

# **RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY PRODUCTS**

**SYMPOSIUM  
organised by the  
European Directorate for the Quality of Medicines & HealthCare  
(EDQM), Council of Europe  
and the European Medicines Agency (EMA)**

3 April 2013  
Strasbourg, France

## **REPORT**



## TABLE OF CONTENTS

Welcome Session .....	5
Session 1: EDQM, EMA and the RCG Working Party .....	6
Session 2: User, manufacturer and academic viewpoints .....	8
Session 3: Break-out sessions .....	15
Concluding remarks .....	18
Acknowledgements .....	19



# **RAW MATERIALS FOR THE PRODUCTION OF CELL - BASED AND GENE THERAPY PRODUCTS**

**3 April 2013, Strasbourg, France**

## **WELCOME SESSION**

Dr Susanne Keitel, Director of the European Directorate for the Quality of Medicines and HealthCare (EDQM), Council of Europe, welcomed the delegates and highlighted her wish to have a constructive and open discussion on the quality requirements of raw materials for the production of cell-based and gene therapy products. She explained that in recent years, an increasing need for guidance on the quality requirements of raw materials used for the production of cell-based and gene therapy products had been recognised both by manufacturers of such products and regulatory authorities. To assist stakeholders in identifying the quality requirements of raw materials and to harmonise the current variable practices, the Symposium brought together 115 delegates from 15 countries representing European and national regulatory authorities, as well as manufacturers and users of raw materials, to seek their views in order to develop a text to harmonise these quality requirements, for publication in the European Pharmacopoeia.

Dr Alexis Nolte, Head of Sector – Quality of Medicines at the European Medicines Agency (EMA) welcomed the delegates and gave an introductory presentation on the role the EMA plays in supporting Advanced Therapy Medicinal Product (ATMP) developers. He explained that the EMA supports developers through the discovery, pharmaceutical development, non-clinical development and clinical development stages and provides a user guide for micro, small and medium-sized enterprises operating in the pharmaceutical sector. The guide's aim was to facilitate understanding of the main aspects of medicinal product legislation focusing primarily on the requirements for authorising innovative medicinal products for human or veterinary use. He highlighted that in developing ATMPs, questions were often raised on the acceptability of the raw materials used in their production and there could be issues at the marketing authorisation application stage about the impact on quality of the raw materials used in ATMP manufacture. He emphasised that quality is key for ATMP development and how it was important that the EMA and EDQM worked together to define the best quality standards.

## **SESSION 1: EDQM, EMA AND THE RCG WORKING PARTY**

Dr Emmanuelle Charton, Deputy Head of the European Pharmacopoeia Department (EPD), EDQM gave an introductory presentation on the “Background to the Council of Europe, EDQM and EPD”. The Council of Europe, based in Strasbourg (France), covers virtually the entire European continent, with its 47 member countries. Founded in 1949, the Council of Europe seeks to develop common and democratic principles, throughout Europe, based on the European Convention on Human Rights and other reference texts on the protection of individuals. The EDQM, a Directorate of the Council of Europe, created in 1964 is a leading organisation that protects public health by enabling the development, supporting the implementation and monitoring the application of quality standards for safe medicines and their safe use. The EPD’s main objective is to provide common quality standards to control the quality of medicines and of substances used in the manufacture of medicines for both human and veterinary use.

The European Pharmacopoeia (Ph. Eur.) is legally binding in European member states with 37 signatory parties (including the European Union) and 25 observers (including the World Health Organization) in 2013. In order to remain relevant, the Ph. Eur. had to continue to adapt and meet new challenges. A workshop had been held in 2011 on the “Future of monographs in the field of biologicals” where opinions of regulatory assessors had been gathered and it had been recognised that there was a need for harmonised quality criteria for key raw materials used to manufacture biological products because they were often only available in ‘research use’ grade and manufacturers of raw materials had difficulty in delivering quality information to customers for subsequent submission to regulatory authorities. In recognition of the need to establish quality requirements for these raw materials, the Ph. Eur. Commission had set up a Working Party in June 2012, named RCG Working Party (RCG WP), to elaborate a text on “Raw materials for the production of cell-based and gene therapy products”. The objective of the Symposium was to provide support for the RCG WP to achieve this objective and, therefore, to explore with European and national regulatory authorities, as well as manufacturers and users of raw materials, the quality standards needed for raw materials used for the production of cell-based and gene therapy products.

