3　ファーマコゲノミクスを利用した臨床試験の情報の提供及び取扱いについて

(1) ２に掲げる情報の提出については期限を定めるものではないが、計画時、着手時等の節目毎に、情報を厚生労働省医薬食品局審査管理課に提供されたいこと。
(2) 提出された情報については、企業の開発状況を反映する知的財産に関わるものが含まれるため、行政機関からの開示はされないものであること。ここでの「行政機関」とは、厚生労働省及び独立行政法人医薬品医療機器総合機構を想定しているものであり、外部の専門家等に対し、情報に関する協議を行う場合は、事前に、情報を所有する企業に連絡するものであること。
(3) 治験依頼者がゲノム検査等を用いた手法により得られた結果を効能効果・用法用量、使用上の注意に反映させるために検証したものについては、薬事法に基づく承認申請時の添付資料としての提出を求めるものであること。例えば、肝ミクロゾーム薬物代謝酵素（CYP）等のゲノム検査などが被験薬の臨床的な成績との関連において検証された場合などが想定されること。
(4) 提出された２に掲げるリストに対しては、指針等の作成過程において、行政機関から照会を行い、具体的な情報の提出を求めることがあること。ただし、その場合においては、(3)に掲げる承認審査に用いることを目的として提出されたもの以外は承認等の行政的な措置に用いるものではないこと。
(5) 被験者の個人を特定できる情報を医療機関又は企業が保有している場合、医療機関又は企業の責任において管理され、行政機関に臨床試験の結果等を提出する際にも、匿名化等について遺漏なく対応すること。個人情報に関わらない臨床試験結果についても、行政機関への提出を求められた場合には、行政機関への提出について被験者の同意内容を尊重すること。
(6) 今後新たに治験又は市販後臨床試験を実施するために治験計画届け又は基本計画書を行政機関に提出する場合は、ゲノム検査等を含む臨床試験であるか否かの情報を当該計画届け又は基本計画書に明記することを求めるものであること。

4　ゲノム検査等を利用した医薬品の開発における留意点について

ゲノム検査等を用いた臨床試験のデザイン等については、医薬品の特性等に応じ医薬品毎に個別に製薬企業等において検討されるべきものである。

なお、既存のバイオマーカーを用いて検査手法を医薬品に対する個人の反応性を予測するための指標を探索する手法について調査が行われた薬剤反応性調査試行的事業（平成１２～１４年度）において得られた知見も当面参考の一助となりうるものであること。（http://www.mhlw.go.jp/shingi/2003/10/s1022-3.html）

5　その他

ゲノム検査等を利用した臨床試験の承認及び再審査における取扱いについては次の点を品目毎に考慮するものであること。

(1) 承認時にゲノム検査等による情報を効能効果、用法用量、使用上の注意に反映させる場合は、再審査において当該効能効果等の確認のために行う臨床試験等を勘案し、通常６年間の再審査期間を１０年を超えない範囲で一定期間延長する方針を検討すること。

(2) ゲノム検査等による情報を効能効果、用法用量、使用上の注意に反映させるため、承認後引き続き、ゲノム検査等を利用した臨床試験（治験又は市販後臨床試験）を計画する場合にあっては，再審査期間中に行う臨床試験等を勘案し、通常６年間の再審査期間を１０年を超えない範囲で一定期間延長する方針を検討すること。

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 21 November 2002
EMEA/CPMP/3070/01

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POSITION PAPER ON TERMINOLOGY IN PHARMACOGENETICS

DISCUSSION AT THE PHARMACOGENETICS EXPERT GROUP	April/September 2001
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1. Introduction

Pharmacogenetic research started from the observations that not all subjects respond in the same way to the same medicine and that these differences between individuals may be caused partially by their genetic profile.

Today the drug development programmes consider (usually for practical reasons) the subjects as coming from a rather homogenous population since it is not possible to accommodate fully in the drug development programme the whole range of inter-individual variability observed within a population. When differences in drug response are anticipated, e.g. in subjects with renal or hepatic disease, or with age-related differences, then studies are requested in the specific subgroup identified.
The contribution of genetic influences to variability in drug response often far exceeds that of any other variable and is what the science of pharmacogenetics aims to unravel. The analysis of a broad set of genetic variations may show that a genotypically defined subgroup of subjects may have a higher probability of responding to a certain drug differently from others in the population. The overall genetic profile may vary according to ethnicity.

