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Workshop on multiplicity issues in clinical trials

Report

Report of the workshop held on 16 November 2012 at the European Medicines Agency

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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Workshop on multiplicity issues in clinical trials

Workshop report

Disclaimer

This report was sponsored by the European Medicines Agency in the context of the Workshop on multiplicity issues in clinical trials. Although the conclusions it contains have been endorsed by the Agency, the views expressed are those of the authors and do not necessarily represent an official position of the Agency.

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1. Agenda

The CHMP points to consider on multiplicity issues in clinical trials came into operation in 2002. Since then, it has been proven to be useful for both, industry and regulators when planning and assessing confirmatory clinical trials. Meanwhile, methodological advances have been made in more complex multiplicity settings. In line with the development of these methods, an increasing complexity of the primary and secondary hypothesis framework is seen in confirmatory clinical trials.

This increasing complexity could be related to different dose groups or treatment regimens, interim analyses, multiple endpoints, and different subgroups. Other aspects like multiregional drug development may also add multiple testing problems for which general guidance is needed. Combinations of different sources of multiplicity may increase the complexity of the multiplicity problem dramatically.

The upcoming guideline is not to give advice on technical questions related to a new methodology. However, the increasing complexity of hypothesis frameworks and methods used may result in new issues and pose questions on general principles that haven't been considered before. These include consistency problems, the construction of simultaneous confidence intervals and the usefulness of newly developed methods, e.g., gatekeeping and fall-back procedures as well as graphical solutions in the regulatory context.

CHMP has recently published a concept paper on the update of the current guidance document. Since the guidance document was first drafted, new methods and concepts for addressing multiplicity in clinical trials have emerged not only in the scientific literature, but also in a growing number of marketing authorisation applications. Therefore, several additions and modifications may be needed to express the current state of scientific knowledge in this guideline.

Objectives of the workshop

- To discuss current standards and strategies to address multiplicity in clinical trials.
- To identify issues where the current PtC document on multiplicity issues in clinical trials needs to be updated and issues where guidance is missing so far.

Outcome of the workshop

The workshop provided an overview of the recent new developments in multiple testing strategies and an insight in multiple testing issues the pharmaceutical industry statisticians are confronted with presented in the various case studies. The guideline principles are still up to date but there are several new statistical methodologies which could be discussed in a regulatory guidance document.

Organising Committee

David Wright (Chair), Medicines and Healthcare Products Regulatory Agency, UK

Martin Posch (Co-Chair), Medical University of Vienna, Austria

Norbert Benda, Federal Institute for Drugs and Medical Devices, Germany

Armin Koch, Hannover Medical School, Germany

Patrik Öhagen, Medical Products Agency, Sweden

Steven Teerenstra, Radboud University, the Netherlands

Amelie Elsäßer, University Medical Center Mainz, Germany

Marisa Papaluca, European Medicines Agency, UK

Falk Ehmann, European Medicines Agency, UK

Programme Chairpersons

Session 1: Tomas Salmonson, Medical Products Agency, Sweden

Session 2: Patrik Öhagen, Medical Products Agency, Sweden

Session 3: Robert Hemmings, Medicines and Healthcare Products Regulatory Agency, UK

Session 4: Armin Koch, Hannover Medical School, Germany

Session 5: David Wright (Chair), Medicines and Healthcare Products Regulatory Agency, UK

List of speakers

Marisa Papaluca, European Medicines Agency, UK

Tomas Salmonson, Medical Products Agency, Sweden

Robert Hemmings, Medicines and Healthcare Products Regulatory Agency, UK

Kathleen Fritsch, Food and Drug Administration, USA

Eisuke Hida and Yuki Ando, Pharmaceuticals and Medical Devices Agency, Japan

Norbert Benda, Federal Institute for Drugs and Medical Devices, Germany

Patrik Öhagen, Medical Products Agency, Sweden

Thomas Zwingers, CROS DE GmbH, a CROS NT Group company

Peter Volkers, Paul-Ehrlich-Institut, Germany

Jiri Hofmann, ZENTIVA, Czech Republic

Thomas Lang, AGES, Austria

Vincent Haddad, Amgen Limited, UK

Franz Koenig, Medical University of Vienna, Austria

Jennifer Shannon, Cardiovascular Metabolic MDC, Statistics, GlaxoSmithKline, USA

Peter Bauer, Medical University of Vienna, Austria

Brian Austin Millen, Elli Lilly and Company, USA

Amelie Elsäßer, University Medical Center Mainz, Germany

Armin Koch, Hannover Medical School, Germany

Alex Dmitrienko, Center for Statistics in Drug Development, Quintiles, USA

Guenther Mueller-Velten, Novartis Pharma AG, Switzerland

Andrew Stone, AstraZeneca, UK

Frank Bretz, Novartis Pharma AG, Switzerland

Martin Posch (Co-Chair), Medical University of Vienna, Austria

David Wright (Chair), Medicines and Healthcare Products Regulatory Agency, UK

2. Abstracts

Session 1: Experiences with the current guidance document – how are multiplicity issues addressed in MAAs and their assessment?

Chairperson: **Tomas Salmonson**, Medical Products Agency, Sweden

"CHMP's view on multiplicity; through assessment, advice and guidelines"

By **Rob Hemmings**, Medicines and Healthcare Products Regulatory Agency, UK

Multiple analyses are needed to summarise and to facilitate inference from the vast amounts of data that are collected in the clinical part of a drug development programme. By convention, a problem of multiple testing arises when there exists 'more than one chance to win', but to win what: a marketing authorisation (MA); a trial that is formally (statistically) a success; or a 'claim' on an individual endpoint; and what defines a 'claim', an indication in Section 4.1 of an SmPC or any data in the product label?