The next introductory presentation was given by Professor Jean-Hugues Trouvin, Chair of the EMA Biological Working Party (BWP) and Committee for Advanced Therapies (CAT) member. He presented the EMA’s views on raw materials for cell-based and gene therapy products and described the legislation in place at a European level including the content of the Regulation EC (No) 1394/2007 on advanced therapy medicinal products (ATMP) which gives definitions for gene therapy, cell therapy and tissue engineered products and established the CAT. He highlighted that raw materials shall be considered as materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance. The ATMP Regulation and also the Clinical Trials Directive set out a requirement that detailed information on the raw materials should be supplied and that a system should be in place to ensure raw materials coming into contact with the cells or tissues can be traced. Volume 4 EU Guidelines to Good Manufacturing Practice (GMP), Annex 2 also sets out that regular audits of the raw material supplier should be undertaken, and the full traceability, source, origin and suitability of biological raw materials should be clearly defined. He also described the EMA guidance available for ATMPs. Finally he provided a brief overview of the issues raised at the EMA during scientific advice procedures which included the requirement to supply certificates of origin/analysis, a requirement for a thorough understanding of the biological nature of the materials to which the active substance has been exposed, the necessity to qualify each new batch of Foetal Calf Serum due to its variability and

that raw materials should be qualified for the intended use. In conclusion, Professor Trouvin acknowledged that raw materials could be a possible source of concern and harmonisation is required. Attention should be given both by the manufacturers and the users to appropriate identification, traceability and auditing of raw materials but there was little information in the various legislation and guidance texts on how to proceed or that defined a sufficient balance between control and acceptance of raw materials.

Dr Jaana Vesterinen from the Finnish Medicines Agency (Fimea) and Chair of the RCG WP, gave a presentation on the role and proposals of the RCG WP. She described that in the production of cell-based and gene therapy medicinal products, a wide variety of biological raw materials are used with many of the raw materials only available in research grade thus the quality, safety and consistency could be difficult to assess and data for full traceability and exact composition may not be available. She outlined the challenges regulatory authorities and users and producers of raw materials face in having adequate and reliable information on raw materials. In response, the EDQM had established the RCG WP in June 2012. She gave information on the members of the RCG WP and explained that the aim of the RCG WP was to deliver an overarching text covering the quality requirements of raw materials used for the production of cell-based and gene therapy products. The scope of the text includes biologically active raw materials of biological origin: for example serum, growth factors, cytokines, antibodies and enzymes, either alone or in a mixture. The quality attributes to be considered included the origin, traceability, composition and viral safety of raw materials and more specific requirements such as identity, product related variance, and biological activity. She further explained that the RCG WP thought it was very important to engage stakeholders, at an early stage, in a dialogue about the quality standards and as a first step had, at the end of 2012, sent a survey to representatives of raw material manufacturers and users, academics and regulatory authorities. The vast majority of responses to the survey had agreed that there was a need to harmonise the quality requirements of raw materials and that this could be done through the Ph. Eur. The RCG WP hoped that the Symposium would help gather further information in order to support the drafting of a text that meets the needs of all relevant parties.

## **SESSION 2: USER, MANUFACTURER AND ACADEMIC VIEWPOINTS**

The session consisted of four presentations and a general discussion.

### **Viewpoint from a User of raw materials**

The first speaker was Dr Sarka Vosahlikova, Quality Assurance Specialist from Sotio a.s., Czech Republic who explained that Sotio was a biotechnology company developing a next generation Active Cellular Immunotherapy based on activated dendritic cells. She described how Sotio have a good manufacturing practice (GMP) quality assurance system which covers both manufacturing and testing of final product and requires the traceability of raw materials for cell therapy products. She further described how processes were often taken from an academic research environment and at the preclinical stage raw materials could be for ‘*in vitro*-use only’, undefined, uncontrolled, xenogeneic or ‘home-brewed’. The solution Sotio employed was to replace raw materials with GMP grade materials, to find alternative vendors or to qualify the materials in-house. However some limitations were often identified such as availability, cost and finding suitable vendors of the raw material. Sotio’s priority was to ensure raw materials were suitable for clinical use and had an adequate Certificate of Analysis (CoA). For raw materials with components of bovine origin there was a requirement for a viral safety declaration and Transmissible Spongiform Encephalopathy/ Bovine spongiform encephalopathy (TSE/BSE) statement and for all raw materials with components of animal origin there was a requirement for a certificate of origin. Sotio had seen issues with ‘research use only’ materials, such as verifying the identity and conformity with written specifications, the reliability of the supplier’s analysis and finding alternative vendors. In summary, she highlighted that there were significant problems with a lack of clear definition of starting materials and raw materials and differences between the European and USA regulatory frameworks. It was difficult to find alternative suppliers of critical materials with equivalent properties and there was often no clinical grade of a raw material available. She suggested that possible solutions were to introduce appropriate systems of quality control, qualification systems for alternative materials, undertaking risk analysis for each kind of material, identifying and testing alternative vendors and suppliers, and attempting to introduce and qualify alternative approaches in the manufacturing process.

