

Protocol of the first meeting of the Special Interest Group (SIG) Regulatory Affairs (SIGRA)

Meeting Date: Monday, 29 September 2003

Start of the Meeting: 10.00 a.m.

End of the Meeting: 3.30 p.m.

Meeting Place: Headquarter of EAPB, Kelchstraße 31, D-12169 Berlin

Participants: Marival Bermejo (Universidad de Valencia)
Annette von Drygalski (metaGen Pharmaceutical GmbH)
Bettina Fiedler (Schering AG) (only 10.00-12.00 a.m.)
Rainer Müller (PharmaSol GmbH)
Axel Wenzel (p.ss.t)
Andreas Woppmann (Biopharm. Consultant)

General information with regard to participants:

A few more representatives of companies had indicated their presence (e. g. Boehringer Ingelheim, NovoNordisk, ProBioGen) but could not make it due to unforeseen circumstances. It needs to be noted that the meeting was organised relatively on short term notice. The next meeting will be fixed much more in advance to enable everybody interested to join the meeting.

TOP 1: General introduction (Müller)

Müller gave a short introduction why this special interest group was founded by EAPB. The aim of this SIG is to use the position of EAPB in Europe to provide actual benefits for its members, especially its corporate members. Regulatory issues should be identified which create problems for the corporate members. The aim is to change laws, guidelines and directives to get things organised in a more pragmatic, workable way. In this SIG four or five important topics should be identified within the next months and the authorities should be approached for improving the regulatory situation. This includes also regulations which might come up in the near future. In such cases EAPB should provide discussion papers which then can be used by the authorities as a working paper for future regulations.

Within this context there was a short discussion how this SIG should be called, that means generating an abbreviation. It was unanimously decided for the name SIGRA (Special Interest Group Regulatory Affairs).

Müller pointed out the three most important points of this first meeting:

1. EU status and EU submission for funds
2. Identification of e. g. three most important topics to work on first (target: development change of guidelines)
3. Structure of the SIG, that means how to organise the work!

TOP 2: Short presentation of each present member

Müller welcomed everybody who joined the meeting. He stressed that this first meeting is of high importance for the future of SIGRA because first aims are defined. There was a strong participation from Berlin, especially it was welcomed that Dr. Fiedler from Schering AG could make it to participate at least in the morning of the meeting.

Everybody introduced himself. It was briefly discussed that also the next meeting should be held in Berlin because so many of the active members are coming from Berlin. For the next meeting also participation from ProBioGen, Berlin is expected.

TOP 3: Members not present but interested

Wenzel informed that there are members who are interested but do not have the time to participate in the meetings themselves, however they would like to be kept informed by being on the mailing list. These people offered to contribute to the work of SIGRA by mailing their ideas and proposals. Basically this is an excellent working platform having a core group and getting input from many other people.

Apart from Dr. Bermejo no academic people were present which is due to the fact that the universities do not provide travel support. To integrate also people with academic background it was considered highly important to get funds from the European Union (see below). In addition it was proposed to lock in external people via teleconference at the next meeting. It should be no problem to have three or four people locked in via teleconference.

TOP 4: Biotech and regulatory affairs: What is different?

Wenzel gave a short presentation highlighting the differences in regulatory affairs between "traditional" drugs and novel biotechnology drugs. This ppt presentation will be put on the EAPB homepage, but accessible by members only (internal part of the homepage).

Action by Müller: Contact Oliver Kayser of EAPB to arrange special SIGRA section on homepage, a part of this section should only be accessible by the standard code word provided to all EAPB members.

Within this context the question was risen: "What exactly are biopharmaceuticals?" In general it was found that the present definition after EU laws and FDA specifications restricting it to drugs being peptides, proteins or composed of nucleic acids might be necessary to revise! One activity of EAPB-SIGRA could be to discuss a new definition of biopharmaceutical drugs (e. g. also including biotechnological drugs) and providing this as a discussion paper to the public and the authorities).

Action by Wenzel and Woppmann: Get initiative started for preparing a discussion paper "New definition of biopharmaceuticals".

