance of the precautionary principle: A decision to apply the precautionary principle may be appropriate even if the available scientific evidence is insufficient to determine how serious the risk is or to quantify the effects.

Discussion:

1. Big companies controlling themselves?

Isn't 'soft' law getting out of hand? To expect that companies will objectively assess environmental risks or adverse reactions of their products seems at best naive. Are the obligation to notify deadly incidents, some procedural laws and gullible recommendations really sufficient to safeguard us? It is an open question whether mere product liability (How extensive? Who is responsible? The seller, the producer, the developer?) can be a sufficient incentive to avoid incalculable risks.

2. Convergent technologies?

Have 'convergent technologies' been taken into consideration? (*Khushf*) No, E.U. directives are clearly focused on short and medium-term developments; convergent technologies doesn't seem applicable so far. (*Rickerby*)

3. Special problems for 'theranostics'?

In combining diagnosis and therapy theranostics may pose particular difficulties, not mentioned so far*(Siep*). Think of the problem of producing 'informed consent' with regard to therapy before knowing the diagnosis.

4. Precautionary Principle

The application of the precautionary principle *sans phrase* makes little sense, it should be proportionate to the level of the risk (*Bennett*)

Resume (Dr. *Johann Ach*) and final discussion:

Theranostics, its definition, ethical, legal and social concerns – a resume

A) There are at least ***four different senses of the term "theranostics"*** which can be found in the literature: it refers first to individualized/personalized medicine (pharmacogenetics); secondly to systems for transfer of diagnosis from the lab to the point of care (fast in-chip tools); thirdly to the application of particles or devices with dual use (release and imaging), i.e. new kind of drug delivery; and fourthly to systems combining diagnosis, therapy and monitoring.

With regard to the third and fourth sense the term "theranostics" could be misleading. Of course no such device will be applied without having, at least, a rough diagnosis. (*Korenstein*) In this context it might be useful to distinguish between primary (rather vague) and secondary (more precise) diagnoses. Interestingly, in classical medicine the so called "diagnosis ex juvantibus" – getting the proper diagnosis via therapeutic success – already played an important role (*Siep*). The whole package of "theranostics" gives us the idea of an emerging 'Gestalt' of a new medicine, of a revolutionary kind of development. (*Khushf*)

B) From the equivocal use of the term it follows, that "theranostics" has not just one set of ***ELSA implications***, but raises very different issues for the different underlying meanings.

With regard to individualized medicine ethical etc. aspects (safety concerns, fear of discrimination, risk of third party misuse etc.) already have been broadly discussed in the literature, which does not, of course, imply that all problems have been met convincingly. There are no *specific* ethical concerns in regard to theranostics in the second or third sense, but maybe new accented problems. However, with regard to the fourth meaning of "theranostics" a problem sui generis may arouse: the threat of an *automation* of medical expertise. This concern could be reinforced by the (so far unrealistic) development and implementation of smart devices, which may be activated by certain disease markers in risk patients many years after their administration, thereby superseding therapeutic decisions (*Weltring*).

C) A much closer connection of diagnostic and therapeutic tools may deeply affect the ***relationship between physician and patient***. Is there a (cultural) shift in a way, that there are more and more areas, where patients could (and are willing to) interpret data themselves (without access being necessarily mediated by physicians or other experts)?

Even if we welcome the greater responsibility of patients in decision-making, there must be a guaranteed possibility of cross-checking. We should be aware "of being mastered by the machine" and oppose the increasing tendency of blind trust in machines. (*Bruce*)

We should prefer techniques which tolerate human mistakes without leading to immediate catastrophe(*Siep*; cf. telemedicine discussion etc.)

D) We should be cautious about concluding that more and more information for the patient will automatically lead to more autonomous decisions. An ***information overload of data*** highly difficult to interpret and to weigh against each other may make the general demand of an informed consent even more illusory. It is an important matter of future discussion to determine in which way such an information overload is dependent on the kind of given information and how it could be handled or possibly mitigated. One lesson can be drawn in any case: patients have to be better educated.

Cutting short the interval between diagnosis and intervention in a radical way may sometimes result in hasty decisions. Capturing analytic data without keeping into account the patient's medical history is in danger of providing nothing more than a (misleading) snapshot. Of course, nanomedicine isn't the only tool of diagnoses, anamnesis remains important.

A new and high amount of personal data arouses the well known problems of data protection, third party misuse etc.

(E) Therapeutic reaction to the determination of special (genetic) *dispositions* to certain diseases may alter the ***common understanding of disease***: new measurement tools may create diseases, so far unnoticed; mere risk factors may turn into a "disease". The life-world of many patients may be disrupted irreversibly; although this tendency is not specific for nanomedicine, the latter will push the process. (*Khushf*)

(F) Who is willing to fund ***research and development of theranostics***? The interests of pharmaceutical industry seem inextricably linked with the establishment and exploitation of ***patents***. But patents seem to be a dubious and inefficient tool in advancing theranostics. Is there a crisis of our patent system (cf. discussion in the U.S.)?

(G) The existing **regulatory framework** seems sufficiently robust to deal with nanomedicine at its present state of development. However, there are cases, where it is unclear whether we are confronted with a medical device or with a medical product. Can a principal function serve as a criterion; can it always unambiguously identified?

The shift in the patient-physician-relationship has to be mirrored in law. For example, constant automation may give us reason to rethink the physician's liability.

There may also be a need of 'externalizing' the *risk assessment* of industrial products. It could be dangerous to rely on the self-control of global companies (*Bennett*)

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