### **Viewpoint from a Manufacturer of raw materials (1)**

The second speaker was Dr Ulf Bethke, Technical Director for Clinical Products at Miltenyi Biotech GmbH, a company founded in Germany in 1989. Today Miltenyi Biotech is one of Germany’s largest independent, privately owned, biotech companies and it produces the Magnetic Cell Separation (MACS, CliniMACS) system. He highlighted that for quality purposes, raw materials needed to be animal and virus free, to have lot-to-lot consistency and be tested to regulatory standards. He explained how the regulatory requirements for raw materials in the manufacturing process of cells are partly covered by guidance and legislation such as the requirements of Article 5 of Regulation 1394/2007, ICH Q7 – Manufacturing of API and CPMP/BWP/41450. For the Miltenyi MACS GMP Media, the key quality features were lot-to-lot consistency, being serum-free, animal-component free, having a lot-specific Certificate of Analysis, traceability, qualification of raw materials and having a defined composition of the media. Miltenyi also reported the sterility and endotoxin levels according to the Ph. Eur., osmolality, pH, functionality (using a cell expansion assay), and storage conditions. Some of the challenges of producing raw materials for use in the ATMP area included that there was not an EU Master File system in place and if a company had to interact with 27 countries plus local authorities it resulted in complicated follow-ups upon changes to

raw material specifications. There were also no guidelines to define the standards for development and production of raw materials. Therefore guidelines applicable for the production of API are used for the production of cytokines, proteins and antibodies. It was also difficult to determine the biological activities of cytokines, when no reference standard was available. He explained that often research products were used/allowed in Phase I and II clinical trials and complex peptides (e.g. cytokines of the TGF- $\beta$ 1 family) could not be produced in bacterial cells and needed to be expressed in mammalian cells which meant that challenging viral testing and viral validation was required. He questioned whether raw materials for ATMPs could be developed and manufactured economically. In terms of harmonisation of raw material quality, he expressed a desire to see what exactly the applicable standards for development and production could be, e.g. would ICH Q7 EU GMP be applicable when raw materials are not APIs. He expressed concern about what would happen to other pharmaceutical products; if standards were defined for ATMP raw materials and what the requirements would be for raw material production environments (e.g. would cleanrooms be necessary). Finally he expressed concern about the extent of process validation required and whether virus removal validation or stability data would be necessary for every product or for product groups. He also observed that many authorities were already requesting preclinical safety data on raw materials.

## **Viewpoint from a Manufacturer of raw materials (2)**

Dr Bernd Leistler, Director of Development & Production at CellGenix GmbH gave a presentation which covered the company and its views on raw materials. CellGenix founded in Freiburg, Germany in 1994 carries out the development, GMP production and marketing of high-quality reagents and services for cell therapy. The company has manufactured recombinant GMP products in-house for 10 years which includes its CellGro® cytokines and CellGro® serum-free media. He discussed how raw materials (or Ancillary Materials) such as growth factors, cytokines media, supplements, and buffers were not intended to be, but could become part of the final product. He described how in Europe there were no specific regulations existing for raw materials but Annex 2 of the EU GMP Guidelines did describe that “*Special consideration should be given to quality of the starting materials, ... , culture media, cytokines, growth factors ... used in manufacture*”. He went on to explain that the EU Tissue & Cells Directives and the Ph. Eur. had no raw materials monographs or accompanying reference standards. In Europe, there needed to be vendor and raw material qualification and control. He described how in the USA, the United States Pharmacopoeia (USP) had chapters on Ancillary Materials for Biological Products; <1043> *Ancillary Materials for Cell, Gene and Tissue-Engineered Products* and <92> *Growth Factors & Cytokines Used in Cell Therapy Manufacturing*. He explained that for CellGro® products the major quality attributes for safety and quality purposes included having an animal-derived-component-free (ADCF) and serum-free policy, using GMP Production for the safety, purity, potency and consistency and providing CoAs for regulatory compliance. He further described how as part of the ADCF policy there were different levels. Level 1 for a cytokine product would see no animal derived components (ADC) as part of any cytokine product. Level 2 for the cytokine production process would see for products designated “ADCF” no ADC used throughout production process, including all material in contact with product during production. Level 3 for raw materials for production would see whenever available, only raw materials certified to be free of ADC used in the manufacture of GMP products. He also described how a comprehensive, ISO 9001:2008 certified QA system had been established (including change control, out of specification (OOS) procedure, etc.). GMP grade materials were also manufactured, tested and released in compliance with the relevant GMP-guidelines. For CoA, CellGenix had the following quality attributes - confirming the identity (2 methods), purity (2 methods), product variance (e.g. oligomers, oxidation products), specific activity, host-cell DNA, protein content, endotoxin content and sterility according to the Ph. Eur. In terms of challenges