As a result of the development within the areas of genetics and genomics, changes are likely to occur in the way drug development is currently being conducted and the way medicines will be used.

The use of terms that are harmonised and widely accepted by the stakeholders would contribute greatly to clarity in the dialogue. At present there is not an agreed set of working definitions crucial for pharmacogenetic clinical research. This is urgently required for protocols and guidelines addressing pharmacogenetic testing to ease communication particularly between ethics committees, investigators and subjects.

Following extensive consultation, the CPMP has agreed on a specific set of definitions directly relevant to the current practices in clinical research, with the understanding that they may have to be revisited in the light of future scientific advance and taking into account emerging legislation. The definitions discussed hereafter are highly relevant to the scenario of individual clinical protocols including pharmacogenetic testing; the principles might however be relevant also for trials involving testing other than pharmacogenetics.

The terms "pharmacogenetics" and "pharmacogenomics" as well as the terms used in the handling of samples and data for pharmacogenetic testing have been defined from the scientific-technical point of view.
The same definitions, following appropriate consultation will then be written in lay-terms and made available in all EU official languages to constitute a useful technical asset for regulatory authorities, ethics committees, health professionals and subjects when confronted with pharmacogenetic testing protocols and consent documents for medicinal product clinical trials.

2. Scope

This position paper focuses on a specific set of critical terms that are frequently used in protocols for pharmacogenetic testing and that are relevant to define appropriate levels of protection for the privacy of the subjects when describing how the results and samples will be used in clinical trials.
The choice of the level depends on the extent to which it is desired or considered possible to link the data and samples to an identifiable subject and corresponds to the defined category of sample linkage.
The most appropriate level for a particular study depends on the nature of the research, the intended use of the data, the regulatory and legal environment and the specific concerns of the investigator and study sponsor. This choice must respect the needs for the privacy of subjects participating in a clinical study.
Generally, the greater the subject privacy in a study, the less are the opportunities for the subject after sample collection and pharmacogenetic testing have been performed to withdraw the individual samples from further analyses or to receive individual results from the study.
Privacy of information, control over the use of samples, and knowledge of study results may all contribute to a subject's willingness to take part in a study, and as a consequence the choice of process may significantly affect enrolment in a clinical trial in which pharmacogenetic testing is planned.

Sample coding procedures should be documented according to Good Clinical Practices (GCPs) and as provided for by relevant EU directives and accompanying guidance documents. Primary study data and original study-related records should be accessible to the competent regulatory authority in order to validate the evidence that is reported. While the regulatory authority can accept different levels of documentation, depending on the particulars of the study and the availability of other evidence or records, there may be times when it is necessary to link a clinical outcome to a particular patient. In principle, there is a framework for protecting patients enrolled in clinical trials now, and this framework may be adequate, perhaps with small changes, to apply to clinical pharmacogenetic trials.

Complete anonymity of the subject without any possibility of linking the samples/data to an individual will have great impact on the usefulness of the results and on what aspects might be verified during a GCP inspection from a competent authority or a sponsor audit. The individual subject record is an important component of data for submission to regulatory agencies and so the use of data from a study involving anonymised samples might not be acceptable for the submission of a claim to be included in the label of a drug or clinical diagnostic assay.
In designing clinical trials, investigators and sponsors should attempt, in consultation with competent authorities and ethics committees, to find the optimum balance between achieving the aims of the study and protecting the subject's safety or right to privacy.
It is recognised that DNA data unique to a subject could potentially be used to reconstruct a link between a subject's medical record and genotype information. Procedures should ensure that in order to respect the subject's wishes and privacy, such links are not reconstructed. For the same reasons, it is further recommended that the code should comprise randomly assigned numbers/letters and should not be based on protocol and site number (and perhaps gender) because if a particular site has included only a few subjects, it might be theoretically possible to reconstruct a link to individual subjects.

3. Pharmacogenetics and Pharmacogenomics

There is at present no consensus in the literature on the definitions of "pharmacogenetics" and "pharmacogenomics". Actually the terms are frequently used interchangeably. The achievement of widely accepted working definitions of the two would be a useful first approach to applying pharmacogenetics and pharmacogenomics in clinical trials. It is important to single out pharmacogenetics and pharmacogenomics from the wider field of genetic testing as the latter encompasses different level of concerns especially in terms of sensitivity of sample handling, data and trial results management.

Pharmacogenetics is the study of interindividual variations in DNA sequence related to drug response.

Pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery, and clinical development

4. Definitions applicable to DNA samples and data in clinical trials including pharmacogenetic testing

Different terminologies relate to the collection of human samples for pharmacogenetic research and the management of the data therefrom. The set of terms described in this paper are a key to correct handling of the samples and the data and to transparency of communication among industry, ethics committees, regulatory authorities and subjects about the pharmacogenetic approach in clinical research, regulatory assessment of medicinal products and clinical practice.
The processes by which samples and data are collected, labelled and stored have a direct effect on how the samples and the results obtained can be used in the future and on the obligations of the investigator and sponsor to the sample subject. This pertains particularly to situations when a subject withdraws his or her consent to further participation in a study and affects the possibility to return information to the subject or his/her physician, the possibility to withdraw a sample from future analyses and verification of data ascribed to a subject in reports and regulatory submissions. Additionally, the readiness and willingness with which a subject would or would not want to take part in a study may be affected by such factors as the uses of the results, the nature of the information the subject might receive, and the perceived risk resulting from disclosure of genetic information to third parties.

Five definitions (See table 1) for the labeling and coding of pharmacogenetic samples and data are proposed describing direct implications for the handling methodology of samples for pharmacogenetic testing and corresponding consequences for the level of privacy protection and use of the information for regulatory purposes. Duration of retention of the sample or its destruction needs to be defined in the protocol and in the consent form. Otherwise, if and when relevant, the timepoint and the procedure for anonymisation of the sample itself should be defined in these documents.

4.1 Identified samples and data

are those labeled with personal identifiers such as Name or Social Security Number.

Identified samples and data are treated in much the same way as those acquired in everyday medical practice. Because the sample and the data generated from it are directly traced to the subject, it is easy to withdraw the sample or the data from the study, update subject information, and return results to the subject. Also, at an inspection of the study it will be possible to verify the connection between the subject and the reported results. On the other hand, since a subject's genotyping results are directly linked to the subject's identity, the use of identified samples offers no extra privacy protection in addition to those generally provided.

Identified samples and relevant data might be coded at the given point in time in order to provide for extra long-term privacy protection following the closure of the trial.
The protocol should also specify when and whether the samples and data might be destroyed or anonymised.

4.2 Single coded samples and data

are those to which a single specific code is attributed for protecting individuals. It is recommended that the code should comprise randomly assigned numbers/letters

The investigator stores the key connecting the code of the sample to the individual's data. This step separates the subject's identity from the results of the pharmacogenetic analysis. The researcher with knowledge of the pharmacogenetic data would not have ready access to the identity of the subject.
Only breaking the code can reveal the subject's identity.
It is possible to withdraw a subject's sample for prospective use or return individual results to the subject or physician if desired.
The maintenance of a link between the subject and the pharmacogenetic information by a single code allows verification of data ascribed to an individual subject. Because the investigator who has coded the sample might also have access to the pharmacogenetic data, the safeguards of the subject's privacy, including doctor-subject confidentiality, are equivalent to those in current clinical trials practice.

4.3 Double-coded samples and data

have an additional privacy safeguard imposed by the use of a second coding system. Adding an additional code to the samples and data provides further protection.

The investigator who only knows the first code does not know this second code. In this way, anyone with knowledge of the pharmacogenetic results can only trace a subject identity to a coded identifier but no further, unless a key is used to link the codes between the data set with subject identifiers and the data set containing the pharmacogenetic information.
The code key linking the double coded pharmacogenetic samples and information is kept by a third party. This should not be the investigator in possession of the key linking coded sample and/or information to the subject.
The key to the double code might be maintained by the sponsoring organisation, in areas entrusted with maintaining confidential information (e.g. legal, quality assurance, clinical statistics) under strict operating procedures. Alternatively, the key might be held by an external entity, such as governmental agency, legal counsel, or other qualified third party not involved with the research.

The individual can only be linked with the sample or data obtained from it by bringing the two code keys together. Although the samples do not carry any information on the identity of

the subject, it is still considered to be possible to identify the subject as long as both code keys exist.

As with single coded samples, the existence of a link between the pharmacogenetic data and the subject's identity makes it possible to withdraw a sample or data (up to the time the results stemming from that data are reported), update subject information, return results and inspect the process. However, the conditions under which the pharmacogenetic information might be linked back to the subject's identity for any purpose are determined strictly by the specifics of the research protocol.
These conditions should be explicitly described in each protocol, and included within the subject's informed consent.