Multiplicity may arise from multiple primary variables, multiple comparisons of treatments, repeated evaluation over time and/or interim analyses and methods to handle multiple testing in relation to the primary efficacy endpoint are well developed and in widespread use.

The talk will set the problem of multiple testing in the context of discussions at CHMP and its Scientific Advice Working Party, highlighting the importance of Type I error control for the primary analysis of a clinical trial but recognising that both licensing decisions and labelling decisions are holistic based on the totality of evidence available.

The talk will reflect on the pros and cons of updating the existing CHMP guidance document on this topic, considering that new methods are available and considering the discrepancy between the emerging trend to adjust for the multiple testing associated secondary efficacy endpoints and CHMP practice for decision making.

The talk will also touch briefly on whether there are any important 'multiplicity' issues associated with multi-regional drug development, or with the use of multiple Statistical Analysis Plans.

"The FDA perspective"

By **Kathleen Fritsch,** Food and Drug Administration, USA

There is generally a consensus that important 'claims' in clinical trials need to have overall Type I error rate control. However, the challenge often is how to translate the claims of interest into primary and secondary endpoints with appropriate and acceptable multiplicity control. Primary endpoints and secondary endpoints that could lead to additional claims need to be multiplicity controlled. However, minor variations on the existing endpoints may not always need to be under the multiplicity control

structure as these analyses would not lead to additional claims. Additional multiplicity challenges arise when studies are designed without a good match between the study goals and the selected multiplicity procedures (e.g. sequential methods proposed for secondary endpoints where there is no natural ordering for the endpoints), as the planned procedures may not lead to accepted outcomes.

"Current experience with multiplicity issues in PMDA"

By **Eisuke Hida**, Pharmaceuticals and Medical Devices Agency, Japan

Multiplicity issues are one of the statistical highly-discussed topics along with and related to adaptive designs, non-inferiority clinical trials, multi-regional clinical trials and subgroup analysis.

There is an ongoing change from avoiding multiplicity issues by focusing on one primary, to consideration of multiple aspects in an appropriate setting. One of the reasons is that there is heightened expectation for more efficient study designs and better characterization of new drugs. We have the experiences of several cases with multiplicity issues, such as multiple endpoints and response to different regulatory agencies, in our new drug review and clinical trial consultation meetings in PMDA. From the regulatory viewpoint, the overall Type I error must be kept at the certain level in confirmatory trials. Methods for dealing with multiplicity issues should be considered and appropriately applied responding to various situations.

Multiplicity is one of important issues in the sense that to improve the efficiency of development, to identify the characteristics of the drug and to provide the appropriate information to public. We should continue to share the experience and discuss more with various expertise between pharmaceutical industry, academia, and regulatory agencies.

"The update of the multiplicity guideline"

By **Norbert Benda**, Federal Institute for Drugs and Medical Devices, Germany

In 2002, the CHMP EMA Points to Consider (PtC) on Multiplicity Issues in Clinical Trials was adopted. It describes, among others, when adjustment is needed and when it is not, claims from multiple secondary endpoints, conclusions from subgroup analyses, interpretation of responder analyses in addition to the analysis of the original endpoint, and handling of composite endpoints. Although the PtC has been proven to be useful for both industry and regulators when planning and assessing confirmatory clinical trials, methodological advances have been made in more complex multiplicity settings. In line with the development of these methods, an increasing complexity of the primary and secondary hypothesis framework is seen in confirmatory clinical trials relating to multiple sources of multiplicity, as different dose groups or treatment regimens, interim analyses, multiple endpoints, and different subgroups.

The presentation briefly outlines the general principles related to multiplicity issues in drug approval, opposes the content of the PtC to newly evolving issues which may need further clarifications, and discusses the comments received on the CHMP Concept Paper on the Need for a Guideline on Multiplicity Issues in Clinical Trials, which was published in 2012.

The discussion includes the role of secondary endpoints, potential consistency and interpretational problems, the construction of simultaneous confidence intervals, issues arising in subgroup analyses, the need for a clearer terminology and how multiplicity procedures could be used to optimally support the risk benefit assessment.

Session 2: Usefulness and limitations of newly developed strategies to deal with multiplicity Part 1

Chairperson: **Patrik Öhagen**, Medical Products Agency, Sweden

"Multivariate Analysis of treatment in Multiple Sclerosis using the Wei-Lachin procedure"

By **Thomas Zwingers**, CROS DE GmbH, a CROS NT Group company

The study was an observer blind, randomized, placebo controlled, phase III trial in patients in an active phase of multiple sclerosis, using a three-group parallel design.

The main objectives of the trial were to determine the efficacy of drug in two different dosages in comparison to placebo. 5 co-primary efficacy criteria were defined:

- progression of the disease through the Expanded Disability Status Scale (EDSS),
- Standard Neurological Status (SNS),
- Ambulation Index (AI),
- the number of attacks requiring corticosteroid treatment, and
- time to the first attack requiring such treatment.

Nature of endpoints:

- EDSS is a scale ranging from 0 to 10 in steps of 0.5,
- AI is a scale ranging from 0 to 9 in steps of 1,
- SNS is a scale ranging from 0 to 99 in steps of 1,
- Number of attacks is a count variable, and
- Time to 1st attack is a duration.

There was no generally acceptable composite score that could be adopted.