TOP 5: Discussion on objectives, procedures, administration of SIG

TOP 5.1: Geographical size of responsibilities (EU, USA)

It was discussed if EAPB and SIGRA should only focus on Europe or extend to have worldwide activities. Müller pointed out that at present EAPB has not the financial power, the manpower and the administrative infrastructure to be a worldwide acting partner. In

addition, worldwide activity would bring us in competition to many other existing organisations, organisations which are already cooperation partners of EPAB (e. g. Biotech Group of AAPS).

It was agreed to follow the present policy, that means having a strong exclusive position in Europe as the only representative for pharma biotech and having worldwide activity by building up a network with cooperation partners. The presently most important non-European cooperation partner is the Biotech Group of the American Association of Pharmaceutical Scientists (AAPS). EAPB is already involved in the organisation of the "US National Biotechnology Conferences" of AAPS. One of the most important topics in this cooperation is regulatory, here could SIGRA play an important role in the future.

TOP 5.2: Which contacts to make?

A very important step in the work of SIGRA is to identify organisations and persons in authorities to talk to. The committees primary targets can be summarised as follows:

EMEA

7 Westferry Circus
Canary Wharf
London E14 4HB
Biotech Working Party: Prof. J.H. Trouvin

DG Enterprise:

Mr. Philippe Brunet (Head)

European Commission, Enterprise DG, Pharmaceuticals
EUROPEAN COMMISSION, AN88 1/06
B - 1049 Bruxelles

Tel: +32 2 29 54 128 Fax: +32 2 29 61 520 SMTP (Internet): philippe.brunet@cec.eu.int

Mr. Nicolas Rossignol (support by LEHMANN Birka?)

European Commission, Enterprise DG, Pharmaceuticals
EUROPEAN COMMISSION, AN88 1/57
B - 1049 Bruxelles

Tel: +32 2 29 87 354 Fax: +32 2 29 61 520 E-Mail (X400): c=be; a=rtt; p=cec; o=dg3; g=nicolas; s=rossignol SMTP (Internet): nicolas.rossignol@cec.eu.int

- Human Tissue engineering products.
- Bioterrorism and related issues.
- Follow up of Commission Communication on Biotechnology.

Members of the European Parliament

Committee on Industry, External Trade, Research and Energy

Ausschuss für Industrie, Außenhandel, Forschung und Energie

PEI

Paul-Ehrlich-Str. 51-59
63225 Langen
Prof. Dr Paul Cichutec
cickl@pei.de

ICH Secretariat,

c/o IFPMA,
 30 rue de St-Jean,
 P.O. Box 758,
 1211 Geneva 13, Switzerland
 Tel: +41 (22) 338 32 06, Telefax: +41 (22) 338 32 30
 admin@ich.org

<p>EU Commission</p> <p>Mr Philippe Brunet Head Pharmaceuticals: Regulatory Framework and Market Authorisations European Commission Brussels, Belgium</p>	<p>Dr Eric Abadie Vice Chairman Department of Registration and Clinical Studies French Agency for the Safety of Health Products Saint Denis, France</p>
<p>EFPIA</p> <p>Mr Brian Ager Director General European Federation of Pharmaceutical Industries and Associations - EFPIA Brussels, Belgium</p>	<p>Dr Yves Juillet Senior Advisor LEEM Paris, France</p>

In a second step, also further depts. of other DGs, members of the CPMP and CVMP and also major industry organisations should be contacted.
 e.g.

EFPIA

Mr Brian Ager
 Director General
 European Federation of Pharmaceutical
 Industries and Associations - EFPIA
 Brussels, Belgium

VBU Vereinigung deutscher Biotechnologie-Unternehmen

c/o DECHEMA e.V.
 Theodor-Heuss-Allee 25
 60486 Frankfurt am Main
 phone: +49 (0)69 - 7564-124
 fax: +49 (0)69 - 7564-169
 email: vbu@dechema.de
 vbu@v-b-u.org
 Contact Persons Dr. Rüdiger Marquardt (-163) ; Dr. Andreas Scriba (-124); Dana Wolf (-161)

TOP 5.3: How to include authorities?