facing the field, Dr Leistler highlighted that there needed to be harmonisation of requirements for the quality of raw materials such as purity/impurities, stability studies, etc. There was also a need for an industry-wide definition of ADCF/“Animal-free” and how to carry out assessment of residual levels and removal of raw materials because they could become part of the final product. He also expressed a desire to see guidelines and monographs for cells as raw materials, in the future. Finally, he indicated that he would also like to see a Drug Master File (DMF) submission system in the EU and suggested that certification of the raw material manufacturing process could be established for vendors.

## **Academic Viewpoint**

Dr Mark Lowdell, Director of Cellular Therapy at the Royal Free Hampstead NHS Trust & UCL Medical School gave a presentation on the need for qualified reagents. He described how there were a number of issues to address including the challenges of sourcing raw materials that met regulatory requirements, the quality attributes required and the raw materials that should be covered by a Ph. Eur. text. He explained that there were a number of challenges to overcome including: often starting materials had very high intra-donor variability, pre-clinical models are rarely informative or even dangerously uninformative, dose calculations are difficult and sterility testing was difficult to carry out according to the Ph. Eur. due to small batch sizes. He described how there were a large number of ATMP cell therapy trials at the Royal Free Hospital and how there were numerous reagents used in the GMP manufacture of ATMPs. He described some of the difficulties experienced, for example, it was difficult or impossible to get a precise CoA for specialised culture media or to obtain details for the traceability of reagents and he highlighted that there was a reluctance of companies to supply media for GMP manufacture because certain companies perceived there to be a litigation risk if the product went on to be administered to a patient. He gave a further example that cytokines were mostly only available “for research use only” and it was unknown what could be permitted as the maximum residual amount. Dr Lowdell explained that non-compendium starting materials were qualified by his department using critical supplier questionnaires, addressing whether suppliers had an ISO standard, the traceability of components, control of suppliers, assessment of contamination / cross-contamination risk and exposure to animal-derived products. For products stated as GMP compliant he needed to identify what the manufacturer meant by “GMP compliant”. He would also look at the history of use of the raw material in other ATMPs using published data and using a network of academic ATMP manufacturers sharing first-in-man data. Finally data from pre-clinical experiments would be used. He explained how these principles had been used for the transplantation of a decellularised and recellularised ‘autologous’ trachea. Dr Lowdell described how there was an urgent need for Ph. Eur. reagents such as recombinant cytokines, monoclonal antibodies for “in process” cell selection, trypsin and specialised media. He finished by emphasising how there was an interdependency between all stakeholders to allow patients access to new, safe and effective treatments.

## **GENERAL DISCUSSION**

The issues discussed in more detail were:

### **Terminology for raw materials**

Delegates highlighted that there was no definition for ‘GMP compliance’ so the end-user still had to carry out validation. It was agreed that user audit was more important than whether the raw material

was called GMP or not.

It was acknowledged that the ‘GMP grade’ term could mean different things to different audiences and there was a need to look beyond the terms used. Delegates were encouraged to consider what quality attributes were required from their experiences of handling raw materials and what the essential things were that need to be included in a Ph. Eur. text.

With regard to the terminology used for these raw materials, a delegate suggested that the same terminology be used as that used in the USP chapter, i.e. “ancillary materials”. It was answered that the terminology used in the EU legislation was “raw materials” and that the Ph. Eur. should align with this terminology in order not to create any confusion among users.