4.4 Anonymised samples and data

are for practical purposes double coded samples where the key linking the first and/or second code is deleted. They may be also previously single coded samples where the single code key is destroyed or even previously identifiable samples where the name/identifier is removed.

Anonymised samples and data do not carry any longer personal identifiers. Once the linking key has been deleted, information related to the subject's identity is no longer linked to data related to the pharmacogenetic results. This offers an additional level of security to the individual's data.

After anonymisation it is not possible to withdraw a subject's sample from analyses, to update subject information for further use, or to return any individual results to the subject or the subject's physician. Similarly, it also is not possible to inspect the study to determine that pharmacogenetic data is accurately correlated to a specific subject.

There will be times when stored samples may provide a regulatory agency additional information related to clinical outcome. The ability to link individual data to a patient will be essential in some circumstances and anonymised samples would be a problem.

In general, anonymised samples are well suited to research studies in which hypotheses are generated, but may be less so for clinical trials on which label claims are based.

4.5 Anonymous samples and data

are those that do not have any link whatsoever between the sample and the individual identity.

Anonymous samples may have population information (e.g., the samples may come from subjects with diabetes) but no individual data that might allow the identity of the subject to be traced. The clinical information is limited to broad categories of data, such as "male, age 50-55, cholesterol > 240 mg / dl". In many instances, the sample has no clinical data at all.
This situation is applicable in cases where the population is large enough and measures are taken in building up the code (see recommendations on page 3 on reconstructing a link).
Anonymous samples are useful in some types of pharmacogenetic studies.

Table 1. Summary table of the five terms of sample labelling.

Sample Labelling Category	Link Between Subject Identity and Pharmacogenetic Data	Records Identifiable for Clinical Monitoring	Actions Possible if subject withdraws Consent	Return of Individual Results to Subject	Scope of Subject Privacy protection
Identified	Yes, directly	Yes	Sample can be withdrawn with immediate effect for any prospective use	Possible	Similar to general healthcare confidentiality
Single coded	Indirectly, via code key	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Standard for clinical research Conforms to principles of GCP
Double-coded	Very indirectly, via two sets of code keys	Yes, via protocol-specified procedures	Sample can be withdrawn with immediate effect for any prospective use	Possible	Double code offers added privacy protection over single code
Anonymised	No. Key(s) identifying the link between pharmacogenetic data and the identity of the subject is deleted	No	Sample and data are not identifiable. Sample cannot be withdrawn once key is deleted	Not possible	Pharmacogenetic data not linked to individuals
Anonymous	No	No	None	Not possible	Complete

EMEA/CPMP Working Group with patients' organisations

The EMEA/CPMP working group with patients' organisations has been created as a result of the EMEA/CPMP workshop with patients' organisations organised in 2002. The mandate of the group is to make proposals for action in the following areas in the context of the EMEA activities: pharmacovigilance, product information, dissemination of information/transparency and interaction between the EMEA/CPMP and patients organisations. This group, which met three times in 2003, involves 8 European patients organisations.

Invented name Review Group (NRG)

The Invented Name Review Group (NRG) met 11 times in 2003 to review whether invented name(s) proposed by applicants for medicinal products would create public health concerns and more particularly potential safety risks. Collaboration with WHO in this field was increased resulting in a systematic participation by WHO in the review process. An interested parties meeting was held with EFPIA in April 2003 to review implementation of the revised guideline adopted in 2002 and process performance aspects. The NRG also welcomed observers from the accession countries to its meeting. In addition a retrospective review of invented names of centrally authorised products versus nationally authorised products in the accession countries was performed as part of the preparation for the EU enlargement.

A new tracking database became operational in 2003 to allow better monitoring of the review process.

The percentage acceptance rate for 2003 is 63 %, based on a total of 107 names reviewed, 67 names accepted, 40 names rejected and 13 names justified by applicants. The average timeframe to complete an invented name review was 39 days, which is in accordance with the guideline.

Ad hoc Working group on (pre-) clinical comparability of biotechnology products

This group met twice in 2003 and finalised an annex to the note for guidance on comparability of medicinal products containing biotechnology-derived proteins as drug substance.

Paediatric Expert Group (PEG)

The Paediatric Expert Group met five times in 2003 and issued two concept papers on renal system and immune system in the context of development of medicinal products for children. The group contributed to guidelines of the CPMP efficacy and quality working parties. The group was consulted by the EC on its proposals for a future paediatric regulation and was requested to prepare a preliminary list of priorities for studies on medicines for children's use to be funded. The PEG liaised with EU paediatric learned societies in order to foster the necessary networking, particularly for clinical trials developments.

