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Closed Workshop on biosimilar monoclonal antibodies and immunogenicity of monoclonal antibodies

Monday 24th October 2011, European Medicines Agency, 7 Westferry Circus, Canary Wharf, E14 3HB London, UK

The aim of the workshop was to create a forum for discussion among stakeholders - academia, learned societies, regulators and industry around the European Medicines Agency (EMA) Draft guideline on 'Similar biological medicinal products containing monoclonal antibodies' (EMA/CHMP/BMWP/403543/2010) and Draft guideline on 'Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use' (EMA/CHMP/BMWP/86289/2010), which were being finalised and were open for public consultation from November 2010 to May 2011.

The final agenda, list of attendees and presentations are available as separate documents.

The draft guidelines are available on the Agency's website.

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Introduction

The biosimilar legal framework has been in place in the European Union since 2003. Since 2006, 14 biosimilar medicinal products (2 somatropins, 5 erythropoetins, and 7 filgrastims) have been centrally authorised. Furthermore, there have been more than 100 Scientific Advice (SA) procedures on biosimilars to date, particularly in recent years within the class of monoclonal antibodies. Until the end of 2011, 28 different biosimilar monoclonal antibodies (mAbs) have received EMA SA in 37 scientific advice procedures. Out of 32 biosimilar SA procedures in 2011, 20 pertained to mAbs (versus 10/16 in 2010).

Activities related to developing the guideline on 'Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use' and the guideline on 'Similar biological medicinal products containing monoclonal antibodies' started with adoption of two Concept Papers by the Committee on Human Medicinal Products (CHMP) in March 2009 and October 2009, respectively. The need for developing these two guidelines was prompted by accumulated regulatory experience indicating the importance of clarifying the position of the CHMP on several important matters relating to the development of biosimilar mAbs and to the immunogenicity assessment of mAbs in general. The current draft versions of the two above mentioned guidelines were released for consultation in November 2010.

The Guideline on 'Similar biological medicinal products containing monoclonal antibodies' is the 7th biosimilar product-class specific guideline. The associated Guideline on 'Immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use' goes hand-in-hand but is not specific to biosimilar mAbs. It rather refers to all mAbs and complements the more general Guideline on 'Immunogenicity assessment of biotechnology-derived therapeutic proteins' (EMEA/CHMP/BMWP/14327/2006).

This was the second workshop organised by the EMA on biosimilar monoclonal antibodies (mAbs). The first one was organised in 2009 and its purpose was to collect stakeholders' views on the topic prior to drafting the relevant guidelines.

The scope of this second workshop on biosimilar mAbs was to discuss with stakeholders specific controversial or otherwise important aspects identified during the public consultation on the two above mentioned Guidelines which ended on 31 May 2011. Controversial aspects that were discussed included: possibility to lower the non-clinical requirements based on a risk-based approach, acceptability of a non-inferiority design instead of an equivalence design in PK/PD or pivotal phase III trials, possibility of a risk-based approach for the immunogenicity assessment of mAbs and studies/data which could be deferred to the post-authorisation phase.

The workshop had an introductory part, where the invited stakeholders expressed their consolidated views on the two guidelines and identified the main issues which would need further discussion. This was followed by 5 sessions. Each session was organised in two parts starting first with short presentations by representatives from originator/innovator industry (companies developing novel biologicals that serve as reference products for biosimilar development), biosimilar industry (companies that develop biosimilars) and regulators followed by a discussion involving all participants.

Introductory part: consolidated views by stakeholders and issues identified for discussion

Presentations highlighting points that require further consideration in the view of the stakeholders were given by representatives from both originator and biosimilar industry.

As part of this introduction session, challenges with clinical endpoints to establish comparability were acknowledged, e.g. Time-to-Progression (TTP) as a primary endpoint in follicular Non-Hodgkin's lymphoma (NHL) with rituximab would require a study that would be much larger than the original pivotal study of the originator product. Therefore, the originator industry would agree that appropriate relevant endpoints for the demonstration of comparability could be considered. Such endpoints should be clinically meaningful and sensitive enough to detect differences between the biosimilar and the reference medicinal product.

The recommendation to perform the pivotal comparative trial in the most sensitive model was also supported by the originator industry. However, ethical concerns and legal aspects were raised against the use of non-licensed clinical indications since the benefit - risk balance would not necessarily have been sufficiently demonstrated for the reference product in the concerned population.

