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# **[EMEA GUIDELINES ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS: CHALLENGES TO THE BIOSIMILAR INDUSTRY]**

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## FOREWORDS:

I am a Masters student studying Biomedicine program at Karolinska Institute, Sweden. I am doing this work as part of my final master thesis at Karolinska Trial Alliance, Stockholm. I would like to sincerely thank my supervisor Dr. Pierre Lafolie who has ably guided me along my work. I would also like to thank Dr. Sanjeevi Carani who has helped me arrange important interviews and all the others who took their time to participate in my study.

## 1. ABSTRACT

Biosimilar drugs are cheaper versions of off-patent recombinant biotechnological drugs. Similar to generics, they can reduce costs but only by around 20-30% of original drugs price. Since the biotech drugs are highly expensive, even this reduction translates to a huge amount of money and wider availability of these drugs. This will also, in turn, sink healthcare costs worldwide. The European Medicines Agency was bold enough to introduce guidelines for these biosimilar products for the first time and approve products in the European Union. But still the guidelines are in its nascence and hence needs more clarifications and amendments. A series of interviews with the Innovator and Biosimilar companies and the Swedish Medical Products Agency as well as questionnaires to European Medicines Agency members, Biosimilar companies, specialist doctors and local Swedish agencies were conducted. Various safety and regulatory concerns were raised by the Innovator companies and the Medical Products Agency. The biosimilar companies discussed the difficulties they face. Overall the Swedish Medical Products Agency, majority of the specialist doctors as well as the local Swedish agencies embraced the arrival of Biosimilars provided they are approved by European Medicines Agency and they are cheaper than the Innovator drug. The Biosimilar products are welcomed as long as the safety of the human being and efficacy of the drug are not compromised in any way.

## Abbreviations

|       |  |
|-------|--|
| CHMP  | Committee for Medicinal Products for Human Use   |
| EMA   | European Medicines Agency  |
| EPO   | Erythropoietin   |
| EU    | European Union   |
| FDA   | Food and Drug Administration of the United States  |
| HGH   | Human Growth Hormone   |
| ICH   | International Conference on Harmonisation<br>: of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IV    | Intravenous route of drug administration   |
| KTA   | Karolinska Trial Alliance  |
| MAA   | Marketing Authorisation Applications   |
| MPA   | Medical Products Agency (Läkemedelsverket) of Sweden   |
| PK/PD | Pharmacokinetics/ Pharmacodynamics   |
| PTM   | Post-Translational Modifications   |
| S/C   | Sub-Cutaneous route of drug administration   |
| SKL   | Swedish Association of Local Authorities and Regions<br>(Sveriges Kommuner och Landsting)                                  |
| TLV   | Dental and Pharmaceutical Benefits Agency of Sweden<br>(Tandvårds- och läkemedelsförmånsverket)                            |

US United States of America

[Table of Contents](#)

|                                       |    |
|---------------------------------------|----|
| 1. Abstract                           | 2  |
| 2. Introduction                       | 5  |
| 2.1 Background                        | 5  |
| 2.2 Aim                               | 6  |
| 2.3 Delimitation                      | 6  |
| 3. Materials & Methods                | 6  |
| 4. Results                            | 7  |
| 4.1 Results from the interviews       | 7  |
| 4.2 Results from the questionnaire    | 19 |
| 4.3 Evaluation of the Doctors opinion | 22 |
| 4.4 TLV report                        | 25 |
| 4.5 SKL report                        | 26 |
| 5. Discussion & Analysis              | 27 |
| 6. Future studies                     | 28 |
| 7. References                         | 30 |
| 8. Appendix                           | 31 |

## 1. INTRODUCTION- Background:

The Waxman-Hatch Act of 1984 in the US marked the arrival of generics and later the EU also followed suit. This allowed generic pharmaceutical manufacturers to submit new Marketing Authorisation Applications (MAAs) without repeating the clinical trials of innovator companies. The patent expiration of insulin, HGH, interferon and other biotech products opens the market for biosimilar manufacturers (2).