Authorities can best be included when we reach a certain status of an "Interested party". Such parties, which represent normally a large number of interested persons / companies etc are informed by the authorities on a regular base about drafted new legislation and asked for comments. They have also the possibility for regular meetings with the authorities to present problems, ideas, points for discussion etc.

For SIGRA, it is important, that we

- represent the whole EABP with its personal and corporate members
- seek contact to the persons mentioned above
- try to organise meetings of the SIGRA with EMEA, DG Enterprise, CPMP etc
- develop ideas, proposals etc and discuss these with the competent authorities

TOP 5.4: Building a data base with biotech regulations (co-op with providers?)

Wenzel pointed out that it would be of interest for members to have a data base regarding biotech regulations. He mentioned 2 **organisations** which provides excellent overview on regulatory issues.

Schultz Interactive Information A/S

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2620 Albertslund
Denmark
Tel.: +45 43 63 40 04
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E-mail: info@tarius.com

Or

reg 123.com

United Kingdom:
reg123.com Limited
No. 1 Farnham Road
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UK
Tel. +44-(0) 1483 549 041
Fax +44-(0) 20 7681 2676
Email: info@reg123.com

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reg123.com Limited (Deutschland)
Eschborner Landstrasse 75
60489 Frankfurt / Main
Germany
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Fax +49 - (0) 69 78991 - 129
Email: info@reg123.com

or

IDRAC :

Paris Office Immeuble 'Le Brochant' 141, avenue de Clichy 75848 Paris Cedex 17 FRANCE Telephone: +33 1 53 06 20 00 Fax: +33 1 53 06 20 10 idrac-info@liquent.com www.idrac.com	U.K. Office Liquent House, 56 London Road, Bagshot, GU19 5HL UK Telephone: +44 (0) 1276 486900 Fax: +44 (0) 1276 476006
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Müller pointed out that there is no manpower to build up such a homepage and it was decided to seek for a partner organisation to which our members (i. e. EAPB homepage) could be linked.

Action by Wenzel: Identification of such an organisation/homepage and information to Oliver Kayser to make a link from EAPB homepage.

Action by Oliver Kayser: Linking the homepages.

Bermejo passed on additional information after the meeting by mail, the link is: <http://www.dti.gov.uk/bioguide/>

TOP 5.5: "Regulatory news": Electronic newsletter?

Wenzel offered to provide a monthly newsletter to all members of SIGRA and members of EAPB.

Müller pointed out that a monthly newsletter involves a lot of work, it would be rather sensible to condense the information and have it every two months or three months. It was unanimously decided that Wenzel will prepare a newsletter every 2-3 months which will then be distributed via the EAPB office in Berlin to all corporate members and all personal members.

Action by Wenzel: Provision of a newsletter every 2-3 months mailing it to Gabriela Karsubke at the EAPB Headquarters in Berlin.

Action by Müller: Provision of a covering letter to distribute the SIGRA newsletter.

TOP 5.6: Funding

Bermejo had identified two areas within the framework program (FP) 6 in which EAPB-SIGRA could apply for funding:

1. Advanced genomics: improvement of biopharmaceuticals' clinical testing and their approval
2. Future research policy developments (which also includes regulatory environment)

Wenzel pointed out that for an EU application SIGRA should call itself rather a "consortium". In addition it needs to have a geographical balance within Europe, it would also be beneficial to have advisors to the regulatory authorities as members of SIGRA.

Prof. Unger/Freiburg was suggested as a regulatory person because he is advisor to BfArM, the German drug registration agency. Müller pointed out that one should avoid to have too many German people in this consortium, he would rather prefer to have e. g. Trouvin from Paris as French regulatory person (**Adresse?**). It was agreed that Müller should write to all EAPB members asking them if somebody would like to join SIGRA for an EU application. From the people interested one would make a selection with geographical balance.

Action by Müller: Mail to all EAPB members asking them if somebody wants to join SIGRA.