It was stressed that, although the equivalence design is considered the most appropriate design for demonstration of comparability, a non-inferiority design may be appropriate in certain instances (e.g. in oncology settings, depending on the endpoints chosen).

Extrapolation from one indication to another was considered reasonable if the mechanism of action and disease process is similar and where relevant studies have been conducted in sensitive populations; (e.g. psoriasis and rheumatoid arthritis have been studied and extrapolation is proposed from rheumatoid to psoriatic arthritis).

Biosimilar industry representatives acknowledged that the guideline on biosimilar mAbs takes into account aspects that are already known about mAbs in general and the reference products in particular. Emphasis was put on the importance of orthogonal methods, including multiple *in vitro* bioassays, to characterise the mAbs and demonstrate similarity. Variability in terms of quality attributes was acknowledged in the context of the development of a biosimilar but was also reported as significant for the reference product itself, particularly in the case of manufacturing changes. In such cases, comparability has to be demonstrated before authorising such changes and there is a close control by Marketing Authorisation Holders (MAHs) and regulatory authorities to ensure there is no impact on the safety and efficacy of the concerned medicinal product.

It was also stressed that it should not be required for *in vitro* biological studies to cover all functional aspects of the mAb since some may not be considered relevant for the mode of action *in vivo* in humans. In addition, the need for some flexibility in the guideline to allow diverging from the use of the 'most sensitive model' in safety/efficacy trials, if justifiable, was highlighted; since such a design may not be feasible in some settings where difficulties in recruitment arise. Finally, biosimilar industry representatives argued that post-authorisation follow-up of biosimilars should not exceed routine pharmacovigilance.

With regard to the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins, it was stressed that biosimilar mAbs should not be treated as a separate class of mAbs and that the approach should be similar to that followed for changes of manufacturing processes in reference products.

Session 1: Non-clinical issues

The first session dedicated to non-clinical aspects for the development of biosimilar mAbs focused on two issues: the occurrence and detection of off-target toxicity and the concept of a risk-based approach for lowering the requirements for nonclinical studies for biosimilars.

The aim of the non-clinical studies as part of the comparability exercise is to establish similar biological activity potentially affecting efficacy and safety based on non-clinical data. To attain this objective a combination of *in vitro* and *in vivo* studies may be envisaged.

One of the key issues in relation to the non-clinical development was the high species-specificity which led to in-depth discussion on the appropriateness of non-clinical *in vivo* studies to evaluate comparability in terms of immunogenicity, efficacy and more particularly safety.

Off-target toxicity - does it occur and how should we detect it?

mAbs exhibit in general high specificity and affinity properties for their target. Nevertheless, off-target binding of mAbs may occur and current non-clinical studies may not be sufficiently informative in this regard. The objective of this session was to discuss the occurrence of off-target toxicity and potential methods of detection.

Representatives from innovator companies stressed that they preferred to speak of "unexpected *in vivo* findings" instead of off-target toxicity. Unexpected findings had been observed in the past with mAbs.

The case of an innovative mAb used to treat auto-immune and inflammatory diseases was presented during the workshop. *In vivo* non-clinical testing with this compound detected the occurrence of rapid profound thrombocytopenia after a single dose in cynomolgus monkeys. Subsequent *in vitro* tests revealed activation and aggregation of platelets in macaque monkey species, but not for baboon or human platelets. In addition, this finding had not been observed with three other mAbs from the same class against the same target and a modification of the Fc portion was shown to reduce the observed effect.

It was highlighted that the cause for off-target toxicity may involve: mechanism of action, Fc-FcR interactions (e.g. driven by CDR or Fc) and/or product quality attributes. Innovator companies were of the view that *in vivo* assessment for potential unpredicted effects is an important part of non-clinical safety testing for innovative as well as biosimilar mAbs, and reference was made to ICH S6 R(1) which addresses the potential for unexpected *in-vivo* effects and recommends performing a short-term safety study in one animal species. Nevertheless, it was acknowledged that it is uncertain to what extent non-clinical *in vivo* findings are translatable to humans. In addition, *in vitro* assays may only address the known effects, but not the unknown.