Vaccine Expert Group (VEG)

The VEG met on five occasions in 2003 including one meeting devoted to influenza pandemic. Plenary sessions are complemented by drafting groups addressing specific issues in a more focussed manner and generating positions papers on topics such as TSE, blood products, viral safety of biological or biotech products. The VEG prepared guidelines on the data and dossier requirements necessary in the event of influenza pandemic in consultation with the European Commission and vaccine manufacturers.

Blood Products Working Group (BPWG)

The BPWG met on four occasions in 2003 including two times as specialist drafting groups.

Ad hoc Expert group on cell therapy

The group met twice in 2003. In consultation with the other CPMP and CVMP working parties, the ad hoc group completed the revision of a concept paper on xenogeneic cell therapy that was adopted by the CPMP and CVMP in December 2003.

Ad hoc Group on gene therapy

During its two meetings in 2003, the group contributed to a BWP position paper related to lenti-viral sectors and discussed topics including insertional mutagenesis and oncogenesis, gonadal signalling and germ-line integration study in order to prepare for the second ICH workshop on gene therapy held in November 2003 as a satellite session of the of the ICH 6 Conference, in Japan. The two scientific meeting reports and the ICH gene therapy workshop communication paper were published by the EMEA.

Ad hoc Group on pharmacogenetics

This group met three times in 2003. The group finalised the English version of the CPMP position paper on terminology in pharmacogenetics in lay language, ahead of its translation into all official EU languages. The Pharmacogenetics expert group finalised a concept paper on Pharmacogenetics briefing sessions, published in January 2003 and participated to three briefing session with companies where pharmacogenetics-specific issues were discussed under the 'safe harbour' concept.

Ad hoc groups on Chemical Threats

At the request of the European Commission, in the framework of action Programme of Cooperation on Preparedness and Response to Biological and Chemical attacks (BITCHAT), the EMEA established a CPMP expert group responsible for drafting a guidance document on medicinal products to be used in the framework of chemical threats. The EMEA guideline was released on 13 May 2003.

2.12 Enlargement and international activities

Major efforts were made in 2003 to allow for a smooth transition for the new Members States in May 2004. Considerable resources were allocated into the PERF III programme and specific training was provided to assessors from accessing countries in order to allow familiarisation with the European procedures.

International activities focussed on involvement in ICH and collaboration with non-EU national competent authorities. The EMEA contributed to the ICH process through the provision of technical coordination and scientific support through its scientific committee and working parties. In 2003 three meetings were organised, one in Europe and two in Japan, the last meeting being followed by the ICH-6 conference and satellite sessions. The EMEA contributed directly to such activities.

The EU and the US Food and Drug Administration (FDA) concluded a confidentiality arrangement that provides a framework for regulatory cooperation. Preparations for an implementation plan were begun. Cooperation with the FDA in 2003 mainly focussed on regular videoconferences in the field of pharmacovigilance.

European Medicines Agency
Evaluation of Medicines for Human Use

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EMEA/3842/04/Final

Understanding the terminology used in pharmacogenetics

What is this leaflet for?

This leaflet is intended for you as a patient or participant who has been invited to participate in a clinical trial that involves pharmacogenetic testing. It provides information regarding your personal privacy – in particular, the options that are available to protect your identity and to safeguard your genetic information.

A clinical trial is a study of medicinal products in people, whether patients or non-patient volunteers, to discover or verify the effects of such medicines on participants and to establish their safety and efficacy.

Pharmacogenetics is the study of how genetic factors may influence our response to medicines.

Clinical trials including pharmacogenetic testing are not designed to identify whether we have inherited – or may be more prone to – a specific disease. Rather, they are intended to investigate the role of genetic factors in determining how people react to individual drugs so that doctors are able to prescribe the appropriate dose of a medicine to achieve the best results with the least possible side effects.

Trials, usually set up by pharmaceutical companies, are necessary in developing new drugs and serve the wider public interest in expanding our understanding of the alternative treatments available for particular conditions, in particular circumstances. In organising any trial, there is a need to balance each participants' privacy against this wider public interest. Sometimes, for instance, the accuracy of genetic findings can only be confirmed by linking the results to clinical data. This means identifying the person concerned. Various levels of privacy and data protection offer different – and possibly conflicting – benefits for those involved in clinical trials (the same concerns may also apply to other types of genetic study).

