

Personalized Medicine: how to Switch from the Concept to the Integration into the Clinical Development Plan to Obtain Marketing Authorization

Laurent Becquemont¹, Régis Bordet², Dominic Cellier³ and participants of Round Table N°3 of *Giens XXVII**

¹ Clinical Research Unit, Bicêtre Hospital, Paris, France

² Medical Pharmacology Department, Faculty of Medicine, Lille 2 University, Lille, France

³ Merck Serono Laboratory, Lyon, France

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Abstract – One of the challenges of the coming years is to personalize medicine in order to provide each patient with an individualized treatment plan. The three objectives of personalized medicine are to refine diagnosis, rationalize treatment and engage patients in a preventive approach.

Personalization can be characterized by various descriptors whether related to the field, biology, imaging, type of lesion of the entity to be treated, comorbidity factors, coprescriptions or the environment. As part of personalized medicine focused on biological markers including genetics or genomics, the integration of the clinical development plan to obtain marketing authorization may be segmented in 3 stages with a known descriptor identified before clinical development, a known descriptor discovered during clinical development or a known descriptor known after clinical development. For each stage, it is important to clearly define the technical optimization elements, to specify the expectations and objectives, to examine the methodological aspects of each clinical development phase and finally to consider the fast changing regulatory requirements in view of the few registered therapeutics complying with the definition of personalized medicine as well as the significant technological breakthroughs according to the screened and selected biomarkers.

These considerations should be integrated in view of the time required for clinical development from early phase to MA, *i.e.* more than 10 years.

Moreover, business models related to the economic environment should be taken into account when deciding whether or not to retain a biomarker allowing the selection of target populations in a general population.

Abbreviations: see end of article.

1. Introduction

The aim of Round Table N° 3 *Giens* 2011 was to answer the following question: **Personalized medicine: how to switch from the concept to the integration into the clinical development plan to obtain marketing authorization**

During the preparatory Round Table meetings, it was decided to:

- limit reflection to personalization determined by biological markers including genetics and genomics. This enabled to focus

on the integration of companion biomarkers^[1,2] in the development of drugs or medical devices; biomarkers having already been the subject of a previous Round Table at *Giens* meetings;^[3]

- segment the clinical development plan not into standard phases 0, I, II, III of clinical development^[4,5] to obtain marketing authorization but in 3 stages for the integration of the biomarker into the development strategy;

- 1st stage: the biomarker is known before clinical development,
- 2nd stage: the biomarker is known during clinical development,

* For the list of participants, see end of article.

- 3rd stage: the biomarker is known at the end of clinical development of post marketing authorization (MA),
- orientate discussions in order to propose recommendations for 5 items:
 - technical elements related to identification and optimization for test conduct,
 - expectations and key objectives for each of the three clinical development stages,
 - methodological aspects related to the key issues of the clinical phases for each development stage,
 - regulatory aspects related to the key issues of the clinical phases for each development stage,
 - Economic aspects: specificity or main steps related to the 3 stages retained in clinical development.

2. Definition of personalized medicine

One of the challenges of the coming years is to personalize medicine in order to provide each patient with an individualized treatment plan. It indicates a paradigm shift from a common attitude for everyone (blockbuster, one fits for all) to an attitude tailored to patient profiles (the right drug for the right person). The three objectives of personalized medicine^[6] are: *to refine diagnosis* by identifying early diagnostic markers and subpopulations of patients with different natural evolution and prognosis; *to rationalize treatment* by switching from a mass concept where treatments are indistinctly applied to all patients to an individualized concept where treatments are determined on a case-by-case basis to optimize the benefit/risk ratio; *to engage patients in a preventive approach* by increasing patient adherence and compliance while adapting prevention programs to patient profiles. Beyond the general concept of personalized medicine, three operational medical modalities are involved, *i.e.* personalized preventive strategies, personalized diagnostic strategies and personalized therapeutic strategies. A personalized medicine strategy can be developed in two stages: (i) identification of individualization factors based on fundamental studies and cohort studies showing evidence of an association between a factor and a diagnostic or therapeutic variability within a population; (ii) demonstration that the identification of an individualization factor at the population or individual level enables to predict this variability and to adopt a preventive, diagnostic or therapeutic personalized strategy. It however appears that stratified medicine is still used in the first stage to identify subgroups likely to respond similarly to a treatment for instance. The final stage consists in an individualized medicine able to adapt the diagnostic, therapeutic or preventive strategy for a given patient.