Biosimilar industry representatives noted that experience with the currently EU-approved mAbs, showed that the toxicity and clinical safety of already approved mAbs were generally related to their biological target. After approval the safety profile of innovative mAbs is in general better characterised and additional adverse events may be detected. Nevertheless, experience showed that none were suspected to be related to off-target toxicity (Giezen et al 2008, JAMA 300:1887). Moreover, changes in the manufacturing process of innovative mAbs have not led to any differences in off-target toxicity, even when a shift in glycosylation profile and ADCC (antibody-dependent cell mediated cytotoxicity) potency was observed (Schiestl, M. et al., Nature Biotechnology 29, 310-312, 2011). Therefore, since

a biosimilar is designed and produced to be similar to the reference product, it is expected to exhibit the same already known safety profile. In the view of representatives from biosimilar companies the current requirements for extensive in vitro characterization are meant to ensure that off-target toxicity is not an issue for biosimilar mAbs.

Regulators noted that although off-target toxicity has been observed, this is a rare event (see presentation 'Off-target toxicity-a regulator's view') and all published cases have been related to new active substance/newly developed mAbs. The biosimilar is expected to have an identical aminoacid sequence and no differences in antigen binding sites or Ig framework in comparison with the reference product. Similarity is controlled by characterisation of all functional aspects of the molecule by sensitive and quantitative *in vitro* assays in addition to a thorough characterisation at the quality level. Therefore, although subtle quality differences may be expected, functional differences and differences in toxicity profile should not be present and there should be no reason to expect off-target toxicity by the biosimilar. When data from clinical trial applications (CTAs) for five biosimilar mAbs were evaluated, all of which included comparative toxicological studies (sometimes with extensive number of animals), only the known effects were observed and there was no evidence for off-target toxicity.

In vitro methods that could be used to detect off-target toxicity were discussed, e.g. the sensitivity of immunohistochemistry is not adequate so that the suitability of this method is questionable, and the prediction power of protein biochip analysis for these purposes is also unclear.

A risk-based approach - rationale and decision points

For non-clinical studies a risk-based approach is proposed, in that the conduct of animal studies will rely on the potential risks identified based on the quality characterisation and the *in vitro* non-clinical studies.

This approach was in general supported by stakeholders. However, innovator industry considered that one animal study with the biosimilar candidate prior to First-in-Man (FIM) clinical studies should be conducted in order to rule out unexpected findings. A proposal was that the endpoints could be combined in one PK/PD study with safety evaluation. Nevertheless, in exceptional cases the sponsor may consider progressing into FIM studies without an in-vivo animal study, based on sound scientific justification and careful risk assessment, e.g. when there is no relevant animal model. Once more thorough experience with classes of biosimilar mAb is obtained, innovator industry considers that the requirements for *in vivo* animal testing may be revisited and adjusted. It was noted that even if not pharmacologically relevant, the rodent may be considered an alternative test species in some cases (e.g. for PK).

The presentation from biosimilar industry stressed the fact that a candidate biosimilar mAb is the result of an iterative engineering, manufacturing and selection process applying state-of the-art techniques and is designed to match the profile of the reference mAb. Therefore, provided comparability has been demonstrated in state-of-the-art comprehensive analytical testing and appropriate *in vitro* non-clinical assays, animal studies are extremely unlikely to detect any difference between the biosimilar and the reference product. Biosimilar industry also stressed the fact that not all existing *in vitro* assays tests are applicable and meaningful for every antibody and the data produced may not be relevant or conclusive. A proposal was also made to request the evaluation of binding characteristics of the relevant Fc gamma receptors only (instead of all Fc gamma receptors) to avoid production of irrelevant data.

Regulators noted the Guideline which has also been based on the scientific advice given so far reflects a science-based approach. Based on the comments received during the public consultation phase, it was concluded that the three steps proposed in the guideline will be maintained (*in vitro* studies, identification of factors of importance, *in vivo* studies if necessary). *In vitro* comparability studies should be performed on an appropriate number of batches in line with the ICH Q5E guideline on comparability studies for a manufacturing change. Since some effects may not be fully characterised *in vitro*, *in vivo* study may be needed. In such a case, emphasis was put on the 3Rs principle that should be taken into consideration when designing the *in vivo* studies. The studies should be designed to maximise the information and involve a minimal number of animals. These could also be non-terminal studies where animals survive. Finally, comparative toxicity studies should not be recommended (inconclusive data expected).