The generic company have to validate that its drug is the same as that of the innovator drug and they are bioequivalent. Their molecule is exactly the same as the innovator. This aided by the fact that their chemical synthesis can be easily reproduced and state of the art analytical techniques like mass spectrometry (MS) provides a complete characterization of the molecule (5). But it is a different case with biotechnological drugs manufactured using recombinant technology. Biologic drugs are made in genetically modified living cells and therefore their manufacture is capricious with inconsistent reproducibility (5). Generic drugs are conventionally small molecules and are less complex compared to biopharmaceutical drugs that are generally proteins with complicated 3D structures. While a small molecule like aspirin has a molecular weight of around 180, a biopharmaceutical like Interferon beta-1b has a molecular weight of 18,500. Further, each individual product also varies in specifications such as its amount of acidic-basic variant content or PTMs such as its glycosylation profile which are difficult to characterize with the current range of analytical technologies (2). Nevertheless, Insulin and HGH are smaller molecules and are comparatively easier to characterize and thereby demonstrate similarities and differences to their innovator counterparts. But as the molecule gets larger, the more difficult it gets to show bio similarity (5). Therefore the boisterousness of the quality aspects and their vigorous monitoring has a huge impact on their safety and efficacy aspects (2).

Innovator drugs have ingenious modes of action and are very valuable to the patient. But they can cost up to 30 times more than a usual small molecule drug (5). As such, even the 20% reduction in costs the biosimilar drugs offer is significant (1). But the road to their approval is riddled with complex technical and regulatory hurdles.

The European Medicines Agency (EMA) has taken the important step in issuing guidelines on similar biological medicinal products. The guidelines recommend preclinical and clinical testing of biosimilars as a prerequisite for MAAs, supplemented with tailored pharmacovigilance of the drugs (7). The guidelines have created a valuable platform for EU legislations to evolve.

#### Project aim:

The aim of this project is to study the various challenges faced by the Biosimilars industry with regard to the new EMA guidelines on biosimilars with a specific focus on Biosimilar Insulins, without compromising on human safety and drug efficacy.

The project also studies the concerns and opinions of the EMA authorities as well as the innovator companies. The study also delves into the thoughts of the prescribing doctors, the Swedish Dental and Pharmaceutical Benefits Agency and Swedish Association of Local Authorities and Regions.

**Delimitations:** The patient population was not included in the study as; in Sweden they do not pay for their Insulin and most other biotech medicines. Therefore it is most likely that they might be indifferent to the biosimilar drugs.

## **2. MATERIALS AND METHODS**

Primary Data was collected from the Medical Products Agency (Läkemedelsverket) of Sweden and other Committee for Medicinal Products for Human Use (CHMP) members, the Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket- TLV) of Sweden, Swedish Association of Local Authorities and Regions (Sveriges Kommuner och Landsting-SKL), Biosimilars companies – Biocon, Wockhardt, Intas Biopharmaceuticals Limited, Ratiopharm and Dr. Reddy's Laboratories, Innovator companies- Novo Nordisk and Sanofi-aventis as well as intellectual experts.

Secondary Data was obtained by searches of PubMed, relevant official websites, science journals, and references from relevant articles, current EU legislations, and guidelines on Biosimilars from the European Medicines Agency (EMA) and relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

Information was gathered from relevant biosimilar and innovator company personals regarding the company perspective of the EMEA guidelines on biosimilars and where the company finds problems with the guidelines. Personals from the Swedish Medical Products Agency were also interviewed on their views and opinions regarding the guidelines present stipulations, about the various factors under their consideration, difficulties and the future of the guidelines. Similarly the TLV and SKL were also interviewed on facts and their views on biosimilars.

Further information was collected using personal contacts, by getting in touch with intellectuals working with biosimilars and the biosimilars industry.

Based on all the knowledge and information gathered, a detailed study was conducted on the various aspects of the EMEA guidelines on Biosimilars, present and possible future challenges, its perceived deficits and ways by which guidelines can be modified to alleviate the difficulties faced by the biosimilars industry, without compromising the safety of the human subjects and efficacy of the drug.