### **Raw materials used in different applications**

It was highlighted that it would be difficult, even impossible for the Ph. Eur. to provide acceptance criteria for every clinical application that a raw material could be used for. Manufacturers of cell-based and gene therapy products would still be required to carry out risk assessments depending on the particular use of a raw material. Raw material manufacturers indicated that they did not want to provide any statements that defined the potential therapeutic use of raw materials.

A delegate suggested that human serum albumin was a poorly standardised reagent and products sourced from different manufacturers would not have the same functionality. It was stated that it was important for manufacturers to provide a sufficient amount of information in order to allow users to establish that test systems were similar and the same raw material would have the same *in vitro* effect.

### **Reference Standards**

It was suggested that making reference standards available would aid testing because it would allow for comparability of different tests and assays which was essential in ensuring harmonisation of the quality requirements for raw materials. Delegates highlighted that raw material manufacturers used an internal standard to demonstrate lot-to-lot consistency but that there was often limited comparability between different manufacturers which resulted in raw material variability due to slight changes in manufacturing conditions. It was also often difficult to take a common approach when testing across different sets of cell donors. Overall, it was agreed that biological activity was often difficult to determine.

It was suggested that having a Ph. Eur. text and reference standard would help to confirm the quality for example, of Interleukin -2 (IL2). A producer would then be able to accept material from a choice of suppliers.

### **Difficulty in standardising assays**

A delegate indicated that it would be very difficult to undertake efficacy testing for culture media because of the effect of using different cells, which had come from different donors, in the test system.

One delegate stated that it would be impossible to standardise the potency of cytokines because of their different effects in different cell systems. In testing cytokine potency, there is potentially a mixture of cells, cytokines, media and donor serum which makes for many variables in the test

system and makes it difficult for a cytokine to be standardised. However, an EDQM representative expressed the view that some form of evaluation of cytokine potency could be carried out using a standardised assay. It was also suggested that reference standards could be established for certain kind of assays.

### **Clinical trials**

The regulators amongst the delegates indicated that the sponsors of clinical trials would need to know the quality of raw materials so that the product is of appropriate quality. Often providers of research grade raw materials were not able to answer the necessary questions on the raw material. In answer to these comments, delegates highlighted that often suppliers of research grade materials were able to consistently supply good quality materials and rather than forcing users not to use these materials, regulators needed to work together with users to improve the traceability rather than excluding these suppliers from the market.

It was highlighted that there were a large number of clinical trials underway and that there should be some form of risk assessment at least to provide minimum information on the safety of a raw material. Regulators recognised the need for harmonised systems amongst EU member states at the level of clinical trials, in order to assure further consistency in marketing authorisations.

### **Use of a Drug Master File system**

Some delegates believed it would be helpful to have a drug master file (DMF) system in Europe, similar to the system used in the USA, because currently the submission of information was specific and depended on the regulatory authority to which the submission was made. Questions were asked over whether the DMF would be for the raw material itself or for its use. It was explained that in the USA, there were DMFs for media and individual cytokines and this could help EU regulators.

Regulatory representatives explained that the European expectations of the regularly environment were different from those in the USA. In the submission of the Marketing Authorisation (MA) for an ATMP, the applicant must have a complete understanding of the raw materials used in the production of the ATMP: a determination of the raw material's impact on the safety and quality of the final ATMP must be included in the MA submission. Therefore, the EU legislation did not allow for a raw material manufacturer to submit a DMF in an independent manner.

A delegate suggested that the lack of a DMF, and the current European regulatory environment, might explain why only one ATMP had been authorised in the EU, whereas thirteen had been authorised in the USA and twenty-two in South Korea. It was recognised that a regulatory support file was needed for clinical trials but as there was such a large number of clinical trials, would a manufacturer of raw materials be able to handle the number of audits required. It was suggested that a central regulatory file would be able to provide a suitable solution.

The regulators could understand the views expressed by ATMP manufacturers but it would not be possible to assess the minimum raw material quality required from a DMF or central reference point. It was also explained that there was now a voluntary harmonisation process for clinical trial evaluation.

The regulators could also foresee confidentiality issues if manufacturers provided information directly to regulatory authorities. It would also be difficult for users to be informed of a change in production if the information was given directly to the authorities. For example, users may not know if there was variability of the raw material between batches. It would therefore be difficult to assure

that the safety and quality of products were not compromised.

Once again, it was suggested that a DMF system or a certification system in Europe would lead to a harmonised approach. However it was questioned how such a DMF system would work and whether this would be for the active substance, for the raw material for the product and who would be able to access the files.