Panel discussion on non-clinical aspects

During the panel discussion the risk to observe off-target toxicities with biosimilar mAbs was further discussed. It was noted that off target toxicity is in most cases not observed after changes of manufacturing processes. Nevertheless, this could be a possibility in case of important changes such as changes in fucosylation (ADCC etc.).

In relation to previously reported cases of off-target toxicity with mAbs, it was questioned how similar to the class were the newly developed mAbs and it was clarified that these were not similar and had different target epitopes.

Regarding the stakeholders' request to waive certain functional in-vitro tests, it was clarified that there may be around 16 different FcR subtypes which not all may be relevant for the purpose of the comparability exercise. In addition, it was noted that some tests may not provide fully relevant information for the use in humans.

It was also questioned whether extensive non-clinical testing would bring more reassurance with regards to off-target toxicity and emphasis was rather made on post-authorisation pharmacovigilance activities. In this regard, consistent pharmacovigilance requirements between biosimilar mAbs and reference products were also deemed necessary.

The design and methodology of non-clinical studies were also discussed. Non-clinical studies should be comparative and should be designed to be sensitive enough to detect differences between the similar biological medicinal product and the reference medicinal product and should not just assess the response per se. A statistical approach including non-clinical equivalence margins would not necessarily be expected; however, the characterisation of the reference product with in-house methods applied is expected to provide relevant information to estimate acceptable margins (minimum-maximum values).

It was clarified that the concerned Guideline is not intended to address quality requirements for the comparability exercise. These would rather be considered in the revision of the quality guideline on biosimilars.

Session 2: Clinical issues, equivalence versus non-inferiority

Could we accept non-inferiority instead of equivalence trials in specific situations?

The second session was dedicated to clinical aspects, particularly the design of pivotal comparability studies. According to the current draft guideline, similar clinical efficacy between the similar and the reference medicinal product is expected to be demonstrated in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blinded and normally equivalence trials.

Discussion on the choice of the statistical design was triggered by several stakeholders during the public consultation phase highlighting that in some scenarios (e.g. oncology setting depending on the endpoints chosen), the equivalence design may not be feasible for the efficacy trial as it would lead to unreasonable sample sizes.

Innovator companies' representatives were of the view that equivalence trials should be the standard and preferred option, and non-inferiority trials could be performed in specific cases if appropriately justified. Non-inferiority design would not allow excluding the possibility of superior efficacy which could imply different safety profile. Nevertheless, non-inferiority could be used in specific situations, e.g. if the target receptor that is well known to be involved in the mechanism of action for the clinical effect, is continuously saturated at the therapeutic dose. In such cases, a hierarchical test should be considered to first test for non-inferiority and then superiority. If superiority is demonstrated, the product can not be considered a biosimilar. Regarding the determination of equivalence margin, different statistical margins may be appropriate or required based on effect size and clinical setting (e.g. in oncology: adjuvant breast cancer versus metastatic breast cancer).

Biosimilar companies' representatives stated that non-inferiority trials for certain efficacy endpoints could be justified provided that comparable safety is maintained. Since it should be demonstrated there are no clinically relevant differences, the non-inferiority margin should be justified on both clinical and statistical grounds. Based on demonstrated physicochemical and non-clinical similarity, it is not expected that the biosimilar would prove to be better with statistical significance in the last step of the comparability exercise. Non-inferiority trials could be considered acceptable when not meeting the upper margin of an equivalence margin would only mean benefit without posing additional risk for the patients especially in certain indications (e.g. ORR oncology, ACR20 in rheumatoid arthritis) and provided comparable safety is maintained. It was considered unethical to use the equivalence design where a non-inferiority one could be appropriate, as this would imply including more patients than necessary.

Regulators highlighted that, although the equivalence design is the preferable option to show comparability between biosimilar and originator product, the current overarching guideline on biosimilars (EMEA/CHMP/BMWP/42832/2005) does not categorically exclude the non-inferiority design since it states 'if a clinical comparability trial design is not feasible, other designs should be explored and their use discussed with the competent authorities.' However product-specific guidelines are only recommending equivalence studies. Reference was also made to the WHO guideline on similar biotherapeutics where the advantages and disadvantages of equivalence and non-inferiority designs are addressed. Equivalence trials allow a confirmation of the absence of clinically meaningful differences and provide good rationale for extrapolation of efficacy data to other indications of the reference product. In addition, experience has been gained with the used of this design. However, it

requires a larger sample size and a finding of superiority would lead to formal failure of the study (although the study may be adequate for stand-alone application). On the other hand, non-inferiority designs have the advantage of smaller sample size, although the potential to extrapolate between indications may be questioned, when the comparability in the indication chosen for the pivotal trial was shown using a non-inferiority design.