- i. Personal Interviews had the General interview guide approach -  
Ensuring that the same general areas of information are collected from each interviewee; the interviews were more focussed, but at the same time allowed a degree of freedom and adaptability in getting the required information from the interviewee.
- ii. Telephone Interviews were similar to personal interview format.
- iii. Questionnaires were either of open format or closed format ending with open format questions. They were designed to get a wider variety of responses which more truly reflected the opinions of the respondents. The open format questions were aimed to encourage the respondents for their unabashed ideas for changes or improvements as well as extract unexpected and insightful suggestions.
- iv. Email correspondences were of the same format as the questionnaires

### 3. RESULTS

#### Personal Interviews: CHMP Guidelines on Similar Biological medicinal products: Swedish MPA, Biosimilar & Innovator Companies

The interview form is based on the CHMP Guideline on Similar Biological Medicinal Products, Guideline on similar biological medicinal products containing biotechnology-derived proteins as

active substance: Quality issues, Non-clinical and Clinical issues and Guidance on similar medicinal products containing Recombinant Human Soluble Insulin, as well as other relevant EMA and ICH guidelines.

From the Swedish Medical Products Agency, the information on the general aspects of the guidelines and the quality aspects were provided by Mats Welin, Senior Expert, Department of Pharmaceutics and Biotechnology and Ann Johnsson, Ph D. Senior expert - Quality Assessor and the information on the nonclinical and the clinical aspects were provide by Mikael Andersson PhD. Preclinical Assessor and Bertil Jonsson MD Senior Expert - Clinical Assessor.

Dr. Inger Mollerup Vice President in Regulatory Affairs heading the group working within the Future Insulin area, Novo Nordisk, Denmark and Marianne Tallavaara, Regulatory Affairs Manager Sanofi-aventis AB, Sweden provided insights on the Innovator Company's views on Biosimilars and their guidelines.

From the Biosimilar companies, the input was provided by A.V.Sriram PhD. General Manager, Quality & Regulatory Affairs, Biocon, India and Bharat Mahajan MD, Medical Advisor- International Clinical Research, Wockhardt, India.

#### **1. What are your views on the regulatory framework and the legal basis for the guidelines?**

Biosimilar companies say that the legal basis totally talks about approvals of marketing authorisation, but it does not talk about interchangeability. EMA still leaves the question of interchangeability to the respective countries. So after doing all the comparative exercises for a marketing authorisation, it is left to the discretion of the individual countries whether the products can be interchangeable. This they say is a disadvantage for a biosimilar company. E.g. France they took a decision that biosimilar drugs are not interchangeable.

MPA comments that Biosimilars are similar to generics and like generics they are also part of EU legislation but they have some peculiarities that some clinical studies are needed. They claim the legal basis is fine as they more or less allow a biosimilar to be on the market.

They also say that the issue of interchangeability is under discussion in the EMA. The MPA acknowledges that it does look odd if the biosimilar drug was shown and accepted to be similar to the originator and still they are not interchangeable. The argument they say against this is,

normally for biotechnology drugs, the patient will need to get titrated before they can change from one product to another. This can be done only at the level of physicians and not pharmacists.

**2. What are the relevant legislative and administrative provisions in force in the EU that should be considered along with the CHMP guidelines on biosimilars?**

The innovator company response was that the clinical guideline ends with a section referencing additional both biosimilar and general guidance for drug development. All EMEA guidelines are available on the EMEA homepage organised by topic and all ICH guidelines are available from the ICH homepage. They suggest, if a company is uncertain about the applicability of certain guidelines, advice can be obtained from EMEA.

They think that in general the current provisions encompass the concept of biosimilars.

E.g. post-approval the maintenance (safety reporting, variations) are handled as for other drugs

The Biosimilar companies also feel the same. They add that there are ICH guidelines that are enforced in EU when it comes to putting specifications, comparability after a change in the manufacturing process, method validation, and process validation and they are clear to them.

MPA also adds on that they have guidelines on characterization of expression cassettes, how to show stability, how should you validate your method, what is expected in terms of validation, how do you put together a quality specification, etc. Their view is that if the guidelines work with the originator company, it should work with the biosimilars also as everything is similar except for the comparability exercise.