Personalization may be based on various descriptors whether related to the field (age, gender, comorbidities, behavioral profile, socio-economic profile, and lifestyle), biology (standard, genomic, proteomic biology), lesions (imaging, pathological anatomy), treatments (drug combinations, sedentary lifestyle, eating habits)

or the environment (place of life, contact with pollutants, stressing environment, etc.).

In this wide context of presentation and discussion on personalized medicine, the definition of personalized medicine adopted for this article after exchanging with all Round Table participants and in view of the elements retained in the introduction after Giens preparatory meetings is:

Means to optimize the efficacy and/or safety of one or several drugs in a given patient based on the knowledge of characteristics directly or indirectly related to the individual's genetic status and/or to one or several genome abnormalities in cell lines which are responsible for the disease.

3. The biomarker

3.1. Definition

According to the National Institute of Health (NIH), a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.^[1,2]

In the case of the companion biomarker, the latter may have several objectives:

- selection of target patients for clinical trial stratification or to define the groups of patients concerned by marketing authorization;
- prediction of therapeutic response by identifying the responders and non-responders with possible support for dose selection or treatment duration;
- minimization or prevention of an adverse drug event (*e.g.*: HLA typing in patients receiving a treatment exposing patients to Stevens Johnson syndrome).

3.2. Characterization

Before being integrated into a clinical development plan, the retained biomarker should be validated with determination of a threshold by using receiver operating characteristics (ROC) curves when the biomarker value in a population follows a Gaussian curve.

With regard to the response, 2 types of biomarkers can be distinguished (figure 1): biomarkers predicting a “all or nothing” response and biomarkers being more or less very sensitive to a given treatment. The threshold may vary and the identification of the latter may raise technical problems.

The evaluation of the biomarker can be more complex as in some pathologies there may be several types of biomarkers. Melanomas fit into this category of pathology with mixed biomarkers,

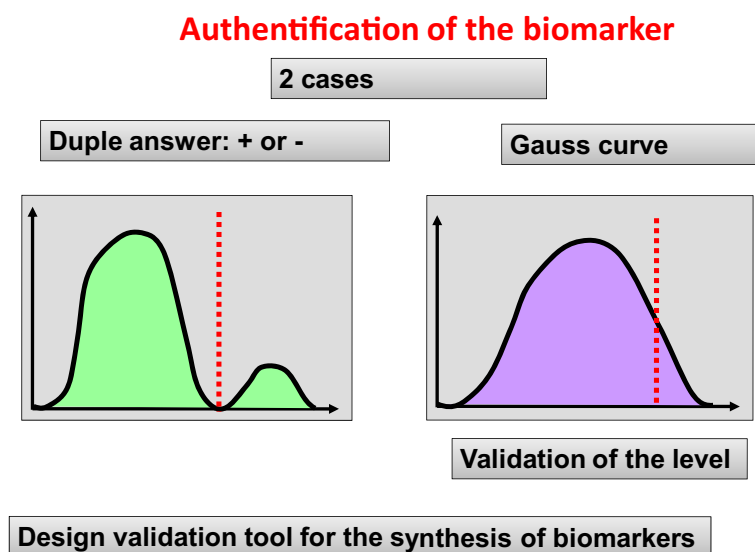


Fig. 1. Definition of the positivity threshold of a biomarker.

as well as breast and lung cancers. The Food and Drug Administration (FDA) keeps up to date a list of pharmacogenetic biomarkers of interest included in MA labeling.^[7]

3.3. Biomarkers and personalized strategies

The identification of these various personalized strategies covers three aspects:

- identification of individualization descriptors;
- assessment of the real effect of these various individualization descriptors (genetic, biological, clinical, morphological) on these various strategies;
- assessment of the impact of the knowledge of the existence of one or several personalization descriptors on the management strategy implemented by the physician, even on patient behavior.

In the first case, identification is achieved through experimental studies, in silico studies, cohort studies and post-hoc analyses of therapeutic trials.