To identify topics which fit into EU application 1 or 2, Müller suggested to go to TOP 7 and to go through the potential issues to be discussed and work on within SIGRA.

Topics identified for EU application 1:

1. Clinical development of molecular targeted therapies – open issues in development and approval
2. Biopharmaceuticals – new definitions considering recent advances in genomics & pharmaceutical biotechnology

Topics identified for EU application 2:

1. Comparability (biogenerics, immunogenicity etc.)
2. The “cell” as a product and respective regulation (topic to be mainly covered by ProBioGen)
3. Tissue engineering

For preparing the EU application (deadline 13 and 15 November, respectively) the following actions were decided:

Action by Müller: Mail to all members asking them if they are prepared to join SIGRA within an EU application.

Action by Wenzel: Collect all the responses, the responses will go CC to EAPB Office in Berlin.

Action by Müller: Provide a well balanced participant list of SIGRA for the EU application, mail it to Wenzel for addition to the EU application sheets.

Action by Wenzel: Fill in forms plus summarise on 3-4 pages the SIGRA activities according to the bullet points above.

Action by Woppmann: Provide half a page of text for EU application 1, topic 2 (biopharmaceuticals). Plus: Try to fill in some text parts in the EU form sent to you prior to the meeting (mail by Bermejo). Text should be sent directly to Wenzel (Müller CC).

Action by von Drygalski: Provide half a page of text for EU application 1, topic 1 (clinical development of molecular targeted therapies). Plus: Try to fill in some text parts in the EU form sent to you prior to the meeting (mail by Bermejo). Text should be sent directly to Wenzel (Müller CC).

Action by Bermejo and Fiedler: If possible contribute some text passages to topics listed under EU application 2. Send directly to Axel Wenzel.

Final responsibility for EU submission in time: Wenzel assisted by Bermejo.

Wenzel pointed out that the EU application is very important because when SIGRA is funded by the EU, it will be an interested party.

In general SIGRA should collect and comment on existing legislation. SIGRA should also make comments about the ICH guidelines.

TOP 9: Arrangement of next SIGRA Meeting

It was agreed that the next meeting should be announced and the dates fixed very well in advance to allow more interested parties to participate. The EAPB Office in Berlin will send a mail to inquire which of the following dates fits to most of the SIGRA members:

Monday, 2, 9 or 16 February 2004

In addition it will be asked if people are basically prepared to meet on a Saturday. Müller pointed out that a meeting on a Saturday is not very popular because most industry people rather prefer to spend the weekend with the family.

Action by Müller: Mail to all SIGRA members to fix the next meeting date in February including inquiry if Saturday is a principle potential meeting day.

Lunch break 12.15 – 13.00

TOP 6: First case (Annette von Drygalsky)

TOP 6.1: Presentation of von Drygalski/metaGen

The presentation itself is also available on the SIGRA we page.

Summary :

Over the past few years a variety of new drugs were developed in oncology targeting critical pathways in cancerogenesis. Surprisingly, most failed to meet the conventional endpoint of improved survival in phase III trials (i.e. Iressa™ in non-small cell lung cancer, Avastin™, Marimastat™ in metastatic breast cancer). With the rapid growth in the discovery of new cancerogenic pathways it becomes evident that multiple critical steps may contribute to malignant cell transformation and that a single agent interfering with a single pathway may not suffice to eradicate cancer.

With large effort and cost, biopharmaceutical companies strive to identify a magnitude of modifiers interfering with important pathways in order to combat cancer. The recent failures to bring drugs to market raised huge uncertainties within medical and biopharmaceutical communities in regard to the most conclusive clinical development of such novel compounds.

Conventional endpoints in clinical drug development accepted by regulatory authorities are until now response rates in phase II trials and survival rates in phase III trials. Meanwhile, there is no doubt, that the clinical development of novel "molecular targeted therapies" requires a different, more comprehensive approach with refined concepts in terms of endpoints, quantification of response and/or patient benefit, appropriate patient selection and strategies to combine molecular effectors early on.