**3. Additional guidance documents/ advice addressing the development of Biosimilars**

Biosimilar companies say that they have only asked for scientific advice on GM-CSF and Insulin analogues which they say they will receive from EMEA.

MPA says that there are discussions going on in EMEA that more Biosimilar guidelines are needed especially product class specific guidelines and this summer of 2009 there will be discussions on biosimilar monoclonal antibodies amid arguments that they are more complex proteins and are therefore difficult to characterize.

**QUALITY ISSUES**

**1. How successful has the guidelines been in addressing quality requirements for biosimilars? What is lacking and any propositions as to how they can be rectified?**

The innovator companies comments that more stringency and clarity of the limitations that cannot be avoided when developing a biosimilar product would be useful. Whereas the biosimilar company can source the innovator product it does not have access to toxicity data and early clinical batches that are crucial in establishing both the experience and specifications. The biosimilar sponsor will not have access to the innovator drug substance and earlier process step materials and the biosimilar sponsor will have to develop their own analytical methods. As a result there is bound to be differences and deficits in the information on assessment of similarity as compared to the assessment that an innovator makes for own process changes. They suggest that it would be useful for the guidelines to acknowledge this to a greater extent.

The Biosimilar companies feel that in the guidelines on manufacturing process, there is not much information excepting that it can be a new organism provided that quality parameters are met. They say that there is enough information on comparability exercise for quality, but not much on other aspects. They say the comparability exercise insists that it has to be a EU reference product. So if they need to introduce the product in the US via the 505 (b) (2) pathway, then they need to get a US reference product and duplicate the entire development. To have multiple reference products for the same drug makes it extremely difficult, expensive and time consuming. They say for example, Insulin cannot be different in different countries.

But the MPA thinks otherwise. They say that for a product in the US, they do not know whether it is representative of the original product or whether it is approved in the EU. They feel if the product is approved anywhere else, then EMA do not know the quality of the product and therefore the comparative trials will be of no relevance. They also say that there could potentially be differences in manufacturing between US, EU or Japan as well as regional variations in evaluation and processing of data. For example, how you look at manufacturing and process validation in Japan and EU are completely different and in Japan sometimes they license on limited data from pilot batches and then they may have variations when they come to the commercial scale. Most companies have products licensed in the EU and US. They suggest that the data can be used as indirect supporting evidence.

## **2. What can change in the manufacturing process of biological medicinal products and how can it affect the product?**

The innovator companies say that many factors can change in the manufacturing process such as composition of fermentation media which can change the degree of glycosylation and the ratio

between product of interest and impurities, scale of fermentation which also can impact glycosylation and they claim several cases of this resulting in changed PK characteristics have been reported. Then they add on that purification steps are optimised, new steps can be added, other steps omitted, formulation can be further optimised. They claim that all these can affect both the impurity profile and the stability profile of the product and therefore they suggest that all these changes be carefully monitored in appropriate comparability programs followed by new stability protocols.

The MPA adds on that there can be differences in the expression system used. This difference is accepted as all impurities need to be qualified on their own and they will not be able to use the same purification process as the impurities would differ regardless. E.g. HGH has both E.coli and mammalian cell products in the market. The catch is then the company would have to do a greater deal to show that the differences are not critical to safety and efficacy.

**3. Which particular parameters (three-dimensional structure, the amount of acido-basic variants or PTM such as the glycosylation profile) do you think are critical to the safety/efficacy profile of these products?**

The innovator company says all these are highly important, the criticality differing from product to product. For example, changes in PTM can result in change in PK characteristics; change in 3D structure can result in altered potency impacting both efficacy and safety. The modified drug may be more immunogenic. Acido-basic variants in some proteins also have reduced potencies. Biosimilar companies also agree that the 3D structure and PTM are critical to the safety and efficacy. Altered glycosylation may affect safety, efficacy, clearance and immunogenicity.