Panel discussion on equivalence versus non-inferiority designs

It was mentioned that intense efforts are made to find those structural modifications that would induce higher potency of the innovative mAb. Therefore in the context of the development of biosimilar mAbs, it is considered scientifically implausible that statistically significantly higher efficacy results could arise from small differences. In addition it was noted that point estimates in a non-inferiority setting should allow for a reasonable estimate.

Stakeholders also stressed that extrapolation may be a challenge even in case of equivalence trials, if the extrapolation is between markedly different conditions. Rather than being dependent on the type of design, extrapolation could be based on the results of the whole comparability exercise.

Participants also discussed the theoretical situation of observing a different safety profile in a non-inferiority trial or observing less immunogenicity with the biosimilar. The former situation would have to be considered in light of the nature of the (different) AEs observed with reference product and biosimilar, whereas the latter situation may have an impact on the efficacy and result in a superiority outcome which would *a priori* not be accepted for a biosimilar. A subgroup analysis in patients that do not mount an immune response was proposed as a solution, but even if the intention to have this analysis was pre-specified the subgroup of patients would be identified post-hoc. In any case, a post hoc analysis in such patients (without an immune response) could be an approach to show comparable efficacy between reference product and biosimilar. Of major importance in these situations would be the clinical relevance of any differences observed, the mechanisms of action, etc, i.e. the scientific plausibility.

Session 3: Clinical issues, indication / product-specific guidance

Is product / indication specific guidance already necessary and meaningful?

In the third session it was discussed whether there would be a need to develop product and indication specific guidelines for biosimilar mAbs.

Although disease-specific guidance is already available for all indications related to mAbs, these may not be relevant for biosimilar development. However, the current guideline on biosimilar mAbs contains product-specific information and refers to indication related issues clarifying that disease-specific guidance is not fully applicable to biosimilars. Since product-specific biosimilar guidelines are expected to be only released after experience has been gained with first biosimilars and scientific advice provides flexibility to discuss on a case by case basis, biosimilar industry was of the view that no additional guideline was necessary at present.

On the other hand, representatives from originator companies would support additional specific guidance to improve transparency and benefit development of certain categories of products/product

classes, e.g. TNF blocking agents or B cell modulating agents. Class-specific or target indication specific guidelines could be envisaged. The rationale for this suggestion was that specific comparability experiments may be warranted for different classes of molecules. When new information is available, this information could be added as annexes for specific drug classes. B cell targeted antibodies represent one example of a product class needing specific guidance, since it has multiple mechanisms of action, such as ADCC, CDC and apoptotic pathways, and many factors influence response.

Representatives from originator companies noted there were advantages and disadvantages in developing indication/product-specific guidelines. The general guideline could be considered as a first step, when further data are available and experience is gained the next steps could be to have more specific guidelines. Those could potentially include requirements for analytical testing, PK or PK/PD requirements specific to distinct targeted populations and molecular class, and guidance on immunogenicity studies in populations expected to exhibit different propensities for anti-drug antibodies formation.

It was suggested by the regulatory agencies representatives that product- or indication-specific guidance may rather be a second step after release of the general biosimilar mAb guideline when more experience has been gained. This would also be supported by the fact that selecting certain products or indications could be seen as unintentionally putting emphasis on that particular class. Further, refining the guideline with respective sections would significantly postpone the finalization of the guideline, and regulatory advice given to companies developing biosimilar mAbs has not yet resulted in a marketing authorisation so far. Any recommendations would therefore be considered premature.

Session 4: Immunogenicity of monoclonal antibodies

How should antibodies against mAb therapeutics be assessed?

This section of the workshop started with a regulator presentation on the challenges and different available assays for the immunogenicity testing of mAbs.