A Bonferroni adjustment was impractical due to the large number of endpoints.

The hypothesis stated in this test is:

H_0 : $\Theta_k = 0$ for all k=1,2,3,4,5 (variables tested)
H_1 : $\Theta_k >= 0$ for all k=1,2,3,4,5 with at least one k>0

Where Θk are the Mann-Whitney-differences between the groups for the variables.

This hypothesis were tested in one combined hypothesis of "stochastic ordered alternatives" by the generalized Wilcoxon-Mann-Whitney test (Wei-Lachin procedure).

The Mann-Whitney difference is also a valid estimator for variables with missing values or censored observations such as the variable "time to first relapse requiring treatment."

The test statistic Z derived from the Wei-Lachin procedure has an asymptotic normal distribution and is defined as:

$$Z = (J'Q) / [J' S J] 1/2$$

with

- Q being the vector of differences between the treatment groups,
- S being the covariance-matrix of Q, and
- J being a vector of weights.

This test statistic is the nonparametric equivalent to Hotelling's one-sided parametric T^2 test.

If the test was significant, all 5 single criteria will be tested with alpha = 0.05 in the sequence EDSS, SNS, AI, number of attacks requiring corticosteroid treatment and time to the first attack requiring such treatment according to the principle of a priori ordered hypotheses.

The sequence of test EDSS, AI, number of attacks requiring corticosteroid treatment, time to the first attack requiring such treatment and SNS was a priori ordered and tests were interpreted as „statistically significant" as long as p-values are less than 0.05. After the first test, which is not significant, no further testing will be performed and differences between groups will be regarded as „not significant" (principal of a priori ordered hypotheses).

Study results:

Table 1: description of cohorts at baseline

	Treatment Group		
	Placebo	5 mg/sqm Mitoxantron	12 mg/sqm Mitoxantron
No. of patients	64	64	60
Type of MS			
Remittent progressive	29	37	28
Secondary progressive	35	27	32
EDS Scale			
3.0	1	7	6
3.5	9	4	10
4.0	20	19	20
4.5	9	5	5
5.0	2	5	0
5.5	6	11	5
6.0	17	13	14
Ambulation index			
0	0	1	0
1	5	4	9

2	29	32	29
3	20	18	8
4	5	6	10
5	5	3	4
SNS			
Mean	20.94	18.88	19.33
Std.	7.67	6.66	8.46
Min.	6.0	4.0	4.0
Median	22.0	19.0	19.5
Max.	40.0	35.0	42.0
Number of attacks			
Mean	1.31	1.42	1.27
Std.	1.14	1.26	1.12
Min.	0.0	0.0	0.0
Median	1.0	1.0	1.0
Max.	4.0	6.0	5.0

Table 2: Results of the the generalized Wilcoxon-Mann-Whitney test

	Placebo vs. 12 mg MTX	
	Mann-Whitney-difference (95% confidence interval)	p-value
Global difference	0.2941 (0.1644 – 0.4239)	<0.0001
Change in EDSS	0.2393 (0.0414 – 0.4373)	0.0194
Change in AI	0.2107 (0.0240 – 0.3974)	0.0306
No. Of attacks	0.3693 (0.1740 – 0.5645)	0.0002
Time to 1st treated attack	0.4431 (0.1974 – 0.6888)	0.0004
Change in SNS	0.2302 (0.0299 – 0.4305)	0.0269

Lachin, J.M., Some large-sample distribution-free estimators and tests for multivariate partially incomplete data from two populations, Statistics in Medicine 11 (1992) 1151-1170.

"Multiplicity corrections in Bioequivalence trials"

By **Jiri Hofmann**, ZENTIVA, Czech Republic

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. There are situations in drug development where design for more than two formulations is desired. In such studies, different comparisons arise which may result in an inflated rate of false positive conclusions (i.e. increase of the patient risk). If the aim of the study is to show that all test formulations are bioequivalent to the Reference product, no adjustment of the type I error is needed to keep the familywise type I error under control ('joint decision rule'). However, if there is the option to choose either one of the bioequivalent test formulations, the familywise type I error has to be adjusted ('multiple-decision rule').

A number of methods are available for controlling the type I error rate when multiple testing is employed. Among these methods, the Bonferroni correction is the most well-known, nevertheless more powerful methods such as method of Holm (1979, Scandinavian Journal of Statistics, pp. 65-70) or Hochberg (1988, Biometrika, pp. 800-802) or method of Dunnett (1955, Journal of the American Statistical Association, pp. 1096-1121) are available. As shown on an example of a 5-period, open label, randomized, cross-over, single-dose in fasting condition, the Holm and Hochberg procedure results in narrower confidence intervals as compared to Bonferroni. The Dunnett method is not compatible with EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr). This guideline requires separate analysis for each comparison after exclusion of the data from treatments that are not relevant for the comparison in question.

We would like to promote discussion on the method for controlling the type I error rate when multiple testing in bioequivalence trials is needed that would be mutually acceptable and would result in guidance recommendation. We would propose the method of Holm or Hochberg as methods of choice.

"Optimal multiplicity adjustment and the necessity to use separable multiple test procedures as gate keeper for secondary endpoint testing: case study"

By **Vincent Haddad,** Amgen Limited, UK

Phase 3 clinical trials may have several active arms and must adjust for multiplicity. Closed procedures such as Holm, Hochberg, Fallback and Dunnett are often chosen, but recent publications indicate that these procedures cannot hierarchically open the gate to the testing of the secondary endpoints and may not perfectly control the alpha risk on the parallel secondary endpoints testing. Only separable multiple test procedures such as Bonferroni or weight-based modifications of these procedures can be used as gate keepers.