It was emphasised by the Chair of the RCG WP that such discussions were not in the scope of the Symposium and if needed should take place elsewhere. The discussion had to focus on raw materials quality requirements.

### **Information exchange between users and manufacturers of raw materials**

It was stated that ATMP developers needed information on the safety of products and that contractual agreements with raw material manufacturers were required in order to obtain this information. Manufacturers expressed that although the composition of media was useful for users to have, there was not a need to provide specific details of the exact formulation of media. Confidential disclosure agreements could be set up between suppliers and users but there needed to be conversations between the user, supplier and regulator to understand what knowledge of the raw material was really required. It was suggested that the qualitative composition could be disclosed to ensure the safety of the raw material for producing an ATMP and this would facilitate a change of raw material manufacturer, if necessary. Delegates commented that suppliers did not provide detailed information because it was deemed proprietary. However, there must be a mutual relationship between the supplier and the user. Delegates discussed the issue of access to information on raw material composition when a manufacturer of raw materials shuts down, as this often left ATMP producers without a supply of certain raw materials. It was suggested this would be disclosed to legal representatives and could be available to ATMP developers but sometimes companies could be bought and the necessary information still remained restricted.

Delegates were unsure that a solution to the relationship between the supplier and the user could be found during the Symposium. Regulatory representatives stated that the composition of a raw material would be needed for regulatory submissions especially where fermentation or animal derived components had been used. This information would also be required for Phase I clinical trials. Additionally, it was stated that the qualitative composition of raw materials would be required for the clinical development of an ATMP so the user could know what the final ATMP was exposed to during production.

The moderators of the sessions Dr Paula Salmikangas of the Finnish Medicines Agency (Fimea), Finland and Dr Sol Ruiz of the *Agencia española de medicamentos y productos sanitarios* (AEMPS), Spain, thanked all speakers for their presentations and the delegates for the fruitful discussions.

## **SURVEY RESULTS AND BREAK-OUT SESSION INTRODUCTION**

Dr Stephen Wicks, Scientific Officer at the EDQM gave a brief overview of the results obtained in the survey, which had been conducted at the end of 2012, on raw materials for the production of cell-based and gene therapy products and their quality attributes as a starting point for Session 3's break-out groups. There had been a large number of survey responses with the majority being from cell based and gene therapy product manufacturers with equal representation from both academic organisations and regulatory authorities and to a lesser extent responses from manufacturers of raw materials. 92% of the respondents had thought that harmonisation of quality attributes was required.

Some respondees had indicated that any standards established should be clear and allow necessary flexibility because certain raw materials could be highly heterogeneous. Some respondents had raised concerns that harmonisation could slow the pace of development, making some raw materials more expensive. A large number of survey respondents would find a Ph. Eur. text useful for the harmonisation of quality requirements for raw materials. Although some respondents thought that the Ph. Eur. could be too strict for some raw materials. There was a divide in the survey responses as to whether a European Pharmacopoeia text on the quality requirements of raw materials should be mandatory or non-mandatory. It had been suggested the text should be mandatory due to the potential impact on the quality and safety of the final product. However, other suggestions had been given that text should be non-mandatory and more in the format of guidance to allow for flexibility. The most critical raw materials identified by the survey were (in order of preference) :

- Serum (which includes human serum),
- Media,
- Growth Factors and Cytokines,
- Enzymes (such as trypsin),
- Antibodies,
- Consumables which may have a biological element e.g. coated dishes or beads,
- Proteins and
- Buffers.

There had been a limited numbers of responses indicating that RNA/DNA and blood components should be included in a text.

Dr Wicks went on to list which requirements or quality attributes could be included in raw material specifications and mentioned in a Ph. Eur. text. He also reminded delegates what was out of scope for the Symposium, manufacturing requirements under GMP, more complex raw materials (such as feeder cells), a certification system (at this stage), international harmonisation (because there was a need to establish what is required in Europe before considering any wider harmonisation). He gave a brief introduction to the afternoon break-out sessions, which were designed to give delegates an opportunity to express their views.

### **Break-out sessions**

The Symposium delegates were divided into four parallel sessions. The outcome of each session is provided below.

## **SESSION 3: BREAK-OUT SESSIONS**

### **PARALLEL SESSION 1 – chaired by Dr Paula Salmikangas, Fimea, Finland**

Delegates agreed that it was important to have quality requirements for raw materials and a family approach for tackling the quality attributes of raw materials was sensible. Additionally, consideration of a risk-based approach should be included in the text. It was also suggested that any text should provide a clear definition of what a raw material is. It was discussed whether plastic ware needed to be included in the text.

