EFSPI-SFdS B&S
Joint European Statistics Meeting
Paris - 18-19 November 2010

Venue : Eurosites République
8 bis, Rue de la Fontaine au Roi
75011 PARIS, France
website: http://www.eurosites.fr/en/index.php

The **European Federation of Statisticians in the Pharmaceutical Industry (EFSPI)** and the **Biopharmacy and Health Group** of the **SFdS** ("*Société Française de Statistique*", French Society for Statistics) welcome you to their joint one and a half day European Statistical Meeting.
Speakers from industry, academia and regulatory will present and discuss on three topics of interest for all statisticians involved in the development on new therapies: **meta-analyses, multi-regional development plans, biomarkers**. A round table on the **future of the European statistical guidances will conclude the meeting**.

This scientific meeting is aimed at all statisticians who have an interest in Clinical Development and Registration of Medicines or wish to gain a greater understanding.

Organising Committee:

François Aubin - EFSPI / SFdS-B&S – Cardinal Systems
Maylis Coste - SFdS-B&S - I.R.I.Servier
James Matcham - EFSPI - Amgen
Emmanuel Quinaux - EFSPI - IDDI
Françoise Tondu - EFSPI / SFdS-B&S – Danone Research

Scientific Program

Agenda:

Thursday, November 18: 14h00-14h30: Welcome and introduction

14h30-17h00: The place of meta-analyses in the regulatory evaluation process

Friday, November 19: 8h30-10h30: The Use of Biomarkers in Drug Development

10h30-11h00: Coffee break

11h00-13h00: Multi regional development plans and EU Marketing Authorisation Applications

13h00-14h00: Lunch

14h00-16h00: The future of the European Statistical Guidance

16h00-17h00: Cloture of the meeting

Thursday November 18th 14h30-17h00

The place of meta-analyses in the regulatory evaluation process

During the decision process on a Marketing Authorization Application (MAA) for a new drug, two types of treatment effects are often considered: first, the effect versus placebo, which assesses the efficacy of a new drug and, second, the effect versus competitors, which enables to compare its benefit with some of the reference drugs.

Meta-analysis is a powerful method to estimate an overall treatment effect from a set of studies with similar objectives, designs, target populations and evaluation criteria, while accounting for variations of this effect across trials.

The efficacy of a new drug is usually estimated using a standard meta-analysis based on the placebo-controlled studies of the development plan. On the other hand, as only a small number of head to head active-controlled clinical trials are usually planned at the phase III stage, information obtained when comparing the new drug versus competitors is limited. As an alternative, indirect comparisons, mixed treatment comparisons and network meta-analyses may be carried out using both new drug trial results and published trial results based on comparators.

Standard and more complex meta-analyses raise several issues, such as the following:

- Selection of studies (comparator, population, evaluation criteria …),
- Trial results availability,
- Methodological/statistical aspects (assessment of heterogeneity and inconsistency, statistical framework – frequentist or bayesian)

The place and role of meta-analyses during the MAA evaluation by the EU agency should be investigated and discussed.

Chairman : Jean Marie Grouin, (University of Rouen, France)

Véronique Robert (I.R.I.Servier, France) : ***Industry views on the place of meta-analyses in the clinical development***

Today meta-analyses play a large part in the clinical development and, more generally, throughout the entire life span of a new drug. Firstly, meta-analyses on active comparators could be helpful to design future trials. Then standard meta-analyses are often carried out to summarize and accurately estimate the clinical efficacy of a new drug versus placebo (in areas where placebo-controlled trials are recommended) in the Applications for the Marketing Authorisation. Later on, indirect comparisons, mixed treatment comparisons or even network meta-analyses maybe sometimes useful to compare this new drug with competitors. For each setting and type of meta-analysis, interests, limits and topics of discussion will be presented.

Norbert Benda (BfArM, Germany): ***Regulatory issues in the use of meta-analyses in drug approval***

Although the pivotal proof of efficacy is usually based on the repeated evidence from individual studies, meta-analyses are increasingly being used for different purposes in the drug approval process. These include the justification of a non-inferiority margin, validation of surrogate endpoints, safety evaluations, especially for rare adverse events, as well as other supportive evidence to be used in the assessment of the risk benefit profile. The presentation covers the most important objectives starting from the EMA Points to consider on Meta-Analyses and extending the list of potential purposes for the use of meta-analyses in order to elaborate the scenarios and assumptions under which the different uses of meta-analyses comply with the statistical principles used in drug licensing.

Ann Whitehead (Lancaster University, UK): ***Meta-analysis methods for determining the effect of a new treatment from active-controlled clinical trials***

In placebo-controlled randomised clinical trials, the efficacy of a new treatment can be evaluated directly. Due to the number of treatments on the market today, it is often unethical to conduct placebo-controlled trials. Instead, the new treatment is compared directly with an already existing treatment (active control). Additional data on the active control may be available from randomised controlled trials of the active control against placebo, and meta-analysis methods may be used to obtain an overall estimate of the effect of the active control relative to placebo. An indirect comparison of the new treatment with placebo can then be made by combining the results from the meta-analysis with those from the active-controlled study. Issues such as heterogeneity between studies and treatment by covariate interactions will be discussed and illustrated by examples.

Friday November 19th 8h30-10h30 am

The Use of Biomarkers in Drug Development

The advent of new biomarker technologies is changing the way we do drug development where the development and use of biomarkers is becoming more and more important in the clinical development of new therapies.

- Biomarkers can be used in the proof of concept stage as surrogate endpoints for predicting whether clinical efficacy may be found.
- Biomarkers of disease are being used to see if the new therapy should only be used in sub-groups of patients.
- Safety Biomarkers are being developed to detect drug induced injury at a much earlier stage of development.