We describe a phase 3 study design with 2 different doses of an experimental treatment and a placebo arm. We use the Hochberg procedure to test the individual dose groups vs. placebo for the primary endpoint. Then we use the Bonferroni procedure to test the primary endpoint as gate keeper leading to the secondary endpoint testing.

The Bonferroni procedure is more stringent than Hochberg. The Hochberg procedure maximizes the statistical power while the Bonferroni procedure ensures strict control of the alpha risks (primary and secondary endpoints), but it may lead to a situation with a significant p-value using the Hochberg but not allowing a subsequent test because the Bonferroni procedure may not be significant. In this scenario, the study will be declared successful regarding its primary endpoint while no secondary endpoint formal testing will be performed.

"Multiplicity Issues in Defining the Testing Strategy for Two Large Outcome Studies"

By **Jennifer Shannon** (as well as Rebekkah Brown, Greg Cicconetti and Rich Davies), Cardiovascular Metabolic MDC, Statistics, GlaxoSmithKline, USA

Background: The STABILITY (STabilisation of Atherosclerotic plaque By Initiation of darapLadIb TherapY) study and the SOLID-TIMI 52 (Stabilization Of pLaques using Darapladib-Thrombolysis In Myocardial Infarction 52) study are two similar, large, randomized, double-blind outcomes study currently ongoing in subjects with clinical manifestations of cardiovascular disease (chronic coronary heart disease (CHD) and post Acute Coronary Syndrome (ACS)). The primary endpoint in each study is the time to first occurrence of any component of Major Adverse Cardiovascular Events [MACE: death due to cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke]. Multiplicity issues arose in defining the testing strategy and controlling the Type I Error both within each study as well as in the pre-planned integrated analyses of both studies. Further issues arose in defining the gatekeeper strategy for conducting the integrated analysis. Consideration was given to the clinical importance of each endpoint as well as to the power the endpoints would have in the individual studies and the integrated analysis.

Decision: To address multiplicity concerns, it was decided that each endpoint would be tested for inference either in the individual studies or in the integrated analysis, but not in both. A hierarchical approach was defined for each study such that the pre-defined endpoints would be tested in a step-down manner at the same alpha level as the primary endpoint. If the primary endpoint in both STABILITY and SOLID-TIMI 52 shows a statistically significant benefit at the 0.20 level, at least one of which is statistically significant, and the integrated analysis of first occurrence MACE is significant at the 0.01 level then the integrated analysis will be conducted. A hierarchical approach will also be used to control Type I error for the endpoints pre-defined for the integrated analysis. A simulation study indicated that the Type 1 Error associated with the first step in the integrated hierarchy is less than 5% with this proposed gate keeper strategy.

Session 3: Implications of multiplicity for estimation

Chairperson: **Robert Hemmings**, Medicines and Healthcare Products Regulatory Agency, UK

"Multiplicity and Estimation"

By **Peter Bauer**, Medical University of Vienna, Austria

Bias and mean square error are discussed in a scenario when - after having observed a fraction r ($0 \leq r \leq 1$) of the planned total sample in each treatment group - only the best treatment and the control are selected for the second stage in a k treatment versus control design. It is emphasized that the maximum (worst case) selection bias is largest in conventional fixed sample size designs when treatment selection is done at the scheduled end. Further the bias at drug registration is shown which

arises from regulatory requirements (e.g., requiring statistically significant treatment effects in a single pivotal trial or in two pivotal trials). Methods to correct for the selection bias are sketched and the problems of constructing multiple confidence intervals dual to multiple step-wise test procedures are discussed.

Session 4: Usefulness and limitations of newly developed strategies to deal with multiplicity Part 2

Chairperson: **Armin Koch**, Hannover Medical School, Germany

"Gatekeeping strategies in Phase III clinical trials with multiple endpoints and doses"

By **Alex Dmitrienko** (and Olga Marchenko), Center for Statistics in Drug Development, Quintiles, USA

This presentation will focus on multiplicity issues arising in confirmatory Phase III clinical trials with multiple sets of objectives. Case studies will be presented to define most common multiplicity problems in confirmatory trials utilizing multiple endpoints and doses to better characterize the efficacy and safety profiles of new treatments. This includes a case study based on the lurasidone development program in schizophrenia (Meltzer et al., 2011). Clinical trials within this program employed several endpoints (a primary endpoint and one or two key secondary endpoints) evaluated at two or three dose levels.

Multiple sets of objectives induce inferential problems with several sources of multiplicity. For example, multiple primary and secondary endpoints in the lurasidone example define one source of multiplicity and multiple dose-control comparisons define another source of multiplicity. In order to protect the overall Type I error rate in complex multiplicity problems of this kind, gatekeeping strategies are commonly used based on gatekeeping procedures that account for the hierarchical structure of tests associated with the endpoints and dose-control comparisons. Gatekeeping strategies have been successfully applied across a large number of development programs to provide information on the treatment effects across multiple trial objectives.

This presentation will discuss key considerations arising in the process of developing and applying gatekeeping procedures:

1. Use of trial-specific information, including logical and distributional relationships among the trial objectives.
2. Criteria for selecting most relevant and powerful gatekeeping procedures.

The methods and principles discussed in this presentation will be illustrated using the lurasidone Phase III trials in patients with schizophrenia.