In the second case, the aim is to prove through efficacy studies, that a parameter which is associated with a diagnosis or variability in response to treatment is robust enough to significantly change the validity of the diagnosis, the prediction of a risk or an expected therapeutic or preventive benefit.

In the third case, the aim is to show through so-called implementation studies that the knowledge of these personalization parameters significantly changes caregiver or patient behavior, leading or not to a change in patient management and to an impact on health care organization, medico-economic parameters and patient health state.

The first two cases do not raise any more methodological problems. Many association studies have been or are being conducted in large populations mostly through international consortia (genome wide Association study or GWAS) with a formalization of the process including in particular the need for performing replication studies. European guidelines have formalized the designs of efficacy studies by proposing basically two types of designs:

- a study design in which patients with a negative marker are excluded and in which positive patients are randomized between the group treated with the drug candidate and the group receiving a placebo or a reference treatment;
- a study design in which the population is stratified according to biomarker results, each stratum being then randomized between the treated group and the placebo group.

The methodology of implementation studies still needs to be formalized but this reflection is beyond the scope of this Round Table.

3.4. Biomarkers integrated in the three stages of the development strategy

Biomarkers can be integrated at various stages of the development plan. Basically, three cases can be distinguished according to the plan (table I) defined by the Round Table:

- biomarkers are known at the beginning of the development plan;
- biomarkers whose potential interest is discovered during development;
- biomarkers which are only identified at the end of development, even after MA is granted: the molecule may have obtained a

Table I. Synthetic table for Round Table discussion and restitution: clinical development phases in relation to the selected item.

	Descriptor known before clinical development	Descriptor known during clinical development	Descriptor known at the end or after clinical development
Screening, optimization, techniques			
Expectations and objectives			
Methodological aspects			
Regulatory aspects			
Economic aspects			

first indication without identification of the biomarker, then secondarily develop a biomarker for patient targeting. Example: Kras and Cetuximab in the indication of colorectal cancer.

In the first case, the biomarker may have been determined in view of the results of fundamental studies, the identification of specific subgroups within cohorts but also in view of *in silico* analyses enabling to identify a relevant individualization marker thanks to modeling.

In the second case, the evidence of a variability in the response to a drug candidate with the identification of a responder or non responder group and also of a group with increased adverse drug events leads to the analysis of markers in blood samples or directly at tumor level in oncology trials in order to identify a biomarker associated with this variability in response or adverse drug events which will be integrated in subsequent therapeutic trials. An example is the identification of epidermal growth factor receptor (EGFR) mutation as a marker of response to gefitinib/erlotinib in lung cancer.

In the third case, the biomarker is identified after marketing, even many years of use of a drug characterized by high interindividual variability.

Recent examples^[7] have been brought by the discovery of common genetic variants to the variability in response and adverse drug events associated with antivitamin K drugs or some platelet antiaggregants (clopidogrel).

In the three considered cases, five aspects of the development plan may require specific answers (table II): screening and optimization of techniques, expectations and study objectives, methodological aspects, regulatory aspects, economic aspects.

4. Synthesis of Round Table N° 3 discussions

A synthesis of the Round Table N° 3 discussions according to the clinical development plan segmented in 3 stages and the 5 retained items (table I) is presented in table II.

The ideal solution is when the descriptor is known from the beginning of the development, in preclinical phase. In this case, the drug development is performed along with that of the companion test which can be validated before clinical study start. The study methodology is standard. However, the main risk of this approach is to exclude some patients because of the biomarker, the development and later on the access to the marketed drug. While this is very easy when the descriptor provides a clear answer (responder/non responder), the situation becomes complex when the descriptor characterizes the population in an unimodal Gaussian form (right panel of figure 1): then, one will set a subjective threshold which will exclude part of the population which will certainly exhibit a lower response but nevertheless a response. In the case of a new drug without other therapeutic options, the biomarker may raise ethical problems. For the time being, the descriptors obtained at a very early stage are mainly those predicting the pharmacokinetics of drugs (*via* their metabolism genetically determined by cytochromes P450 and their transport).