Protecting data is important not only to make sure that the results are not used to discriminate against you but also to make sure that you have control over how your sample and the results from it are used.

Pharmacogenetics and Clinical Trials; Protecting your Privacy and Data

During clinical trials new medicines are tested for safety and efficacy and may also involve "pharmacogenetic testing" which is a new technology designed to define, through analysis of the genes contained in the cells of people participating to the trials, whether a particular pharmacogenetic profile is shown to match a response to a specific drugs.

This type of genetic analysis is not aimed at discovering whether an individual is prone to develop specific diseases.

How clinical trials are to be carried out is controlled by various parts of legislation and codes of ethics and practice.

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Three of the most important responsibilities to be jointly fulfilled by the sponsors, the ethics committee and the investigators are to:

- give the person taking part in the trial all relevant information so they can make an informed decision on whether to take part or not;
- protect the people involved against any harm; and
- protect the privacy of the people involved.

As far as the first two points are concerned, you keep the right to decide to take part, to refuse or withdraw from a clinical trial, without it affecting the quality of your normal routine medical care.

With regard to protection of your privacy, it is important to remember that pharmacogenetic data are subject to the same level of confidentiality as all other medical information. Moreover additional protection might be provided. In very general terms, the greater the degree of privacy you are given, the lower is the likelihood of linking you to the sample and the genetic results derived therein. In turn, this lowers the later possibility of verifying the meaning, the accuracy and reliability of the overall results generated in the clinical trials in which you have been enrolled.

Therefore, the choice you make should take into account not only your own desire for privacy (this may vary between individuals) but also your wish to know your individual results, the nature of the research, the need to verify the reliability of genetic information and how regulatory authorities that supervise medicinal research or approve drugs, use the results.

How is your sample handled and which are the consequences for your privacy protection?

This paper intends to provide you with some preliminary information on the meaning of terms used to define samples taken for pharmacogenetic testing and data in clinical studies. You will be receiving additional information by the investigator both verbally and in writing within the documents provided to you for your consent to the participation to the clinical trial.

Anonymous samples and results

Your sample on which to carry pharmacogenetic testing, is taken for medical research purposes and there is no link with your identity: samples and data taken are defined as 'anonymous'. This type of collecting and coding of samples is usually only used for general medical research.

This way of handling samples and genetic data only allows for the link between the genetic results and the clinical record but not to your identity. It gives the highest level of additional privacy protection, but also implies that you might not be able to withdraw your sample from further analyses or receive your individual results from the study.

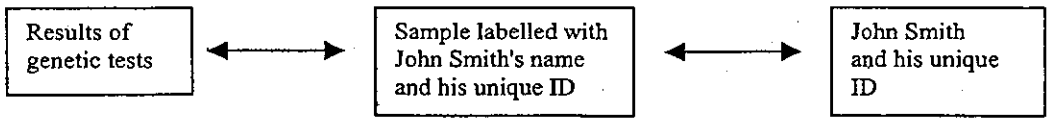
This also has an additional consequence - regulatory authorities in charge of supervising Good Clinical Practices in clinical trials will have no opportunity to check how accurate and reliable the pharmacogenetic results are, as there may be times when they need to check and link a clinical response to a particular participant and his or her genetic profile.

Coded samples

a) Identified samples and results

The sample taken from you will be labelled with your name (for example, Mr John Smith) and other unique ways of identifying you (for example, the hospital records number ABC23DEF).

Your results are directly linked to your identity and there is no extra protection, which will apply on top of the secrecy, which normally applies to medical records.



With this category of coding, it is possible to fully identify which person the pharmacogenetic information relates to. With this level of privacy protection:

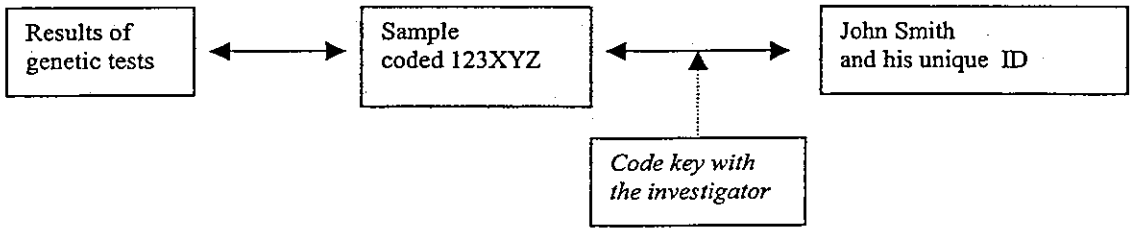
- John Smith can easily ask for feedback about his pharmacogenetic information.
- He can also ask the company to destroy his sample or stop it being used in further analysis.
- If necessary, regulatory authorities can also check the accuracy of the information supporting the claim that a specific pharmacogenetic profile is associated with a certain type of response to a medicine.

b) Single-coded samples and results

Your sample will be labelled with a code (for example, 123XYZ).