For each new use of biomarkers, some common problems exist. How do we demonstrate that a biomarker assay is reliable? How do we decide which biomarker to use? How do we validate a biomarker for use in clinical development, or even in clinical practice?
The statistical issues surrounding the development and use of biomarkers in drug development will be discussed in the context of some real examples of their use.

Chairman : Emmanuel Quinaux (IDDI, Belgium)

Tomasz Burzykowski (IDDI and Hasselt University, Belgium): ***Practical issues related to the use of biomarkers in a seamless Phase II/III design.***

Todd and Stallard (Drug Information Journal, 2005) proposed a seamless Phase II/III clinical trial design, which allows the use of a biomarker for a selection of a treatment in the Phase II stage of the trial. In this talk, the issues related to the practical use of the design will be described and illustrated by considering the set up of a trial in ophthalmology.

Eric Abadie (EMA): ***Use of Biomarkers in drug development. An EU regulatory perspective***

The talk, illustrated with real examples, will cover the following topics: Role of EMA in qualification of Biomarkers; Pharmacogenomics, drug approval, and CDx; Pharmacogenomics and post approval drug development; Genomics and drug label; Global regulatory thinking; Clinical trial designs; Personalised medicine and scientific bottlenecks and show how Genomics could change the global paradigm of drug development pre and post approval

Stefan Michiels (Institut Bordet, Belgium) : ***Integrating biomarkers in clinical trials: an overview***

Biomarkers have a growing role in clinical trials. Biomarkers can be based on imaging or on physiological parameters, but with the advent of the targeted therapy era, molecular biomarkers are becoming increasingly important. This talk focuses on biomarkers that modify the prognosis of individual patients ("prognostic" biomarkers) and on biomarkers that predict how individual patients will respond to specific treatments ("predictive" biomarkers, also called "effect modifiers"). Specific phase II and phase III clinical trials designs are reviewed in detail for their ability to validate the biomarker and/or to establish the effect of an experimental therapy in patient populations defined by the presence or absence of the biomarker. Contemporary biomarker-based clinical trials in oncology are used as examples.

Friday November 19th 11h00 -13h00

Multi regional development plans And EU Marketing Authorisation Applications

Drug development plans often include phase III clinical trials, which may be conducted exclusively or partially in non-European countries. The number of such trials has been increasing over the last decade.
Submissions are usually based on a common core Marketing Authorization Application (MAA) file but during the evaluation procedure, several issues are frequently raised on the transposition of the results of multiregional studies to the local population.
In order to anticipate these issues at the planning or analysis phase of the trials, several methodological and statistical aspects may be considered:

- Design and conduct (e.g. choice of inclusion/exclusion criteria, minimal number of EU patients, standardisation of criteria),
- Primary statistical model of analysis (e.g. handling of small centres, specification of key covariates, missing data),
- Definition of specific subgroups (e.g. intrinsic or extrinsic risk factors, geographical area),
- Extension and/or extrapolation of results from trials conducted partially or entirely outside Europe, to the EU target population.

Illustrated by actual examples, these topics will be discussed in the European context.

Chairman : Maylis Coste (I.RI.Servier, France)

Loïc Darchy (Sanofi Aventis, France) : ***Assessment of consistency of treatment effects in Multi-Regional Clinical Trials (MRCTs) & Sample size considerations for Japanese patients in a multi-regional trial based on MHLW guidance.***

The current trend of global new drug development strategy is to have a multi-regional trial approach (using primarily but not necessarily ICH definition of region, i.e. US, Europe and Japan). Regulators encourage sponsors to adopt a global development strategy while highlighting the underlying limitations and issues. In this context the extrapolation of results of clinical studies from a region to another one becomes more and more a key consideration. The main objective of this talk is to provide a statistical framework to assess the consistency of treatment effects in Multi-Regional Clinical Trials; A particular focus is on sample size considerations in the light of the Japanese guidance on Basic Concepts for Joint International Clinical Trials (September 2007). Adaptations to new requirements and/or environments can easily be implemented.

Andrew Thomson (MHRA, UK): ***Multi-regional trials: A regulatory perspective***

The talk will cover various methodological aspects of the current European regulatory position regarding the use of data generated outside the EU in applications for marketing authorisation application. Particular focus will be given to the data that are necessary and sufficient to allow 'bridging' from non-EU data in different circumstances. The regulatory requirements and expectations will be discussed, along with a series of examples across different therapeutic areas.

Friday November 19th 14h00 -16h00

Round table:
The future of the European Statistical Guidance

Since the publication of the CPMP Note for Guidance 'Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products' in December 1994, numerous guidance documents relevant to statisticians working in the field of clinical development of medicines have been adopted by the EMA. The release of the International Conference on Harmonisation (ICH) E9 (September 1998) and E10 (January 2001) notes for guidance, to cite only a few, with their worldwide field of application has been followed by the adoption of new purely European guidance documents (diversely named Points to Consider, Guidance, Reflection papers…). Some of these documents have a US equivalent when others do not.

The panel will discuss several aspects of the future of the European statistical guidance, e.g.

- Is a review of the oldest guidelines of interest?
- What is the impact of recent/future FDA guidelines (Adaptive Designs, Non Inferiority, …) on the European guidance?
- How should differences between European/US guidance documents be handled?
- Proposals for new guidance documents

Panelists :

- **Christophe Sauce (Boeringher-Ingelheim, France)**
- **Bernhard Huidfeldt (Consultant, Sweden)**
- **Norbert Benda (BfArM, Germany)**
- **Andrew Thomson (MHRA, UK)**
- **Kit Roes (Julius Center – UMC Utrecht, NL)**
- **Andy Grieve (ClinResearch - Germany)**