It was stated that as for other biological therapeutics, the principles of immunogenicity testing as outlined in the general immunogenicity guideline are applicable to monoclonal antibodies. Every monoclonal antibody needs to be evaluated individually and appropriate strategies adopted for assessment of immunogenicity taking into account the product characteristics, the nature of the intended use and the therapeutic indication.

It was stressed that the risk of immunogenicity varies between different mAbs so that the strategy for assessing it should be adapted accordingly. Key elements to be addressed during immunogenicity testing (sensitivity, interference, biological/functional consequences) and additional considerations (long half life, interference from other substances, pre-existing Abs, Ab controls) were mentioned.

A multi-tiered approach which includes valid and sensitive assays capable of detecting all relevant Abs should be employed. An overview of some the commonly used assays (enzyme-linked immunosorbent assay, radioimmunoprecipitation, surface plasmon resonance, electrochemiluminescence, other technologies) and their main characteristics was provided including the detection of antibodies in the presence of residual therapeutic and assessment of the neutralizing capacity of induced antibodies.

The presentation concluded that the guideline on immunogenicity of monoclonal antibodies should be read in conjunction with the general immunogenicity guideline, that no single assay for the detection of ADAs can be universally recommended or accepted, but rather that the testing strategy should be

individualised and adequately justified, and that a neutralizing assay should be performed in case of positive results in the detection testing. Distinguishing between neutralizing and non-neutralizing antibodies is essential independently of their risk level. Correlation of antibody expression with clinical outcome is important and has to be thoroughly evaluated.

Risk-based approach – What are the risk factors? Is there anything special for mAbs as compared to other biologicals?

The biosimilar industry argued that the risk assessment process for mAbs should be similar to those used for all biotherapeutics because mAbs as a class have inherently a low risk for causing clinically meaningful anti-drug antibody responses. They also considered that the existing experience and the prior knowledge with the reference product is valuable in designing immunogenicity assays and in the risk assessment, so that the immunogenicity assessment of biosimilars should not be much different from a process change for the reference product. Such immunogenicity assays should be developed to detect clinically meaningful responses and that they should be as sensitive as possible, balancing assay sensitivity and considerations on assay drug tolerance.

The innovator industry stressed that when it comes to immunogenicity assessment of mAbs, the likelihood of an immune response is related to product, process and patient specific risk factors, but also relates to the extensive micro-heterogeneity of mAbs and the often high circulating drug levels. Severity risk factors are predominantly loss of efficacy and hypersensitivity, but also include unexpected activity due to cross-linking and enhanced clearance due to immune complex formation. Post-authorisation monitoring may be necessary in some cases and, finally, assessment of neutralizing potential and allergic reactions requires careful consideration of assay capabilities. They requested clarifications as to whether novel mAb-based analogues (Fc-fusions, mAb conjugates, mAb fragments and mAbs with multi-functional domains) should involve a different immunogenicity assessment strategy and whether it is a choice or a requirement for the sponsor to conduct immunogenicity prediction assays (*in silico* or *in vitro*).

The regulator presentation raised the question whether mAbs can or cannot be considered as low risk products for the development of immunogenicity. The presentation described the processes of risk identification and risk assessment. These included aspects relating to product- and patient-related factors as well as on the clinical context and the nature of the consequences from development of ADAs, ability/necessity to control factors, to reliably detect unwanted immune responses (including an early response), to detect loss of efficacy and to follow patient's clinical responses. Inclusion of a risk minimization/mitigation (considerations on standardisation/systematic approach in assessing immunogenicity-extent of analysis warranted, extent of safety database pre-approval, control for risk factors in clinical trial, need to power for safety rather than efficacy, extent of post-marketing activities) strategy was also recommended.

In the panel discussion, it was considered whether there was a requirement for a minimum number of patients for the immunogenicity assessment pre-authorization. It was considered that no general recommendation could be made for this as it requires a case by case consideration. This would depend on the level of risk, the disease being treated, data accumulated for the reference product (for a biosimilar mAb) etc. For a biosimilar mAb, differences in immunogenicity compared to the originator product would need to be explained, as would differences between the originator's data and that generated by the biosimilar manufacturer.

Similarly, the extent of post-authorisation studies (comparative or not in case of a biosimilar mAb) would depend on differences in unwanted immunogenicity and the level of risk perceived. Assay harmonisation in a post-authorisation setting would be desirable to be able to compare spontaneous reports between products.