Delegates thought that the text should include minimum requirements for critical raw materials and some form of risk assessment. Some of the critical raw materials listed by the delegates included plasmids, viral vectors, peptides for activation of cells, human serum albumin and blood components, platelet lysates and carrier proteins.

The quality attributes that should be included in a text included microbiological safety, mycoplasma, product related variants, biological activity and stability. However, some delegates believed it would be difficult to define the biological activity. Delegates felt that for safety purposes, it was important to ensure the consistency and traceability of the raw materials.

Delegates also saw potential bottlenecks in getting disclosure on the qualitative composition of raw materials from manufacturers. They did not think it was easy to get information from small and medium-sized enterprises and asked if it was possible to incentivise suppliers to provide such information. Delegates discussed GMP requirements and the need for minimum quality standards for production of raw materials. The Chair of the session explained that GMP requirements were outside the scope of the Ph. Eur.

There was discussion of the difficulty of defining quality requirements for composite products such as media containing sera or growth factors. Delegates thought that each component should comply with the quality requirements defined in the Ph. Eur. text. The general feeling amongst the Group was that the RCG WP was on the right track, that any text should be non-mandatory and the text should adopt a risk-based approach. Although, delegates acknowledged that being non-mandatory, the harmonisation required may not be achieved

Finally the delegates discussed that raw materials may have differing risk levels and where raw materials of animal origin were used different risks applied. These risks could preferably be dealt with by TSE certification.

### **PARALLEL SESSION 2 – chaired by Dr Thomas Hinz, PEI, Germany**

Delegates of Session 2 could not agree on a fixed, exhaustive list of quality attributes because they determined these depended on the type and use of the raw material in ATMP production. The delegates believed that the list of raw materials proposed by the RCG Working Party was sufficient and it was preferable to group the raw materials by family, although there was also suggestion that the raw materials could additionally be grouped by risk. Additionally, some delegates indicated that they would find individual monographs more instructive.

In providing examples of how to structure the text for cytokines, the delegates thought that the

quality attributes should include, identification, potency (content), purity, sterility and stability and for media, the sterility and identity would be required but defining the potency would be difficult to achieve.

Some delegates suggested that there was some justification in providing information on the raw materials based on the risk to patients so there could be potential differences in the amount of information required in preclinical development compared to the clinical development of a product. However, other delegates believed that by the clinical development stage, it could be too late to change a raw material so information on quality was required at an early development stage. It was also suggested that auditing manufacturers might impact on risk and subsequently the amount of testing of quality attributes required.

When discussing the bottlenecks, the delegates indicated that it was often difficult to obtain detailed information on a raw material and the amount needed could vary depending on the stage of development of the product. Delegates agreed that ensuring the consistency of a raw material supply was very important. Delegates believed that there was too little exchange of information/discussion between users and suppliers of raw materials and suppliers may not receive all the necessary information from a manufacturer. Delegates agreed that more detailed information was needed for research grade materials.

### **PARALLEL SESSION 3 – chaired by Dr Sol Ruiz, AEMPS, Spain**

Session 3 delegates agreed that a Ph. Eur. text should be non-mandatory and flexible, with a risk-based approach. The scope of the text should remain wide enough to encompass both products at a marketing authorisation application stage and in clinical trials. They also agreed that there should be an element of using a risk-based approach in considering whether a raw material was destined for use in the clinical development of a product or a Phase III clinical trial.

Delegates were in agreement that there was a continuing issue that needed to be addressed regarding the terminology used for raw materials such as, research grade, clinical grade and GMP-like.

Delegates considered that the use of a family approach in order to group the materials was acceptable. In determining the quality attributes, delegates believed that general quality requirements should address safety issues and that there should also be risk assessments. For manufacturers there should be the inclusion of quality attributes such as functionality and biological activity but these were more difficult to determine as they were often defined by the use of the raw material. Delegates thought that it would be impossible for a text to satisfy all potential users of a raw material, so a user must be capable of qualifying the raw material. There should also be adequate information for the traceability of a raw material especially when a supplier was not the manufacturer.

