FDA invites pharmacogenomic data submissions

At present most pharmacogenomic data are exploratory in nature and FDA regulations do not require them to be included as part of a regulatory submission. However, in order to prepare for the future, the FDA has asked applicants to submit pharmacogenomic data on a voluntary basis.

It is not usual to submit pharmacogenomic data as part of an investigational new drug (IND), new drug (NDA) or biologics licensing application (BLA). However, FDA scientists do need to develop an understanding of the relevant scientific issues. Therefore, in a new Guidance for Industry on Pharmacogenomic Data Submissions, the FDA has asked sponsors to consider providing pharmacogenomic data to the FDA on a voluntary basis.

The guidance also announces the formation of an Interdisciplinary Pharmacogenomic Review Group (IPRG), which will review voluntary pharmacogenomic data submissions (VGDs). It will also
• communicate with sponsors
• provide guidance to reviewing divisions on required submissions
• work on ongoing pharmacogenomic data submission policy development.

The new guidance is intended to support scientific progress in the field of pharmacogenomics and to facilitate the use of pharmacogenomic data in drug development. It provides recommendations to sponsors holding INDs, NDAs and BLAs on
• when to submit pharmacogenomic data to the Agency during the drug development and review processes
• the format and content of submissions
• how and when the data will be used in regulatory decision-making.

Submission policy

Because FDA regulations have different requirements for the different types of applications, the guidance sets out different submission algorithms for each category. In doing so, it
• clarifies how the Agency will use pharmacogenomic data in regulatory decision-making
• distinguishes between pharmacogenomic tests that may be considered as probable or known valid biomarkers and other less well-
developed tests that are either observational or exploratory
• distinguishes between valid biomarkers that have been accepted in the broad scientific community and probable valid biomarkers that appear to have predictive value for clinical outcomes, but may not yet be widely accepted or independently verified.

Benefits of voluntary submissions
Voluntary submissions can benefit both the industry and the FDA, by providing a means for sponsors to ensure that regulatory scientists are familiar with and prepared to evaluate appropriately future genomic submissions. Knowledge of the following scientific issues is particularly relevant:
• the types of genetic loci or gene expression profiles being explored by the industry for pharmacogenomic testing
• the test systems and techniques being employed
• the problems encountered in applying pharmacogenomic tests to drug development
• the ability to transmit, store and process large amounts of complex pharmacogenomic data
• the scientific rationale for standardising naming and characterisation of the genes used on different genomic analysis platforms and for developing bioinformatics software programs used to evaluate pharmacogenomic data
• facilitating the identification of predictors of safety, effectiveness or toxicity.

The guidance contains a useful reference table (see Table 1) summarising the requirements for voluntary pharmacogenomic submissions.

Assurance on FDA review of VGDSs
The guidance also deals with how the FDA will use pharmacogenomic data in the application review process. It acknowledges concern over whether
• the Agency will raise new questions and require additional data based on findings from exploratory pharmacogenomic studies
• new studies will be required based on preliminary pharmacogenomic data
• indicated populations will be narrowed or restricted, based on the pharmacogenomic results in sub-populations
• new studies in sub-populations will be required if retrospective analysis suggests differential responses based on pharmacogenomic sub-grouping
• there are staff experts in the interpretation of pharmacogenomic data.

Within the guidance, the FDA makes a clear statement that it will not use genomic information submitted through the voluntary process for regulatory decision-making on INDs, BLAs or NDAs.

Table 1. Summary of the requirements for pharmacogenomic submissions.

<table>
<thead>
<tr>
<th></th>
<th>IND</th>
<th>New NDA, BLA or supplement</th>
<th>Previously approved NDA or BLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known valid biomarker</td>
<td>Must be submitted</td>
<td>Must be submitted</td>
<td>Must be submitted in annual report and as synopses or abbreviated reports</td>
</tr>
<tr>
<td>Probable valid biomarker</td>
<td>Does not need to be submitted, but FDA welcomes voluntary submission of such data in a VGDS</td>
<td>FDA recommends submission</td>
<td>Must be submitted in annual report and as synopses or abbreviated reports</td>
</tr>
<tr>
<td>Exploratory or research pharmacogenomic data</td>
<td>FDA welcomes voluntary submission of such data in a VGDS</td>
<td>FDA recommends submission. FDA also welcomes voluntary submission of such data in a VGDS</td>
<td>FDA welcomes voluntary submission of such data in a VGDS</td>
</tr>
</tbody>
</table>
FDA issues final risk minimisation guidances

On 24 March 2005 the FDA issued three finalised guidance documents, designed to help develop new ways and improve methods to assess and monitor the risks associated with drugs and biological products. These guidance documents, which apply to products in both clinical development and general use, form part of the FDA’s efforts to minimise risks while preserving the benefits of medical products.