The intermediate situation in which the descriptor is identified during development is more delicate. It may on the one hand "save" a drug candidate which would not have obtained any MA without any segmentation of the responder population (*e.g.* gefitinib in lung cancer): most targeted cancer therapies (kinase tyrosine inhibitors) are developed like this. However, the methodological aspects are still very unclear. In fact, in this second case, no randomized studies on the biomarker are available. The phase III study is ongoing or has just been completed and the biomarker is in fact tested *a posteriori* (*post hoc* study) on biological samples. While this approach would be considered inadmissible in the standard development of a drug candidate, in oncology it is almost about to become a habit leading to MA. Reflection on the need for additional studies is absolutely required.^[8,9]

The last situation in which the descriptor is identified after marketing authorization is for the time being the most frequent case. There are some interesting examples regarding HLA susceptibility loci for immunoallergical accidents (Lyell, drug reaction

Table II. Clinical development phases in relation to the selected item: reflections resulting from Round Table N° 3.

	Descriptor known before clinical development	Descriptor known during clinical development	Descriptor known at the end or after clinical development
Screening, optimization, techniques	<ul style="list-style-type: none"> . Target/physiopathology Metabolism . <i>In vitro</i> tests . Biological test validation 	<ul style="list-style-type: none"> . Subgroup analysis/response variability/identification of variability factors . Type of individualization marker to be adapted according to the therapeutic area 	<ul style="list-style-type: none"> . Subgroup analysis/response variability/identification of variability factors . Appearance of a serious adverse event (SAE) . Type of individualization marker to be adapted according to the therapeutic area
Expectations and objectives	<ul style="list-style-type: none"> . Go/no Go in phase I: Identification of responder population . Validation of the interest of the test 	<ul style="list-style-type: none"> . Validation of the existence of a target subgroup . Optimization of the biomarker 	<ul style="list-style-type: none"> . Understanding the effect observed: no effect, moderate, very significant . Understanding the absence of response in a subgroup . Exclusion of patients at risk: protection objective . Taking into account of new scientific information (very rapid evolution of scientific breakthroughs)
Methodological aspects	<ul style="list-style-type: none"> . Test: reliability, reproducibility, towards test accreditation . Study design: Phase I: introduction of the test to validate its implementation/extension to other indications (in oncology) Phases II and III Binary test: patient screening Test +/-: stratification according to response (response threshold) 	<ul style="list-style-type: none"> . Early phase: identification of patient subgroups/adaptive methods . Prospective late phase: patient screening and stratification . Technological development of the biomarker (feasibility, standardization, reliability) . Prospective implementation studies 	<ul style="list-style-type: none"> . <i>Post-hoc</i> studies . Phase III: no new trial due to development cost issues . Retrospective implementation studies (e.g. AVK) . Prospective studies: very important in this type of clinical development

Table II. Continued.

	Descriptor known before clinical development	Descriptor known during clinical development	Descriptor known at the end or after clinical development
Regulatory aspects	<ul style="list-style-type: none"> . If MA authorization: evolution towards test evaluation and EC labeling . Scientific advice recommended prior to MA application . Industrial strategy: coupling or not the new drug of the class with the biomarker according to its innovating character . Regulatory guidance and monitoring: evolution of the technology 	<ul style="list-style-type: none"> . If MA authorization: evolution towards test evaluation and EC labeling . Questioning on the management of patients with negative biomarker . Scientific advice during development with validation of the test in view of the clinical data . Industrial strategy: coupling or not the new drug of the class with the biomarker according to its innovating character decoupling 	<ul style="list-style-type: none"> . Decision of the authorities: post-hoc studies or studies performed at the request of the regulatory authorities (validation of development plan) . Reproduction of the post-hoc analysis on other trials . Questioning on the management of patients with negative biomarker
Economic aspects	<ul style="list-style-type: none"> . Possible industrial reorganization: public-private partnership or integration in the pharmaceutical strategy (acquisition of startups) . Taking into account of the biomarker in pricing (valorization due to the restriction of the treated target: responder patient) 	<ul style="list-style-type: none"> . Reserve the drug for the population which will most benefit from it, then fix or adjust the price. . Price differentiated according to the subgroups (economic constraints linked to the context to be evaluated country by country) 	<ul style="list-style-type: none"> . Reserve the drug for the population which will most benefit from it, then fix or adjust the price . Price differentiated according to the subgroups (economic constraints linked to the context to be evaluated country by country)

AVK: anti vitamins K; MA: marketing authorisation

with eosinophilia and systemic symptoms [DRESS] syndrome) which already enable to exclude subjects with AE risk for the prescription of drugs like abacavir.