TOP 6.2: Discussion, actions and conclusions

The case presented by von Drygalski can be separated in two points SIGRA needs to deal with:

1. Lack of consensus of oncologists on surrogate makers
2. Lack of a new guideline for clinical testing of molecular targets adapted to present state of art.

It was decided to undertake the following actions:

1. Von Drygalski will put together two separate papers for points 1 and 2. These papers will describe in a condensed (!) form the problem and propose solutions which are pragmatic and workable for the pharmaceutical companies. It should be taken care that the paper is not too long but long enough to contain the main issues and proposals.
2. Von Drygalski will discuss inside metaGen if these two papers will be put together by metaGen only or alternatively if metaGen contacts competing companies from which they know that they have identical problems in their formulation development.
3. These discussion papers will be published in NewDrugs and the information letters of MEGRA and PEFRAS. Müller will try to get them published in the AAPS News Magazine. Target is that these papers will be public knowledge, that means state of the art. When the company discusses procedures of registration with the authorities, they will discuss it in the light of the state of the art. By publication of these papers they will become state of the art. Additional comment by Müller made during dictating of the protocol: These working papers could also been published in the European Journal of Pharmaceutics and Biopharmaceutics in the section Pharmaceutical Biotechnology. This section is being run by EAPB (that means controlled), the journal is a full scientific journal with a high impact factor which makes the discussion papers even more relevant.
4. Based on the recommendation by Wenzel metaGen will make an application for scientific advise at the EMEA. During the discussion they can refer to the state of the art created by publishing the two discussion papers.
5. SIGRA will make an official approach to the following organisations, committees:
 - a) CPMP via Prof. Cichutek as official representative of Germany. Beneficial is that Cichutek will be on the new Board of EAPB after the election in October
 - b) DG Enterprise
 - c) EMEA

Action by Drygalski, Müller and Wenzel: Perform actions listed in points 1-5.

To summarise the aim of this first initiative:

Up to now markers for a successful therapy in oncology are e. g. the prolongation of survival time. New biotechnology drugs do not necessarily increase the survival time but tremendously improve the quality of life. However, aspects like this are not a marker in clinical studies, therefore no superiority of the biotechnology drug can be proven compared to traditional treatment. This needs to be changed by defining other markers for a therapy success!

In principle it would be preferable to have a few companies working on the two position papers because it provides a broader basis.

TOP 8: Call to prepare and present further REAL cases

The next two real cases to be dealt with should be decided at the next SIGRA meeting in February next year. In addition a mail should be sent to all corporate members of EAPB to

inform them about the first initiative taken, list the five areas defined for the EU proposals 1 and 2 and ask them for further "real cases".

Action by Wenzel: Preparation of this letter and sending it to EAPB Office in Berlin. Important: In this letter should be clearly expressed that responses do not go back to the office in Berlin, but directly to Wenzel!

Action by EAPB Office: Mailing of this letter to all corporate members.

TOP 10: Miscellaneous

TOP 10.1: Regulatory information by SIGRA

This info letter was suggested by Wenzel and as discussed above it will be sent to:

- a) members of SIGRA
- b) corporate members
- c) all EAPB personal members

TOP 10.2.: Seminars by SIGRA

Wenzel put the question on the table if seminars should be provided. Müller supported this idea but pointed out that EAPB has not the infrastructure to do this. However, offering seminars would be a good publicity for EAPB.

Therefore Müller proposed:

Wenzel is already organising seminars on his own account as consultant. These seminars could be announced as official EAPB seminars. The profit of these seminars stays completely with Wenzel. At the same time this is a compensation for the time he is investing as an independent private consultant. The seminars will officially be announced in NewDrugs (15.5000 copies per issue), by mail to all corporate and personal members and via AAPS News Magazine (only for seminars in English).

Wenzel raised the question if he should cover completely the financial risk for the preparation of such seminars (e. g. printing costs for flyers) in case they have to be cancelled. According to Müller there should be very little costs because announcements will be generally made not by surface mailing but electronically and in NewDrugs, but generally this point of seminars and financial framework should be discussed and decided at the next meeting of the Board of EAPB.