Based on concept papers from March 2003 as well as comments made after a public workshop and the publication of draft guidances in May 2004, the final documents cover the following topics:

- pre-market risk assessment
- development, implementation and evaluation of risk minimisation action plans (RiskMAPs)
- good pharmacovigilance practices and assessment of reported adverse events.

Pre-market risk assessment

The guidance on pre-market risk assessment (available at <www.fda.gov/cder/guidance/6557fni.htm>) focuses on measures that companies might consider throughout all stages of clinical drug development. Thus, the section on special safety considerations describes how risk assessment can be tailored for products intended for chronic or paediatric use. General recommended risk assessment strategies include the use of long-term controlled safety studies, the enrolment of diverse patient populations and Phase III trials with multiple dose levels. Key components of the guidance include:

- providing recommendations to industry for improving the assessment and reporting of safety during clinical trials
- providing best practices for analysing and reporting data derived from a pre-approval safety evaluation
- building on existing FDA and ICH guidances related to pre-approval safety assessments.

RiskMAPs

The guidance on RiskMAPs (available at <www.fda.gov/cder/guidance/6358fnl.htm>) describes how the industry can address specific risk-related goals and objectives, and suggests tools to minimise the risks of drug and biological products.

Key components of the guidance include:

- establishing the consistent use and definition of terms, and a conceptual framework for setting...
up systems and processes to assure product benefits exceed risks
• broader input from patients, healthcare professionals and the public with regard to risk minimisation interventions
• evaluating RiskMAPs to ensure efforts are successful.

Pharmacovigilance
The guidance on pharmacovigilance (available at www.fda.gov/cder/guidance/6359OCC.htm) recommends reporting and analytical practices to monitor the safety concerns and risks of medical products in general use. Key components of this guidance include describing
• the role of pharmacovigilance in risk management
• good pharmacovigilance practice for identifying and describing safety signals, through investigation of signals beyond case review and interpreting signals in terms of risk
• the development of pharmacovigilance plans to expedite the acquisition of new safety data for products with unusual safety signals.

Latest developments in pharmacovigilance inspections in the UK

The annual symposium on Pharmacovigilance Inspections held by the Medicines and Healthcare products Regulatory Agency (MHRA) took place in London on 22 February 2005. Dr Julie Meeson of J3I Quality Management Services summarises the key news from the meeting:

• The inspectorate now falls within the ‘Inspection and Standards Division’, with ‘Enforcement and Intelligence’ becoming a separate group.
• Within the inspectorate group there are three GMP groups (with approximately 17 experts/inspectors), a GLP/Good Distribution Practice group (approximately seven experts/inspectors), one GCP group (three inspectors) and one pharmacovigilance inspection group (five experts/inspectors).
• UK Statutory Instrument SI 2004/3224 was implemented in January 2005, although a show of hands revealed that the audience was largely unaware of this new legislation. The legislation implements Regulation 726/2004 and Directive 2004/27/EC for nationally approved products. It covers a wide range of pharmacovigilance-related issues, including the responsibilities of the Marketing Authorisation Holder (MAH) with respect to preparation of risk management plans, communication of benefit/risk information and electronic reporting of adverse drug reaction reports from November 2005.
• Thirty routine statutory pharmacovigilance inspections have been conducted since July 2003. Whilst all the inspections were considered to be routine, in a number of instances known issues were used as triggers for scheduling the inspections of MAHs - these included poor compliance with the 15-day report timelines, poor-quality Periodic Safety Update Reports (PSURs) and other product quality issues. The pharmacovigilance inspection group has also participated in three CHMP-requested inspections for centrally authorised products.
• The strategy of the MHRA includes inspecting all MAHs within a 3-year period, with repeat inspections being conducted according to a risk-based approach. Companies with poor compliance may be re-inspected earlier. The MHRA also plans...
to implement a system of earlier notification of inspections, giving MAHs 3 to 6 months’ notice.

• The Summary of Pharmacovigilance System (SPS) Document, which collects information about the sponsor’s pharmacovigilance systems and products, is currently being revised. The updated version will be made available on the MHRA website.

• The inspection plan for the 2005 financial year (April 2005/6) was reported to include 60 pharmacovigilance inspections. Inspection fees are currently under review, but 2004/5 levels were £3542 (one to four products per MAH) to £10,120 (>50 products per MAH).

• The review of clinical trial safety reporting forms a routine part of the pharmacovigilance inspection. Common inspection findings in this area have included a lack of expedited reporting to investigators and ethics committees; suspected unexpected serious adverse reactions (SUSARs) not being unblinded prior to reporting to the MHRA; no review of non-serious adverse drug reactions; a lack of reconciliation between the safety and clinical databases; poorly controlled emergency contact details; and out-of-date Investigator Brochures.