**4. What are the major limitations in the current methods and techniques available today for the full characterization of biosimilar medicinal products?**

Innovator company says that the main and major limitation is the lack of ability to link characterisation/chemical data to safety and efficacy. The innovator company argues that bioequivalence is not the same as bio-efficacy. They say that biosimilar insulin molecules do not have the same efficacy even if they are qualitatively similar to the innovator insulin. For them, it is difficult to say that the efficacy is the same just based on the fact that the molecules are similar. They state the case of Marvel Insulins where one of the reasons why they withdrew their application for bio similarity was that their efficacy was not the same as that of the reference product. The complexity of the molecules is also an important factor. They say that even for

them it is very difficult to characterise their molecule. They have 20 years of experience with the product and still do not fully know all the implications of their molecule. Further, small amounts of impurities below the threshold of what can be characterised with modern methods may still have unwanted side effects like immunogenicity.

For Biosimilar companies, they feel their limitations when it comes to more complex antibodies. They say it is difficult to characterise the glycosylation pattern or the higher order/ 3D structure and will require multiple confirmatory techniques. They also say that they may not be able to do today 3D structure as a batch release test to show the consistency of the batches. Another limitation is the complexity is in determining a similar glycosylation pattern. They say that even innovator companies do not get the same glycosylation pattern when they do multiple batches. So they feel what is important is the process which should be as consistent as possible to ensure minimum variability from the set pattern. But otherwise they claim they have most of the required facilities and even if they lack on some technique, they can rely on contract testing labs. MPA feels that companies have used state of the art technologies and they have elegantly shown that their biosimilar products are similar or they are within the variability. They say that the level of denaturation can be a problem as characterisation by mass spectrometry uses energy which can denature the protein. They add that it is difficult to compare a value obtained in one assay to a value obtained in another assay.

They also say that there are some differences in glycosylation in innovator products and often it is very difficult to say what its impact is. Therefore it is important to understand the structure-effect relationships and recommends Biosimilar developers to compare with different batches of the innovator product. They feel Factor VIII will be a challenge as it is extremely glycosylated and has a complex 3D structure.

**5. How thoroughly can a highly purified product (such as some biotechnology derived medicinal products) be characterized and what can be the clinical implications?**

The Innovator company says that this depends on the size of the molecule, the pattern of posttranslational modifications as well as other factors. For example, they say that the main component of insulin can be characterized extensively; the impurities are present in very small amounts leading to lack of ability to fully characterize these. Large proteins with post-translational modifications: even a highly pure large molecule will have a pattern of post-

translational modifications where some can be mapped out, others present in lower amounts cannot.

The Biosimilar company classifies proteins as non-glycosylated less complex proteins and glycosylated more complex high molecular weight antibodies. They claim that they can study the impact of the manufacturing process change on the quality attributes with advanced scientific techniques like Nuclear magnetic resonance, X-ray crystallography, mass spectrometry, etc to study primary, secondary and tertiary structures of proteins. So it should be possible from the advances in scientific techniques to characterise the impact of process change to show that they have minimal effect on the quality attributes and in turn the efficacy.

**6. What kind of information about the reference medicinal product is needed so that firm conclusions can be made on their similarity with a new biosimilar drug?**

The innovator company says that the information in the European Public Assessment Report (EPAR) about the reference product such as production organism is necessary. The amount of information available in EPAR is roughly the same for various products - more for products newly approved than for products approved many years ago. They say that the less there is available, the more the biosimilar company will have to generate. Other information that the Biosimilar company can avail of is in the public domain, patents and published papers and this varies tremendously between companies. They feel that access to further information will not reduce the amount of documentation necessary to support approval for Biosimilars.

The Biosimilar company feels that there is hardly any information available other than what is available from the EPAR which itself is a reduced version. They say that firstly, there may not be anything about the quality or clinical parameters in terms of whatever end points were used. This could ensure that the biosimilar is comparable to the innovator. Secondly, they do not have access to the active drug substance of the innovator. This they feel is a problem because when they try to extract the active substance from the innovator product they are altering the substance. They may have an indirect conclusion that they have not significantly altered but the tampered drug product is not the same as the original product. So the biosimilar companies feel that the EMA should remove the active substance comparability and instead ask only for the final product comparability. Their argument is that active substance comparability has a lot of limitations and it cannot give a true picture and besides what is going into the patient is the final drug product.