However, as in the first situation, patients should not be excluded too rapidly for a given treatment: a rather illustrative example is clopidogrel for which a genetic biomarker of bioactivation was identified 10 years after marketing. Genotyping enables to identify “good responders” and “poor responders”. For the latter, we do not know precisely the extent of the clinical benefit gained but they probably gain some (even if it is low). In the absence of alternative treatment to clopidogrel, these poor responders should still have access to the treatment even if their chances are poor. Fortunately, there is a therapeutic alternative for these poor responders

which enables to use the pharmacogenetic biomarker for the patient’s benefit without any risk of losing chances.

In this third case, at the methodological level, we only have retrospective studies or prospective cohort studies without control group thus involving biases and requiring many replications of data before using these descriptors discovered post marketing.

Finally, in all cases, the financial aspect of biomarkers always raises problems: should their price be included in that of drugs? Should pharmaceutical companies take them in charge? This usual lack of clarity regarding biomarker funding is however always settled in the same way: for tumor response biomarkers, the *Institut national du cancer* (french National Institute of Cancer [INCA]) financed platforms so that patients could have access to the tests.

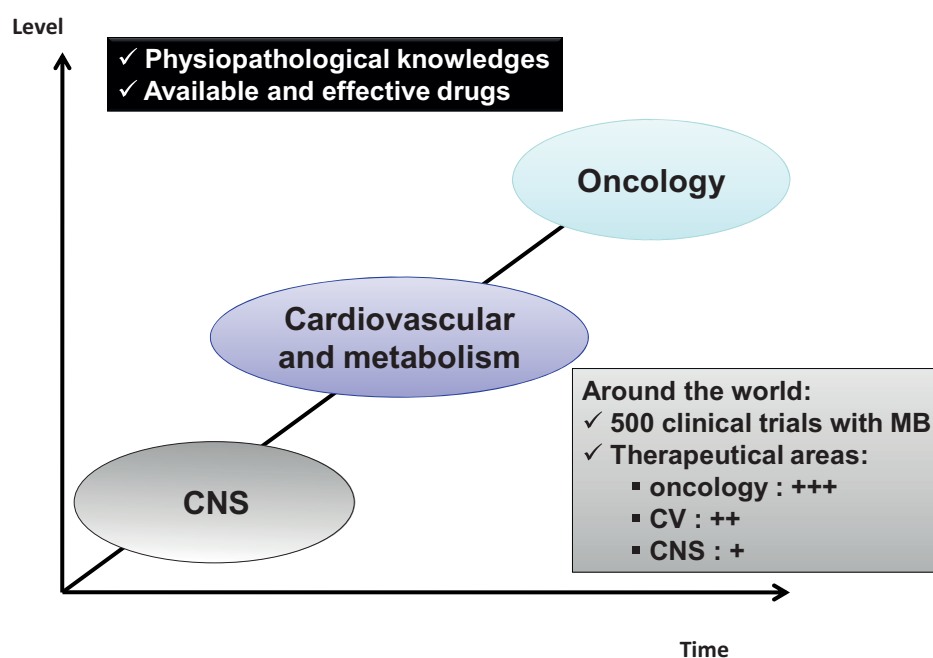


Fig. 2. Therapeutic areas and state of knowledge on biomarkers.

When a drug is contraindicated in case of renal failure or when it requires regular monitoring of transaminases or international normalized ratio (INR), this is taken in charge by our health care system. Therefore, why should it be different for new biomarkers if patients gain substantial benefits?

5. Recommendations

5.1. Monitoring regulatory changes

In view of the rapid evolution and technological breakthroughs during clinical development to obtain MA, it is recommended to regularly monitor regulatory changes to adjust the development plan models according to the evolution of regulations. Though having limited its scope of analysis to biological markers including genetics and genomics, the Round Table N° 3 recommends following the evolution of the European Medicine Agency (EMA) and American Food and Drug Administration (FDA) recommendations. Depending on the clinical development stages and the level of knowledge on the biomarker, the impact of regulations may vary. If the descriptor is known before clinical development, the latter should be included as discriminating factor in all clinical studies. When the descriptor is discovered during clinical develop-

ment, the impact of regulatory changes is to be measured case by case. Analyses in subgroups of patients defined according to the presence or not of predictive markers will have to be performed as part of the development plan.