• The ICH-E2E guideline “Pharmacovigilance Planning” was finalised in November 2004 and is awaiting implementation into European legislation. This document outlines the basis for safety specifications and pharmacovigilance plans, dynamic documents that require review and updates as new data become available and/or new issues arise.

• The key areas routinely covered during a pharmacovigilance inspection include: the role of the Qualified Person for pharmacovigilance; signal generation; the safety database; case processing and reporting; regulatory compliance; interactions with internal and external groups; pharmacovigilance audits; and the generic aspects of the system covered by SOPs, personnel and archiving.

• During a pharmacovigilance inspection conducted at one pharmaceutical company in 2004, it was reported that in excess of 40 interviews were conducted and approximately 200 documents requested.

• The Pharmacovigilance Consultative Committee was described as a group set up to facilitate communication between the MHRA and relevant professional organisations/trade associations (eg. the Association of the British Pharmaceutical Industry). The purpose of this consultative group is to provide a forum for advice, discussion and consultation with respect to Good Pharmacovigilance Practice and pharmacovigilance inspections. One of these meetings has already been held, with more expected in the future. A similar group - the GCP Consultative Committee - has been set up within the GCP area.

• The Pharmacovigilance Inspection Action Group (PV IAG) is a cross-agency group set up to help ensure that MAHs meet the required regulatory standards. Any critical/serious issues arising from pharmacovigilance inspections are referred to this group. In response to a question about imposing sanctions as a result of pharmacovigilance inspections, it was stated that although no legal sanctions have been taken against any MAH as a result of a pharmacovigilance inspection, cases relating to two companies have been forwarded to the PV IAG for follow-up. The issues that provoked these referrals included a lack of adequate global processes to ensure that local adverse reactions were reported; no access to the adverse drug reaction data at a single point within the European Economic Area; PSURs developed from a local perspective without including relevant global information; the Qualified Person for pharmacovigilance not being suitably experienced or trained; and no auditing to oversee the pharmacovigilance processes.

Details of other MHRA meetings can be found on the MHRA website at <www.mhra.gov.uk/conferences/index.htm>.

Whilst we try to ensure that all facts are correct prior to publication, readers should ensure that they validate any information provided prior to use.

News of the European data processing network and management system, EudraVigilance, can be found on the website <www.eudravigilance.org>.
Investigator fails to impress inspectors

A US investigator has recently received an FDA warning letter informing him of objectionable conditions found during a FDA inspection. It can take years for the consequences of problematic inspections to be overcome. Sponsors and investigators should take note of the problems, and ensure that they prevent them in their own trials.


Inadequate informed consent
21 CFR 50.20 requires an investigator to obtain the legally effective informed consent of the subject or their legally authorised representative before entry into a study. This must be done using a written consent form that embodies the required elements of informed consent (21 CFR 50.25). The form must be approved by the Institutional Review Board (IRB), and signed and dated by the subject or the subject’s legally authorised representative at the time of consent. Examples of the investigator’s failure to comply with these requirements included:
• that the consent document had no explanation of any alternative procedures that might be advantageous to subjects, and did not describe any reasonably foreseeable risks or discomforts to the subjects, or any reasonably expected benefits from the research
• a lack of documentation showing that the informed consent form used in the study was reviewed and approved by an IRB
• failure to provide all subjects with a copy of the informed consent form.

Inadequate records
21 CFR 812.140(a) requires a clinical investigator to maintain accurate, complete and current records relating to their participation in an investigation. The inspection revealed that the investigator had failed to meet this obligation:
• a file of correspondence with the IRB and the sponsor regarding approval of study protocols, informed consent, periodic reports, and submission and approval of advertisements was not maintained. For example, there was no documentation indicating that an advertisement run in a local Pennsylvania magazine recruiting subjects was ever submitted for IRB approval
• records of exposure to the device under study, including the date and time of each use, were not completed for all subjects.

Investigator part of IRB
The FDA also raised its concern that the investigator was a voting member of the IRB that reviewed the inspected study, noting that minutes from the IRB meeting of 21 January 2001 revealed he had been elected President of the IRB and that he had voted on the study. He participated and voted on issues relating to the study on four other occasions from January 2001 to February 2004.

Source: <www.accessdata.fda.gov/scripts/wlcfm/subject.cfm?fL=><wbr>

New guidance for device studies
The International Organization for Standardization (ISO) ISO14155 has become the international standard for the conduct of studies involving medical devices in Europe, the USA and Japan. A new book by Professor David Hutchinson and Dr Joris Bannenberg covering the essential ISO requirements will be available in June. Entitled “10 Golden ISO14155 Rules for Medical Device Studies”, it will be available from Canary Ltd (<www.canarybooks.com>).
Advice on study site closure

The Study Site Closure visit is usually the last occasion on which a study monitor visits a trial site. As part of a series of articles on SOPs in clinical research, Quality Assurance Journal (2004, Vol 8, p 271-277) has published examples of SOPs for this important visit.