Pharmacogenetic results are thereafter derived from the sample labelled 123XYZ.

However, only the investigator knows the identity of the person (in this case, Mr John Smith) to whom this code (and the results of the genetic tests) applies. With this category of coding, there is one specific code that links you to the sample and the results. The investigator usually holds the key to the code.



This key separates your identity from the results of the analysis. Only by breaking the code can you be identified and linked to the results. It is possible for you to withdraw your sample for any further use in the future. You or your doctor may also ask to see the results of the test. If necessary, it is also possible for the investigator, the sponsor and the authorities to check the authenticity of the genetic results and their link to John Smith.

c) Double-coded samples and results

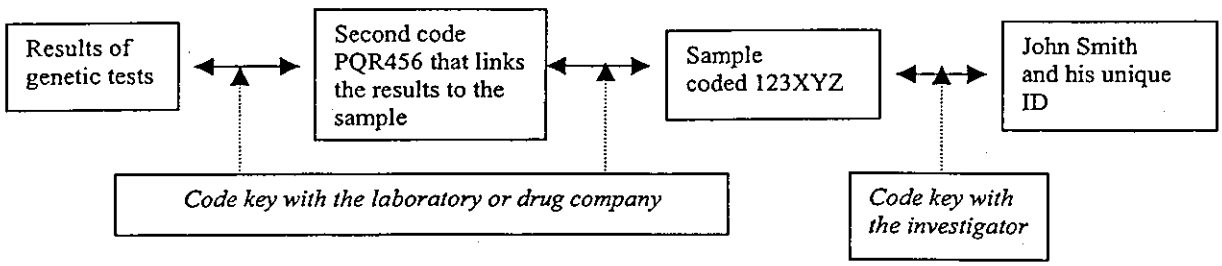
The investigator assigns the code to your sample and only the investigator can link you (John Smith) with the sample (coded 123XYZ). Then a second code (for example, PQR456) is provided to link the already coded sample to the pharmacogenetic results.

The investigator holds the key to the first (sample) code but does not know the second code assigned to the genetic results.

The laboratory or drug company are not aware of the first code but they know the key to the second code.

Unless the two codes are linked, the sample and the results of genetic testing cannot be linked to you.

The key step is the link between the first code 123XYZ (which links the sample to John Smith) and the second code PQR456 (which links pharmacogenetic results with sample coded 123XYZ).



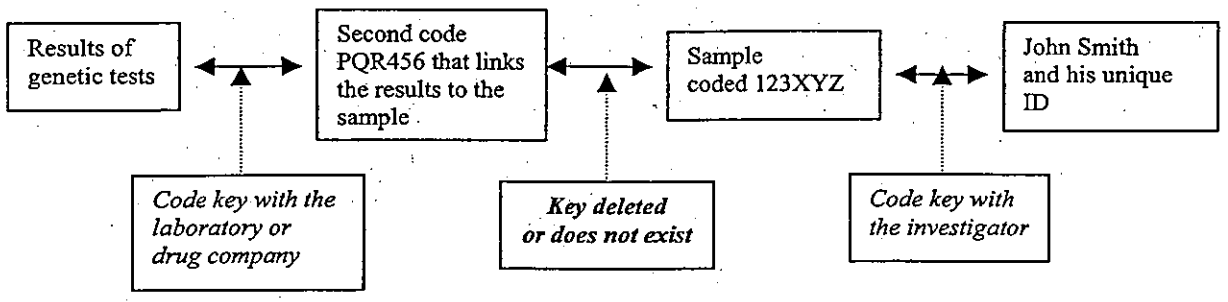
While providing extra privacy, this level of coding provides the same advantages of single-coded samples in terms of:

- the participant and their doctor having access to the results;
- withdrawing the sample from further analysis; or
- regulatory authorities may check the accuracy of the data.

d) Anonymised samples and results

For a set period of time, which is specified and you are informed about, the sample and the results have or had been linked to you using a coding system. The duration of this link will depend on the objectives of the study and may range from a few weeks to years. At the end of the set period of time, the links between you and the results are permanently broken by destroying the codes and the code keys.