"Novel multiple testing procedures for structured study objectives and families of hypotheses"

By **Guenther Mueller-Velten** (as well as Frank Bretz, Bjoern Holzhauer and Willi Maurer), Novartis Pharma AG, Switzerland

Confirmatory clinical trials are becoming increasingly more complex, often comparing multiple doses or treatments with a control for several primary and secondary endpoints. The multiple study objectives are reflected by structured families of hypotheses that are characterized by multiple groups of "parent"

primary hypothesis and “descendant” secondary hypotheses. Novel graphical approaches for constructing and visualizing complex multiple testing procedures with a focus on structured families of hypotheses are well suited to provide transparent decision strategies. In addition many “classical” multiple testing procedures as well as recently developed gatekeeping procedures can be represented visually by using the graphical approaches. Their main advantages are, however, that multiple testing procedures tailored to structured clinical trial objectives can be easily communicated to clinical teams und inherently control strongly the overall Type I error rate across all primary and secondary hypotheses.

We illustrate this methodology with a large Phase III trial for the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients, where three doses of a test drug are compared with placebo. The primary endpoint is time to first occurrence of a major adverse cardiovascular event (MACE). The two secondary endpoints are (i) time to first occurrence of a composite of MACE and hospitalization for unstable angina requiring revascularization, and (ii) time to new onset of Type 2 diabetes among those patients with pre-diabetes at randomization. The overall Type I error rate has to be controlled for the resulting nine hypotheses, where the three endpoints form a structured "parent-descendant" relationship for each of the three dose-control comparisons. A further level of multiplicity is introduced through pre-specified interim analyses that allow for early stopping for either futility or convincing evidence of efficacy.

“Multiplicity: Is it of value to make it so complicated?”

By **Andrew Stone**, AstraZeneca, UK

Approaches to control multiplicity have become increasingly sophisticated, which are underpinned by the concept of strong control of Type I Error. The presentation challenges whether it is of value to make our multiplicity approaches so complicated, which, in order to satisfy Strong Control*, is in danger of becoming self-defeating and disregarded in interpretation. We should then question whether the extra complexity adds value in the assessment of medicines.

It is argued that we should instead take a more considered approach in order to:

- Decide whether a drug should be licensed
- Provide analyses that inform prescribers as to the nature of the benefit and risks

After a reminder of the approaches to ensure a trial is not falsely declared as positive, the presentation will be structured as follows, and exemplified by means of examples:

- How Strong Control requires a ranking of endpoints and a blurring of the boundaries between primary and secondary endpoints
- Describe the tension in any hierarchy to choose whether to focus on those endpoints that are most likely to be significant or those that are less likely to be significant but would be regarded as medically most important, and creation of strategies to cope with both desires.
- How complexity starts to increase as more experimental arms (e.g. multiple dose arms) are added
- The further level of complexity required for group sequential designs as this necessitates consideration of all possible permutations of correlation between endpoints and true effects, even though the inflation on type I error is at worst marginal in all realistic scenarios

The presentation will conclude by questioning whether rigorous application of Strong Control may lead to creation of an approach that will largely be disregarded. An alternative approach is then presented where the focus is on rigorously and fully controlled Type I Error amongst the primary endpoints;

where if the trial is positive, the role of secondary endpoints is to describe the nature of any benefit. Nevertheless, in the proposed approach, the analysis plan for secondary endpoints should be sensible and group endpoints according to the separate clinical questions they address– and within those groupings exercise alpha control.

Finally, a reminder is given that we should also concentrate as much on design and trial conduct measures to minimise possible bias so that Type I Error is actually controlled as intended regardless of methodology.

*Strong control defined as: The probability of rejecting any (i.e. one or more) true null H is at most 2.5%, irrespective of how many and which Hs that actually are true or false.

Session 5: Closing remarks

By **David Wright**, Medicines and Healthcare Products Regulatory Agency, UK

3. Biographies of the chairpersons and speakers

David Wright

David Wright has worked at the MHRA for 13 years as a statistical assessor and is the Chair of the MHRA Scientific Advice Letters Review group and Deputy Manager of the Statistics Unit. He is the Chair of the Biostatistics Working Party (BSWP) and is an alternate member of Scientific Advice Working Party (SAWP). David writes assessment reports on methodological aspects of licensing applications for CHM and CHMP, advises companies on methodological aspects of their clinical development programme via national and CHMP scientific advice, is involved in writing methodological guidelines for CHMP. Before joining the MHRA David was a Lecturer in Medical Statistics at University College London.

Martin Posch

Martin Posch is professor of Medical Statistics at the Medical University of Vienna. Lastly, he worked as statistical expert at the European Medicines Agency (London, UK) in the Human Medicines Development and Evaluation Unit, where he contributed to guideline development and the assessment of study designs. He is currently also observer of the Biostatistics Working Party (BSWP) since September 2012. He has a PhD in Mathematics from the University of Vienna and was scientific assistant and associate professor at the Medical University of Vienna until January 2011. His research interests are group sequential trials, adaptive designs and multiple testing, focusing on applications in clinical trials and Bioinformatics. Martin Posch serves as Associate Editor of Biometrics and Biometrical Journal.