Session 5: Pharmacovigilance

What data/studies could be deferred to the post-authorisation phase?

As general remarks, the pharmacovigilance approach for biosimilars should in principle be viewed as more than a tick-box approach, i.e. more than the fulfilment of a number of typical/formal requirements. The new pharmacovigilance legislation (Directive 2010/84/EC) places a lot of emphasis on traceability of biologicals and specifically mentions biosimilars, so that all stakeholders should do their best to strengthen traceability. Pharmacovigilance plans and post-authorisation measures should be equally stringent for reference and biosimilar products. Finally, Good Pharmacovigilance Practices (GVP) to facilitate the performance of pharmacovigilance in the European Union are being developed and will provide relevant guidance.

On general pharmacovigilance aspects, the innovator industry considered that the same pharmacovigilance standards must be applied for biosimilars as for reference products. Moreover, unique product identification of each mAb is required, so that as proposed by the new pharmacovigilance legislation the exact identification of the biological product used in each case is strongly supported. Finally, innovator industry was of the view that biosimilar mAbs should have the same Rapporteur as the reference product. On the specific question posed, post-approval studies should not be a substitute for an adequate pre-approval programme. Furthermore, consideration should be given to what data could be deferred to the post approval phase in case of extrapolation of indications. Innovator industry representatives had somewhat differing views as regards requirement for post-approval indication-specific safety data.

The biosimilar industry representative agreed that there should be consistent requirements for all biologicals, whether originator or biosimilar. In terms of traceability for ADR reporting, this can be achieved by means of the trade name and the batch number and in their view no variation in the INN compared to the reference product is necessary towards this end.

The regulator presentation mentioned the new pharmacovigilance legislation and the emphasis placed in it on biologicals and biosimilars, particularly with regard to traceability. Reporting of trade name and batch number is specifically foreseen in the relevant Directive (Directive 2010/84/EC) for the purposes of traceability. On the issue of substitution, it was reminded that this is handled at the national level and that it is outside the remit of the EMA/CHMP to make recommendations on this. It is debated whether data from the clinical comparability programme should be mentioned in the SmPC of the biosimilar alongside data from the reference product, as this may create confusion. On the risk of off-label use of the biosimilar in indications of the reference product in which the biosimilar is not authorised, it was reminded that the risk of any off-label use is foreseen in the Risk Management Plan (RMP) and that the RMP of biosimilars should cover this aspect. With regard to post-authorisation safety studies (PASS), these should ideally be performed in collaboration between MAHs of reference and biosimilar products and participation of biosimilars in registries should be encouraged.

On the specific question regarding study deferral to the post-authorisation phase, it was mentioned that an RMP should always be submitted for biosimilars, as it is also mandatory for biologicals in

general. Safety data from the reference product should be mentioned in it. Immunogenicity should always be covered and potential off-label use is also of interest in this respect. In case of existing disease- and drug-specific registries, the biosimilar mAbs are expected to participate in these. This would facilitate the collection of additional immunogenicity data, as it will allow a relevant comparison to the reference product to be made.

In the discussion, the issue of regulatory consistency in terms of RMP assessment and update between reference and biosimilar product was raised. As the RMP is not a public document, regulatory authorities are solely capable of ensuring such consistency, which could be achieved, for example, through the appointment of a common Pharmacovigilance Rapporteur, for both reference and biosimilar products.

The extrapolation of safety data in case of extrapolation of indication was a much debated topic. The question raised was whether an indication can be granted in the absence of any clinical data in the clinical setting of this indication. In response it was advised that the acceptability would depend on the overall data package (comparability in all critical quality attributes, reassurance in clinical data collected etc). Safety data may be different in different indications, but rather than studying all indications, one could put the comparability data into perspective with the originator data.

Indication-specific data in indications not covered during the clinical comparability exercise could always be collected in follow-up safety studies post authorisation. However, the extent of such requirements would depend on the data already generated, the level of risk identified etc. This issue would of course become more complex in case of off-label use.

Conclusion of the workshop

In general, the workshop concluded that it is correct, from the scientific viewpoint, to state that a biosimilar mAb development programme is not ‘abridged’ but rather tailored and science-driven. Some of the relevant discussed aspects will be considered in the final revision of the draft guidelines.