Even previously identifiable samples, where the name or identifier is removed, may become anonymous samples (then they are called "anonymised"). After that there is no link whatsoever between yourself and the results or the sample.



Because of this, it is not subsequently possible for you to withdraw the sample from further analyses or to update information for further use. And, it is not possible to give you or your doctor results. There are also no prospects of checking the accuracy of the results of pharmacogenetic tests from the study or gain any extra information related to clinical outcome.

Conclusion

When designing clinical trials, investigators and sponsors of new drugs should try, by consulting regulatory authorities and ethics committees, to find the best balance between achieving the objectives of the medical research, providing useful and usable pharmacogenetic data and putting in place measures adequate to protect the rights of the participant to privacy and to information.

The participant to the clinical trial should be provided - in advance of the finalization of the consent process and in advance of the sample for pharmacogenetic testing to be taken - verbally and in writing from the investigator with adequate information on the importance of your participation in the clinical trial. The participant should be given opportunities to choose whether or not to contribute to the pharmacogenetic testing, without this choice affecting the quality of his/her medical care.

Guidance for Industry

Pharmacogenomic Data Submissions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

Guidance for Industry

Pharmacogenomic Data Submissions

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to facilitate scientific progress in the field of pharmacogenomics and to facilitate the use of pharmacogenomic data in drug development. The guidance provides recommendations to sponsors holding investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) on (1) when to submit pharmacogenomic data to the Agency during the drug or biological drug product[2] development and review processes, (2) what format and content to provide for submissions, and (3) how and when the data will be used in regulatory decision making. Key information, including examples of when pharmacogenomic data submissions would be required and when voluntary genomic data submissions (VGDSs) would be welcome are provided in a separate companion document (*Pharmacogenomic Data Submissions, Attachment: Examples of Voluntary Submissions or Submissions Required Under 21 CFR 312, 314, or 601*).

For the purposes of this guidance, the term *pharmacogenomics* is defined as the use of a pharmacogenomic or pharmacogenetic test (see glossary for definitions) in conjunction with drug therapy. Pharmacogenomics does not include the use of genetic or genomic techniques for the purposes of biological product characterization or quality control (e.g., cell bank characterization, bioassays). The FDA plans to provide guidance on those uses at a future time. *Pharmacogenomics* also does not refer to data resulting from proteomic or metabolomic

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), in cooperation with the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug* or *drug product* includes human drug and biological products.

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techniques. This document is not meant to provide guidance on pharmacoproteomics or multiplexed protein analyte based technologies. However, the voluntary submission process described in this guidance may be used to submit such data if so desired.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The promise of pharmacogenomics lies in its potential to help identify sources of inter-individual variability in drug response (both effectiveness and toxicity); this information will make it possible to individualize therapy with the intent of maximizing effectiveness and minimizing risk. However, the field of pharmacogenomics is currently in early developmental stages, and such promise has not yet been realized. The Agency has heard that pharmaceutical sponsors have been reluctant to embark on programs of pharmacogenomic testing during FDA-regulated phases of drug development because of uncertainties in how the data will be used by FDA in the drug application review process. This guidance is intended to help clarify FDA policy in this area.

Sponsors submitting or holding INDs, NDAs, or BLAs are subject to FDA requirements for submitting to the Agency data relevant to drug safety and effectiveness (including 21 CFR 312.22, 312.23, 312.31, 312.33, 314.50, 314.81, 601.2, and 601.12). Because these regulations were developed before the advent of widespread animal or human genetic or gene expression testing, they do not specifically address when such data must be submitted. The FDA has received numerous inquiries about what these regulations require of sponsors who are conducting such testing.

From a public policy perspective, a number of factors should be considered when interpreting how these regulations apply to the developing field of pharmacogenomics. Because the field of pharmacogenomics is rapidly evolving, in many circumstances, the experimental results may not be well enough established scientifically to be suitable for regulatory decision making. For example:

- Laboratory techniques and test procedures may not be well validated. In addition, test systems may vary so that results may not be consistent or generalizable across different platforms. A move to standardize assays is underway, and much more information should be available within the next several years.

- The scientific framework for interpreting the physiologic, toxicologic, pharmacologic, or clinical significance of certain experimental results may not yet be well understood.