Norbert Benda

Education and scientific training:

1992	Awarded Doctorate in Mathematics, Free University of Berlin, Germany
1988	Awarded Diploma in Mathematics, Technical University of Aachen, Germany
1982-1988	Study of Mathematics, Technical University of Aachen, Germany

Professional career:

Since 2/2010	Group Head Biostatistics and Special Pharmacokinetics, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany
	since 2010: Alternate Member of the EMA Scientific Advice Working Party
	since 2011: Member of the EMA Biostatistics Working Party
2006-2010	Expert Statistical Methodologist, Statistical Methodology/CLASS, Novartis Basel, Switzerland
	2009-2010: Senior Expert Statistical Methodologist
1997-2006	Biostatistician, Schering AG, Berlin, Germany
	2005-2006: Principle Statistical Researcher
1993-1997	Research Assistant, Department of Medical Biometry, University of Tübingen, Germany
1989-1993	Research Assistant, Institute of Mathematics, Free University of Berlin, Germany
1984-1988	University Tutor for Mathematics and Statistics, RWTH Aachen, Germany

Armin Koch

Professor Armin Koch studied mathematics and chemistry at Heidelberg University. He has been a research assistant at the German Centre for the Research on Cancer (DKFZ) between 1984 and 1991. Thereafter he has been an employee at the institute of Medical Biometry at Heidelberg University until in 1999 when he joined the Federal Institute for Drugs and Medical Devices (BfArM) in Germany. From 2001 to 2008 he was head of the unit “Biostatistics and Experimental Design”. Since 2008 he is Director of the Institute for Biostatistics at Hannover Medical School. Prof. Koch is a member of the Scientific Advice Working Party (SAWP) and the Biostatistics Working Party (BSWP) at the European Medicines Agency (EMA).

Patrik Öhagen

September 2005	MPA, Regulatory Agency, Statistician
January 2000-September 2005	SLU, University, Teaching/Consulting statistics and epidemiology
August 1995 – January 2000	Pharmacia, Pharmaceutical industry, Statistician
August 1990-August 1995	Statistics Sweden, Census Bureau, Survey Statistician

Steven Teerenstra

Steven Teerenstra is statistical assessor at the Dutch Medicines Evaluation Board, member of the Biostatistics Working Party and biostatistician/researcher at Radboud University Nijmegen Medical Center.

Amelie Elsäßer

Dr. Amelie Elsaesser studied statistics at the Ludwig Maximilian University of Munich, Germany. During her studies she spent two terms at the University of Glasgow, Scotland. Since 2008 she has been working as a biostatistical researcher and consultant for medical doctors at the Institute of Medical Biometry, Epidemiology and Informatics (IMBEI) at the University Medical Center Mainz, Germany. In 2011 she joined the EMA as a National Expert on Secondment.

Marisa Papaluca

Internal Medicine specialists, Marisa Papaluca joined the European Medicines Agency (EMA) in London, UK in late 1994 and occupied scientific and managerial positions in the EMA Unit for Human Medicines Development and Evaluation. Deputy Head of Quality up to 2002 and of the Efficacy and Safety Sectors up to 2009, Marisa is currently Head of Section for Scientific Support and Projects providing scientific support to the Agency core activities in transversal and multidisciplinary areas such as clinical trials statistical methodology, raw data analysis, non-clinical drug development, pharmacogenomics and nanotechnology.

The Section is also in charge of the EMA Innovation Task Force, reference group at EU and international level for innovative pharmaceuticals developments with current increasing activities on novel clinical trials designs, genomic biomarkers, combined products, nanomedicines, and synthetic biology. The section also runs the Business Pipeline activities contributing to the Agency's preparedness toward the upcoming Marketing Authorisation submissions.

Falk Ehmann

Falk Ehmann, MD, PhD, MSc, is currently working in the Scientific Support and Project Section of the European Medicines Agency (EMA). His main responsibilities include holding the Scientific Secretariat of the Innovation Task Force promoting Innovation and new methodologies in drug development and being involved in the development of policies, guidelines and the annual working program in these areas. Areas of expertise include Pharmacogenomics, Nanomedicines and Borderline and Combined Medicinal Products (including Devices), and other -omics especially in connection with Personalised Medicine. He has special expertise in the development of Similar Biological Medicinal Products with focus on monoclonal antibodies and Vaccines. He held various positions and responsibilities at the EMA since 2004, including Scientific Advice during product development and working in the Oncology and Anti-Infectives therapeutic area of the EMA Unit for Human Medicines Development and Evaluation.

Prior to joining the EMA, Dr. Ehmann was a Public Health Researcher at the Robert Koch Institute in Berlin and Medical Intern at different University Hospitals including Bordeaux, Munich, Berlin, Geneva and Tanzania where he achieved his Master in Public and International Health. Falk Ehmann wrote his PhD thesis in the department for Cellular Signal Transduction at the University Hospital Hamburg-Eppendorf in the Centre of Experimental Medicine of the Institute of Biochemistry and Molecular Biology.

Tomas Salmonson

Tomas Salmonson, M.Sc., PhD, brings outstanding experience and expertise from a long career in the regulation of medicines both on a national and European level to his new role. A pharmacist by training, he is currently senior scientific advisor at the Swedish Medical Products Agency (MPA) in Uppsala, Sweden. He has been a member of the CHMP for more than 12 years. Since 2007, Dr Salmonson has been the elected vice-chair of the Committee. He has been acting chair of the CHMP since April 2012 and is also chair of the EMA Pharmacokinetics Working Party.