The Study Site Closure visit is often the final opportunity to ensure that everything is in order prior to either audit or archiving. Closure procedures are undertaken to fulfil administrative, regulatory and human subject protection requirements following completion or premature termination of a trial at a particular site; in both cases they should be completed in accordance with an approved SOP. Once all subjects at a site have had their last study visit and all follow-up activities have been completed, the monitor should:

- make arrangements for the Study Site Closure visit;
- review previous visit reports and correspondence to identify any outstanding issues, paying particular attention to ongoing adverse events, unresolved protocol violations, clinical trial supplies, etc.; and
- prepare to take all outstanding items to the site.

During the visit

During the course of the Study Site Closure visit, the monitor should:

- sign and date the monitoring visit log and obtain a copy for the in-house files;
- ensure that a confidential subject identification list is available;
- meet with all relevant site staff, including pharmacy and local laboratory personnel if appropriate;
- collect all remaining documentation, eg. data query forms, serious adverse event reports and drug accountability records;
- clarify arrangements for the collection and/or destruction of remaining investigational medicinal product;
- make arrangements for the collection of emergency code-break envelopes and the removal of study samples;
- collect unused study documents, eg. case report forms, other materials and equipment;
- remind the investigator of his/her continuing obligation to clarify data until the database is locked; to follow up on study subjects, as required; to notify the ethics committee (IEC) that the trial is now complete; and to provide a final report or summary to the IEC;
- discuss requirements for document retention, and ensure that the investigator signs and dates an agreement to file and retain the documents appropriately;
- inform the investigator of the requirement for him/her to sign the final clinical report;
- make sure that the investigator understands the publications policy.

After the visit

Having completed the Study Site Closure visit, the monitor should:

- complete, sign, date and file the approved Study Site Closure visit report;
- send final letters to on-site personnel confirming the status of the study;
- provide the investigator with an end-of-study summary to sign and forward to the IEC;
- make arrangements for any outstanding site payments;
- inform relevant internal groups of site closure and update relevant tracking system(s);
- arrange for the investigator to sign the clinical study report, if required.

Premature termination/suspension

When a study is terminated prematurely, steps must be taken to maintain the safety of trial subjects and ensure all appropriate authorities are informed. Each site should be informed about how to deal with subjects who are currently enrolled in the trial.
FDA describes 2004 accomplishments

The FDA has issued a Talk Paper outlining its accomplishments in contributing to the protection and advancement of public health in the USA during 2004. A number of measures were taken last year to strengthen the safety of FDA-approved drugs. These included:

- an in-depth study of the effectiveness of the system that currently protects the safety of marketed drugs
- a programme for ensuring the opinions of the agency’s scientific reviewers are formally incorporated into decision-making processes
- workshops and advisory committee meetings to discuss complex drug safety and risk management issues
- publication of the Counterfeit Drugs Task Force Report
- activities of the Calories Count Obesity Working Group
- the Critical Path Initiative focusing on developing new medical breakthrough technologies
- Current Good Manufacturing Practices, an initiative designed to modernise the rules under which FDA-regulated products are manufactured
- The Good Tissues Practice Rule, defining the protection of patients treated with new technologies involving the use of human cells and tissues.

In 2004, the Center for Drug Evaluation and Research (CDER) met or exceeded its 2003 performance with regard to product approvals. Significant new products approved by CDER included:

- apomorphine hydrochloride for the treatment of patients with advanced Parkinson’s disease
- bevacizumab for metastatic cancer of the colon or rectum
- clofarabine for use in children with lymphoblastic leukaemia
- ziconotide for the management of chronic pain
- erlotinib for the treatment of metastatic non-small-cell lung cancer.

The Center for Biologics Evaluation and Research (CBER) continued to take responsibility for the safety of the nation’s blood supply and the safety and efficacy of counter-terrorism and other vaccines and anti-toxins, as well as cutting-edge technologies such as somatic cell and gene therapies. A number of significant approvals of new biological licences and biological licence supplements were granted.

Source: <www.fda.gov/bbs/topics/ANSWERS/2005/ANS01346.html>

Aims & Scope:

To keep readers informed of:

- changes in regulations, codes of practice, guidelines and new clinical research procedures
- clinical research methodology, statistical and legal issues
- news from important meetings and conferences
- correspondence, questions and answers, the grapevine, solutions to problems
- important information in publications and on the Internet
- training courses, jobs and other opportunities.

To provide information on:

- ICH developments and progress
- inspection and audit findings and their avoidance.

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