The MPA also shares the Biosimilar company's view on active substance extraction. MPA says that extraction of the active substance can change the substance and then it will need to be validated. The MPA suggests company can do a dummy extraction, take their own active substance, do the same extraction to their substance and then compare the new substance and the initial substance. There will be difficulty in active substance extraction if the substance is stabilized with human serum albumin. The substance can be drowned in thousand of folds of albumin and it takes a very well validated method to get rid of the albumin and analyze the active substance. They also say that in some cases it is possible to do comparative studies at the finished product stage and if they can do this then that is the best and the easiest way. MPA also suggest that the company set some specification based on their experience of the variability of the innovator product. Then they can use their own variability, the innovators variability and their experience from analysis of the innovator in their studies.

**7. What is your opinion on ICH Q5E guideline for process changes during development ?**

The Biosimilar company says that the guideline can be more specific, for example, what all needs to be done if there is a clone change. Even in clone change there can be major/minor medium change. So the company proposes that the definition of process change should elaborate classification of what is considered as a change and what is required to be done.

**8. What are the usual patterns of impurity profiles and product related substances seen with biotechnology derived drugs? What is considered a significant contamination?**

Innovator company answers that the impurities are formed by chemical and physical degradation-product related impurities as well as impurities coming from the manufacturing process- process related impurities. The latter are completely process dependent, not possible to generalize. They state the example of HGH where it has been demonstrated that the increased level of host cell protein led to increased formation of antibodies against HGH (Omnitrope® EPAR).

Biosimilar company states that the impurity profiles of protein therapeutics are different from generics as the former have non-toxic impurities. So they believe they can be given a higher rebate on the amount of impurities. At the best they might have a potential impact on immunogenicity. That too they believe is more hypothetical rather than practical.

For small molecules, the allowed impurity level is 0.15%. They claim they have enough evidence to show that protein product impurities at the level of 0.15-0.25% are not toxic and

believe impurities can be regarded significant only in levels as high as 2%. Product related substances are the des-amido forms, aggregates, oxidized forms, partially reduced forms, etc. Most of them are active, have similar pharmacodynamic action and no toxicity. They claim that these substances may also have same potency as potency with the bioassay has a variability of 10-15% and so one will not be able to make out the difference in their potencies. They claim the substances may be equally active forms. They add that as long as there is a proper control on process related impurities, particularly host cell DNA and proteins, they have no clinical significance both in terms of efficacy or safety.

MPA believes each product is unique in terms of their process and product related immunities and they may have effects which should be looked for. Higher degrees of variability in glycosylation and charged forms need to be addressed. More variability in the range of carbohydrates is easier to characterize than if another expression system introduces glycosylation at different amino acids compared to the reference product. For them, what is not clear is the safety and they believe safety needs to be addressed by trials with very large populations. Impurities are not part of the comparability but they should be adequately characterized. E.g. it was an issue with one biosimilar that desamido forms in their HGH were too high. Desamido forms are still active forms and it is not necessarily a clear impurity but it is a deviating form from the intended.

### NON-CLINICAL

- What is your opinion on non-clinical comparability studies?

Biosimilar company states that EMA already asks for a very good amount of comparability exercises for quality. They suggest that there should not be any insistence on non-clinical comparability because they feel that animals are unnecessarily being sacrificed for establishing the safety of products which have already been in the market for a long time and human safety data documented and available. They see no reason why comparative preclinical studies with the reference product need to be done just to show comparability. That way they can also save six months time. Biocon claims to have 3 ½ years of experience with insulin.

The MPA says that this is just a minimalistic program to look at differences and thus do not give any meaningful toxicological picture of the product. The basis of the program is that the safety and efficacy of the innovator product is already established and the new product must show similarity. If there are any findings in the study, then the company needs to do follow up studies

in order to exclude any concerns. If they fail to do that, then though it does not mean that the product is any worse in terms of safety or efficacy, but it means the company cannot really claim bio similarity.