Robert Hemmings

Rob Hemmings is a professionally qualified medical statistician. He has been with the Medicines and Healthcare products Regulatory Agency (previously Medicines Control Agency) for 11 years and heads the group of medical statisticians. Much of Rob's time is spent educating medical colleagues in the importance and artistry of clinical trial statistics; their use in proof and in obfuscation. Rob currently holds the following positions within the European drug regulatory system:

- CHMP member: CHMP is the body responsible for preparing the opinions of the European Medicines Agency on all questions concerning medicinal products for human use. Rob is one of the 32 voting members of this key European committee.
- Chair of the CHMP's Scientific Advice Working Party (SAWP) with responsibility for preparing advice to the pharmaceutical industry on the appropriate tests and trials to conduct in the development of a medicine for marketing authorisation. This group includes approximately 50 regulatory scientists from across the European regulatory network and handles approximately 400 scientific advice / protocol assistance and qualification of biomarker procedures each year.
- Rob is also a member of CHMP's Biostatistics working party with responsibility for giving advice on matters relating to clinical trial methodology across the EU regulatory network.

Rob regularly speaks at national and international scientific meetings on a broad range of topics relating to medical statistics and drug licensing.

Kathleen Fritsch

Kathleen Fritsch is a Mathematical Statistician at the U.S. Food and Drug Administration (FDA). As a statistical reviewer she reviews protocols and drug and biologics applications primarily for dermatology and dental products. She is a member of the Multiple Endpoints Working Group at FDA that is preparing a draft guidance document. She received her Ph.D.in statistics from The Ohio State University. Prior to joining the FDA, she was an assistant professor of mathematics and statistics at the University of Tennessee at Martin.

Eisuke Hida

Experience:

2011 – Present	Biostatistics Reviewer: Office of Drug III
2007.10 - 2010.12	Senior Researcher: Department of Technology Assessment and Biostatistics, National Institute of Public Health, Japan
2002.10 - 2007.09	Biostatistics Reviewer: PMDEC (Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences, - 2004.03)
	and Reorganization PMDA (2004.04 -)

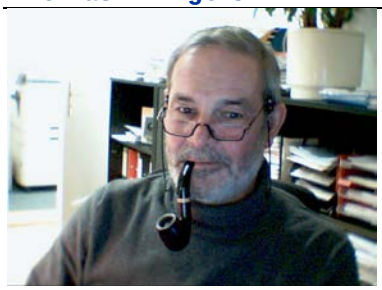
Education:

Doctoral Program in Mathematics, University of Tsukuba, Japan

Ph.D., Natural science

Graduation Date: March 2002

Thomas Zwingers



Thomas Zwingers graduated at the Technical University of Munich, Germany. After 10 years working at the university in a biometric center for therapeutic studies, he founded his own CRO, estimate GmbH, in 1992. In 2010 he joined CROS NT as a scientific director and later became Senior Director Consulting. His long experience made him an expert in statistical design and methods to optimize clinical trials. He was a consultant to pharmaceutical companies in regulatory processes and member of Independent Data Monitoring Committees in his role as independent statistician. His main experience is in Oncology, Dermatology and Multiple Sclerosis.

Peter Volkers

Peter Volkers is a mathematician and holds a Ph.D. in econometrics. After his university career he worked as a biostatistician in the pharmaceutical industry. Since 2001 he is at the Paul-Ehrlich-Institute (PEI), Federal Agency for Sera and Vaccines of Germany, heading the section Biostatistics. This section is responsible for all statistical issues related to licensing and regulation for drugs in the responsibility of the Paul-Ehrlich-Institute. As a member of different working parties (EWP (until 2010), VWP (until 2010), BSWP (since 2009)), Peter Volkers participated in various regulatory activities at the European Medicines Agency (EMA).

Jiri Hofmann

Dr. Hofmann studied pharmacy at the Charles University in Prague, Czech Republic. He obtained his Ph.D. at the Swiss Federal Institute of Technology (ETH), Zurich, Switzerland. During his thesis work, he was focused on studying tight junctions as a possible target for drug transport enhancement. In 2007, he joined Zentiva (a sanofi company) where he currently works as Clinical Development Manager. In his position, he is responsible for design, planning and realization of bioequivalence trials for generic oral dosage forms with particular interest in enteric coated drug formulations. He is also focused on pharmacokinetic and statistical evaluation of bioequivalence trials.

Thomas Lang

Thomas Lang has more than 16 years of experience in the field of biostatistics. He spent eight years in academic medical research, followed by almost three years in clinical research in the pharmaceutical industry. He currently works as senior statistical assessor for the Austrian Agency for Health and Food Safety. At the Agency, Thomas is heading the Group Statistics and Methodology.

As a member of the Scientific Advice Working Party and as co-chair of the Biostatistics Working Party at the EMA, he is heavily involved in different tasks related to methodological and statistical issues in the regulatory field. Thomas has published and co-authored in statistical and medical journals, covering a broad spectrum of medical and methodological domains, including adaptive designs. In the past, he gave many biostatistics courses and lectures, especially for non-statisticians.

Vincent Haddad

- Graduated from the ENSAI in Rennes (France): National School of Statistics and Information Analysis.
- Worked as an epidemiologist in various places.
- Then as a biostatistician in the largest cancer hospital in France (Institut Gustave Roussy).
- Now at Amgen Ltd in Cambridge (UK) for nearly 6 years.

Franz Koenig

Dr. Franz König is currently Assistenz Professor at the Section of Medical Statistics at the Medical University of Vienna, Austria. From 2008 till 2010 he was seconded to the European Medicines Agency (London, UK) as statistical expert in the Unit Human Medicines Development and Evaluation. At the EMA he held the Scientific Secretariat of the then newly founded Biostatistics Working Party (BSWP). He was involved in the development of guidelines and assessment of statistical methods and clinical trial protocols. His main research interests are multiple testing, adaptive/flexible designs, interim analyses and data safety monitoring boards (DSMB). Franz König has served as Guest Editor for Special Issues in Biometrical Journal and Statistics in Medicine.