Taking into account the differences in regulations between the European and American authorities and other regulations specific to the countries concerned can have some impact on the development strategies and result in marketing authorizations obtained in a noncontemporaneous way.

5.2. Having a biomarker in preclinical development or in the early phase of development

The very early identification of a biomarker helps define the profile of the patients who are responding best to the concerned treatment. The biomarker identified in view of the results from fundamental studies enables to optimize the profile of patients. Modeling can be performed at this stage to reduce the number of patients in development plans and thus save time in the development of the molecule until marketing authorization is obtained.

In view of the few examples of complete development including a biomarker from early development phase to marketing, the Round Table N° 3 drew the attention on the risk of losing eligible

candidates for treatment due to the too early exclusion of molecules identified and retained on the basis of a biomarker.

5.3. Defining a business model

In view of the current experiences for the limited number of products having obtained a marketing authorization and integrating a biomarker, the taskforce recommends that a Round Table specifically dedicated to the economic impacts of the products integrating a biomarker in their development be held.

Some issues have emerged regarding the business model, such as:

- cost of the test related to the molecule: Are we talking about the global cost of molecule plus test (the drug being considered as a global entity which enables to take in charge the cost of the drug plus that of the test performance)?
- cost of the drug and its economic valorization: does patient targeting which limits the number of patients concerned by the treatment justify a valorization of the treatment cost?
- as the global allocations dedicated to therapeutic management have been reduced because of the economic environment in France but also in the European Community, a reflection on the economic consequences is required. With regard to cancer treatment, does the personalization of treatment change the business model of the current management?
- with regard to cancer treatment, should the change from an acute treatment to a chronic disease thanks to the therapeutic breakthroughs integrate this dimension in the new business models?

The questions which were raised during the Round Table justified holding a subsequent Round Table specifically dedicated to business models for treatments falling within the scope of personalized medicine.

The taskforce drew the attention on the fact that the questions were restrictive as the scope of work was limited to biological biomarkers including genetics and genomics. A significant field of discussion on business model could be covered on the technological tools enabling to optimize personalized medicine.

5.4. Opening the therapeutic fields to other therapeutic areas than oncology

The observation of a biomarker study performed by *Alliance pour la recherche et l'innovation des industries de santé (ARIIS)*^[10] shows today 500 clinical trials associating a biomarker in the clinical development plans to obtain marketing authorization. These clinical trials cover the 3 stages retained by the taskforce for the integration into the development strategy, *i.e.* whether the biomarker is known from the preclinical phase (stage 1) or during development (stage 2) or even at the end of development (or

post MA) [stage 3]. The mainly concerned therapeutic areas are oncology, cardiovascular diseases and nervous central system.

Today, both regarding the overall early knowledge on biomarker research or the registered drugs integrating a biomarker, oncology remains a precursor field and thus the most advanced in this type of research.

5.5. Reacting to pharmacological or clinical signals during development

In view of the experience gained with several molecules, the taskforce recommends that clinical or pharmacological signals be reported very early, like for instance: immunoallergic effect during development, detection of the appearance of resistance mutations (example of variability in response and adverse events related to anti-vitamin K agents or some platelet antiaggregants (clopidogrel).

5.6. Ensuring test access

The introduction of the test to select patients eligible for treatment raises problems:

- realization problems related to the technical training of the teams, hence some possible inequalities in patient management;
- reliability problems in the reproducibility of data, the latter being discriminating for patient eligibility to a treatment responding to the tests;
- rapidity problems related to the availability of the results before introducing the selected treatment according to the response to the tests;
- financing problems related to the availability of the platform and the team allowing patient management for the performance of the test.

5.7. Sharing biological collections

As personalized medicine is evolving very rapidly, the discovery of new biomarkers requires the availability and protection of biological materials. The increasing number of technologies and biomarkers favors the increase in research on materials – sometimes old and limited. Sharing biological collections is a means to meet these increasing demands while making it possible to centralize both the samples and the data analyses.