Theoretically, according to Müller the seminars should be highly profitable when organising them at a low cost venue (e. g. special discount rates in hotels in Munich according to Wenzel). Because when announced via EAPB:

- Advertising in NewDrugs will be free of charge
- Electronic mailing is also free of charge, in addition more than 1000 members will be contacted
- All presenters will present free of charge because they are doing it for EAPB (and not for a private consultant), therefore only travel costs have to be covered.

From this, even one day seminars with just 15 people at 800 Euro per day should be a good profit.

Woppmann is also an independent consultant engaging himself for EAPB. Therefore there is the possibility that he contributes to such seminars or Wenzel and Woppmann organise joint seminars and share the profit.

TOP 10.3: Question of financial recognition for contributions to SIGRA

It was briefly discussed that running an SIG for EAPB takes a substantial amount of time. In case EAPB members working in such groups are employed by a company, they are working in the interest of the company. When they are investing their time, they are doing it during their normal working time and are financially compensated by the salary. This is different for independent consultants being self-employed. Here it appears necessary to think about some financial recognition on the long term.

Müller made it clear that at the moment EAPB is still in its building up phase, that means there are no possibilities for financial recognition. However, the target is that EAPB will be a fully professional organisation on the long term, that means having a full own office with staff running the business (comparable e. g. to VfA in Germany). Because this requires that the corporate membership fees need to be increased distinctly, that means similar to the level of VfA. This is possible when the SIGs worked successfully and the corporate members have fully recognised the value of EAPB for their companies.

TOP 10.4: Homepage of EAPB/SIGRA

There should be a special section on the EAPB homepage for SIGRA, there should also be the possibility to click a button under which professional company advice is offered by regulatory experts, that means by Wenzel and Woppmann. Of course this advice will be charged. The implementation of this "company advice offer" is considered also as a kind of recognition for the time invested in EAPB by Wenzel and Woppmann. At present EAPB cannot financially compensate, but EAPB can fully assist in increasing business opportunities.

Action by Wenzel/Woppmann: Provide text for homepage.

Action by Kayser/EAPB Office Berlin: Place text on homepage.

TOP 10.5: SIGRA organisation structure and working procedure

The "real cases" to be dealt with by SIGRA cannot be discussed in detail at the group meetings. For each topic a specialised group inside SIGRA should be formed consisting of 2-4 (or what is necessary) experts. The experts prepare a detailed discussion paper including the articles to be published, these papers will then be finally approved (or slightly modified) at the regular SIGRA meetings.

To summarise, there will be:

- 2-3 annual meetings of the SIGRA group
- meetings of "working groups" for each topic.

TOP 10.6: Schering views about SIGRA topics

Fiedler informed that for Schering presently the most interesting regulatory topics are gene therapy and comparability issues (statement made before leaving at 12.00).

TOP 10.7: Task sharing

Müller discussed with Wenzel how the tasks to run SIGRA should be shared in the future. Basically Wenzel will completely run SIGRA, that means e. g. providing all correspondence and press releases, being in direct touch with the corporate members to identify new working cases and process them, organising the activities of the "working groups" including documentation of the activities via protocols of the meetings. The dates of SIGRA meetings will also be directly organised by Wenzel in direct mailing to the SIGRA members via the mailing list.

The EAPB Office will assist in running SIGRA, that means the tasks of the office are:

- mailing letters and info provided by Wenzel to corporate EAPB members
- organisation of the SIGRA meetings in Berlin (i. e. provision of room, hardware, drinks and food, hotel info)
- provision of a backup list of the SIGRA members.

The present protocol was written by Müller and supplemented with additional comments by Wenzel. The future protocols will directly be written by Wenzel or somebody identified as being in charge at the SIGRA meeting. The EAPB Office cannot provide capacity for providing a person to write protocols during the meetings or to type them afterwards. By now each SIG writes on its own the documentations.

Berlin, 8 September 2003

Rainer H. Müller/EAPB Office Berlin