Jennifer Shannon

Jennifer Bourbina Shannon received a Bachelors and Masters of Science in Biostatistics from the University of North Carolina at Chapel Hill. Ms. Shannon has been an employee of GlaxoSmithKline since 2002 in the Cardiovascular therapeutic area. Ms. Shannon has been involved as a lead statistician in the darapladib program since 2009. She has previously worked in the areas of Overactive Bladder and Benign Prostatic Hyperplasia. Statistical interests include time to event data, categorical data and multiplicity.

Peter Bauer

Peter Bauer graduated at the Technical University of Vienna in 1966. After that he worked in the Computer Unit of the Medical Faculty at the University of Vienna. He got his PhD in applied mathematics from the Technical University of Vienna in 1970. From 1971 to 1972 he stayed as a Research Fellow at the Department of Statistics, University of Edinburgh. Then he joined the Department of Medical Statistics at the University of Vienna, from where he changed to the University of Cologne in 1985, having been appointed as the Director of the Department of Medical Documentation and Statistics. In 1994 he accepted an offer to return to Vienna for chairing the Department of Medical Statistics at the University of Vienna. He retired from his university career in 2010 as the head of the Center of Medical Statistics, Informatics and Intelligent Systems at the Medical University of Vienna. Professor Bauer has published numerous original research papers on statistical methodology and cooperative research with medical scientists. His main research interest is in sequential and flexible designs, multiple inference and quality control. He has been chief editor of Biometrical Journal and member of various scientific societies, editorial boards of scientific journals, in scientific advisory boards, in data safety monitoring boards, ethical committees and in advisory boards for governmental regulatory institutions. Currently he serves as an expert in the Paediatric Committee of the European Medical Agency.

Brian Austin Millen

Brian A. Millen, Ph.D., is a Research Advisor and Group Leader within Global Statistical Sciences at Eli Lilly and Company, where he provides statistical and strategic consulting for late-phase psychiatry product development programs. Dr. Millen's current research interests include multiple testing procedures, design and analysis methods to enable tailored therapeutics, and quantitative benefit-risk assessment. In addition to methodological research and his drug development contributions, Dr. Millen teaches statistics courses to broad audiences in the industry and is a committee chair of the American Statistical Association. Dr. Millen holds a B.A. in Mathematics from the University of Georgia and an M.S. and Ph.D. in Statistics from The Ohio State University.

Alex Dmitrienko

Alex Dmitrienko, PhD, Executive Director, Quintiles Innovation, has been actively involved in biostatistical research and has published over 70 papers on key topics in clinical trial statistics, including multiple comparisons, subgroup analysis, adaptive designs, and analysis of safety data. He has authored/edited two SAS Press books (*Analysis of Clinical Trials Using SAS*, *Pharmaceutical Statistics Using SAS*) and a Chapman and Hall/CRC Press book (*Multiple Testing Problems in Pharmaceutical Statistics*). He is an Associate Editor for Statistics in Medicine and Biometrics, and a Fellow of the American Statistical Association.

Guenther Mueller-Velten

Guenther Mueller-Velten, Director Statistical Scientist, Novartis Pharma AG, Basel is Diplom Wirtschafts-Mathematiker (Mathematics and Economics) with emphasis on Statistics from University of Trier, 1987. He has 25 years experience in international clinical drug development including 10 years as Trial and Project Statistician at Behringwerke in Germany in multiple therapeutic areas; 5 years as Head of Biostatistics and Clinical Statistics Americas at Centeon / Aventis-Behring in USA; since 10 years at Novartis in Switzerland in various roles (Group Head Biostatistics in the Cardiovascular, Transplantation and Infectious Disease areas, Global Program Head and most recently Clinical Science Unit Lead Statistician for the Cardiovascular disease area). In his current role, he provides strategic and scientific input to all cardiovascular clinical development programs and ensures that state-of-the-art and novel statistical methodologies are implemented consistently in cardiovascular trials (including large outcome trials) sponsored by Novartis. Areas of interest and expertise include multiplicity, recurrent event data analysis, and sample size re-estimation.

Andrew Stone

Andrew Stone is the Therapeutic Area Statistical Expert for oncology at AstraZeneca. Andrew joined AstraZeneca, then called ICI pharmaceuticals, in 1992 having obtained an MSc in Medical Statistics. In his current role he advises the Therapeutic Area Leadership Team on statistical aspects of oncology projects at AstraZeneca. Prior to his currently role, Andrew has worked within the project teams for many of the oncology drugs.

Frank Bretz

Frank Bretz joined Novartis in 2004, where he is currently Global Head of the Statistical Methodology group. He has supported the methodological development in various areas of drug development, including dose-finding, multiple comparisons, and adaptive designs. He is an Adjunct Professor at the Hannover Medical School (since 2007) and the Shanghai University of Finance and Economics (since 2011). He was treasurer of the German Region of the International Biometric Society (IBS) from 2004 until 2010, head of the working group on “Statistical Methods in Bioinformatics” of the German Region / IBS from 2004 until 2007, council member of the IBS from 2010 until 2012, and is currently a member of the American Statistical Society (ASA) Committee on International Relations in Statistics. He currently serves as an associated editor for Biometrics, Statistics in Medicine, BMC Medical Research Methodology, and Journal of Biopharmaceutical Statistics. He has authored or co-authored more than 80 articles in peer-reviewed journals and four books.