6. Conclusions

Personalized medicine opens new prospects and research paths in order to provide new molecules or new technological innovations.

The aim is to obtain new personalized therapeutic solutions to optimize patient management. These new research paths require not only the update of stakeholders with the vocabulary and the understanding of these new therapeutic approaches, but also the creation of interfaces between the pharmaceutical world and industrial techniques.

Personalized medicine raises problems related to the development of standard molecules and also to the testing technology in connection with biomarkers.

It is important to take into account the test measurement reliability of the technology standardization and the accessibility to techniques in the development of treatments which will meet the concept of personalized medicine.

Personalizing medicine, which is the challenge for the coming years, should allow each patient to find the best management or best therapeutic solution. However, even if it is important in the future to think so that each patient can benefit from a therapeutic alternative, it should be considered that early targeting may exclude molecules too early because of patient profiles which do not meet the personalization criteria defined by the therapeutic solution.

In conclusion, the economic impacts of this new approach which is the challenge for the coming years should be taken into consideration very early. The development of these molecules should be valorized in order to have the technical and financial means required to provide new therapeutics falling within the scope of personalized medicine.

Participants.

Marc Bardou (CIC, Dijon), Philippe Beaune (Hôpital européen Georges Pompidou, Paris), Chantal Belorgey (Afssaps, Saint Denis), Frédéric Bibeau (CRLC Val d'Aurelle, Montpellier), Jean-Pierre Boissel (UCBL, Tassin la demi Lune), Soizic Courcier (GlaxoSmithKline), Frédérique De Broucker (Medtronic), Jacques Demotes-Mainard (MESR, Paris), Isabelle Diaz (Leem, Paris), Jean-Yves Fagon (CEPS, Paris), Danièle Girault (Novartis Pharma), Sylvia Goni (Laboratoire Lundbeck), Rémy Hanf (Genfit, Loos), Marie-Annick Hermann (Bristol Myers Squibb), Patrick Mismetti (CHU, Saint-Étienne), Monique Morali (Merck Serono), Mira Pavlovic (HAS, Saint Denis la Plaine), Elena Perrin (Lilly France), Yannick Plétan (Pfizer), Christophe Sauce (Boehringer Ingelheim), Gilles Vassal (IGR, Villejuif).

Conflicts of interest. None.

Abbreviations. DRESS syndrome: drug reaction with eosinophilia and systemic symptoms syndrom; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; FDA: Food and Drug Administration; GWAS: genome wide Association study; INCA: *Institut national du cancer* in France (National Institute of Cancer); INR: international normalized ratio; MA: marketing authorization; NIH: National Institute of Health; ROC: receiver operating characteristics.

References

1. ANSM biomarqueurs et produits de santé. 2011. [http://ansm.sante.fr/Activites/Biomarqueurs/Biomarqueurs-et-produits-de-sante/\(offset\)/0](http://ansm.sante.fr/Activites/Biomarqueurs/Biomarqueurs-et-produits-de-sante/(offset)/0)
2. Biomarqueur: definition working group: biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001; 69 (3): 89-95
3. Gueyffier F, Dib M, Boissel JP. Biomarqueurs - Utilisation au cours du développement et pour l'enregistrement des médicaments Biomarqueurs : utilisation au cours du développement et pour l'enregistrement des médicaments. *Therapie* 2001; 56(4): 355-61
4. FDA. Drug development and approval process. <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm>
5. EMA. Clinical efficacy and safety guidelines. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp&mid=WC0b01ac0580027549
6. EMA. Personalized medicine. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000347.jsp&mid=WC0b01ac05800baeda
7. FDA. Pharmacogenomic biomarkers in drug labels. <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>
8. EMA. Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid=WC0b01ac058002958e
9. EMA. Concept paper on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid=WC0b01ac058002958e
10. ARIIS. Le biomarqueur comme outil de diagnostic compagnon de produits thérapeutiques. 2010. <http://www.ariis.fr/wp-content/uploads/2011/03/biomarqueurs-etude-version-complete-130-slides.pdf>

Correspondence and offprints: *Dominic Cellier*, Merck Serono Laboratory, 37 rue Saint Romain, 69379 Lyon Cedex 08, France.
Email: dominic.cellier@merckgroup.com