### **PARALLEL SESSION 4 – chaired by Dr Margarida Menezes Ferreira, Infarmed, Portugal**

Delegates of Session 4 thought that grouping raw materials into families was appropriate and that a risk-based approach should also be adopted. The delegates suggested that general requirements applicable across all the families could be used as an introduction in the text and that individual raw material texts in the Ph. Eur. should not be ruled out, although it could be too early to consider

drafting such texts. A risk-based approach should be adopted as a second level within each part of the text. Delegates also suggested that separate families for media and sera should be established and there should be cross-referencing between families for complex raw materials.

The delegates discussed the relative importance of quality attributes and believed that identity, total protein, microbial contamination and stability should be included. In addition they discussed the use of the following attributes:

- Purity, if suitable testing was available for a raw material family.
- Biological activity, although some delegates believed that the use of existing reference standards might not be suitable for this purpose.
- Impurities, if an impurity profile could be defined.
- Process related impurities: it was not clear to delegates how far the history of the raw material needed to be documented in order to satisfy this attribute.
- Viral safety/TSE: all delegates recognised the need for assessment according to existing Ph. Eur. requirements

The delegates were not in favour of having the responsibility for testing for viral safety solely at the ATMP manufacturer level because it would not be possible for the user to assess potential cross-contamination during manufacturing.

In discussing bottlenecks, some delegates indicated that it was difficult for raw material manufacturers to provide the required information and that often users could not find the desired quality of raw materials. There was concern that if confidential information was supplied directly to regulatory authorities it would be difficult for users to know how to proceed if the information was inadequate for their particular use of the raw material. It was also stated that there was currently a lack of harmonisation between the different requirements asked for by the different regulators in Europe.

Delegates also thought that any text should clarify if there were different attributes required for the commercial or development phase of a product and perhaps this could be determined using a risk-based approach.

The participants took note of the outcome of the four break-out sessions and acknowledged that the conclusions were often heading in the same direction. The moderator of the feedback session, Dr Voltz-Girolt, of the EMA, UK explained that this material would be further used by the RCG WP for the elaboration of the future Ph. Eur. text.

## CONCLUDING REMARKS

Dr Vesterinen thanked delegates for their active participation and for generating such interesting discussion. She hoped that delegates had had the opportunity to meet with other stakeholders and to discuss issues that they felt were important in relation to the quality of raw materials. It was a welcome opportunity for the EDQM, EMA and the RCG WP to gather the views of stakeholders on the proposed Ph. Eur. text and to inform them of the work of the EDQM, EMA and the RCG WP.

She summarised that delegates had recognised that the current lack of harmonisation in the quality standards for raw materials represented a challenge for all stakeholders. She was pleased that delegates had felt that the current variability in approaches was undesirable and that a Ph. Eur. text could improve the situation by providing necessary guidance. The discussion groups held at the Symposium further helped to highlight particular types of raw materials and quality attributes that would need to be included in a Ph. Eur. text.

Dr Vesterinen explained that the RCG WP would review the information gathered during the discussion of these issues and would use delegates feedback as a point of reference when developing a Ph. Eur. text. Working in collaboration, the RCG WP of the Ph. Eur. and relevant EMA Working Parties (such as BWP and CAT) would consider how to facilitate harmonisation. She acknowledged that it was important to define the quality of raw materials whilst not limiting access to them. She further explained that according to the usual procedure of the Ph. Eur. Commission, once the Working Party had elaborated the text, it would be published in the forum of the European Pharmacopoeia, *Pharmeuropa*, in order to gather comments and suggestions from all stakeholders.

Dr Vesterinen wished delegates a safe trip home and once again thanked them for a fruitful meeting.

## **Acknowledgements**

The EDQM and EMA would like to gratefully thank the following contributors for their active roles as speakers and moderators of the Symposium sessions: Dr Ulf Bethke, Dr Thomas Hinz, Dr Bernd Leistler, Dr Mark Lowdell, Dr Margarida Menezes Ferreira, Dr Alexis Nolte, Dr Sol Ruiz, Dr Paula Salmikangas, Prof. Jean-Hugues Trouvin, Dr Jaana Vesterinen, Dr Caroline Voltz-Girolt, Dr Sarka Vosahlikova.

The authors gratefully acknowledge the contributions of Dr Mihaela Buda, Dr Sylvie Jorajuria and Dr Laure Taconet during the Symposium and in the drafting of the report. We would also like to thank Mrs Caroline Larsen Le Tarnec, Ms Fiona Gilchrist and Mrs Clare Williams-Stoeckel for their role in organising the Symposium.

## **Authors**

Dr Stephen Wicks  
Dr Emmanuelle Charton