## CLINICAL STUDIES

### 1. What is your opinion regarding the guidelines for design of comparative PK/PD studies?

The innovator company feels that the hurdles are related more to the area of disease than the origin of the product. For Insulin, study population and design have to take into consideration that endogenous insulin will impact the study.

For Biosimilar company, the guidelines are not difficult. They say that if they want to minimize variability they can go for 200 patients but then it becomes expensive. But they feel that, based on history and information they have, EMA can define the number of patients needed for the comparative PK/PD studies. Their argument is that if EMA can come up with a minimum of 28 day preclinical studies to show safety of product, then they can state the minimum number of patients. They suggest 30-50 patients per study with each formulation.

The MPA states that for short acting Insulin, the glucose clamp model is the most sensitive model to pick up possible differences. It is a little bit difficult with long acting insulin but MPA says that also has been done. The rationale is that if the kinetics is comparable and they do not see any differences then the molecule is similar to the innovator from a biological perspective. And then there should be no need for further studies. The only concern then is about immunogenicity. This is the general principle for all biosimilar products. If the company can define the PK/PD characteristics of their product with well designed studies, then they can say that it is a biosimilar product and should have all the indications irrespective of the area. The MPA then says that due to reasons of immunogenicity they also want to see long term comparative studies to show that immunogenicity is similar. The duration of the studies should in principle relate to what is known about the immunogenicity for the innovator. They think that 1 year should be sufficient in general and they can extend depending on the behavior of the innovator from an immunological perspective.

Further, they also state that this type of studies can incorporate efficacy trials as well. They say that the extent to which it is necessary is arguable. The reason they give is when it comes to efficacy, normally the effect of an add-on hormonal therapy is relatively small and the study would not have the possibility to detect differences in activity. Besides, the relationship between

dose and efficacy is rarely seen because dose for the innovator is frequently determined based on short term tolerability studies. In Europe, the MPA believe, many want efficacy studies to be reassured that there is no real difference but for them as long as they get good PK/PD studies they are satisfied.

**2. In case the originally authorised medicinal product has more than one indication, how will it be for the biosimilar drug E.g., Insulin in type 1&2 diabetes?**

The biosimilar company says that for products like insulin, the mechanism of action is very well characterized and understood. The trials can be done on type 1 patients and results can be extrapolated to type 2.

The MPA says that if the company has good characterization data really concluding that theirs is a biosimilar product, then they would be happy to extrapolate from studies on one indication to all the other indications. But the MPA laments that it is rarely that they get so good data which come with relationship between dose and efficacy. So the company will have to use other types of information or just reasoning based on what they normally know about the type of molecules and that MPA thinks is tricky. For Insulin, the MPA do not think there is a need to clinical trials on both type 1 & 2 patients.

**3. In certain cases, comparative PK/PD studies between the Biosimilar and the Reference medicinal product may be sufficient to demonstrate clinical comparability, provided certain conditions are met: What is your opinion regarding this statement? Are there any concerns in circumventing efficacy/comparative clinical trials?**

The innovator company states that clinical trials are always required to establish comparable safety/immunogenicity. Still, there could be differences in safety not picked up in these trials, and small differences in efficacy could also be unnoticed. They could also miss out on those patients that are not in a homogenous group and respond differently.

The biosimilar company says they are characterizing the drug at the molecular level to show that the mechanism of action is similar. Good PK/PD studies should reduce clinical trials. They can do limited trials to show comparability and that too looking from an immunogenic perspective. Their argument is that with generics, by just doing bioavailability and bioequivalence studies, they can sufficiently characterize the product. So if they can sufficiently characterize insulin also then they should not have a different criterion of six months comparative safety/efficacy studies.

The MPA also states that the only worry is about immunogenicity. To show that biological substances are identical would need impossibly large studies. So they say that they have to accept some degree of uncertainty around the efficacy estimate. The MPA adds that there are cases where PD markers are difficult to get as with trastuzumab and herceptin. They need to look at the tumor tissue and this cannot be done in short term studies unlike insulin, GM-CSF and anti tumor monoclonal antibodies which have good PD markers.

**4. Who and what determines the number of subjects/design needed for the trials?**

Innovator company says that this is done according to standard guidelines for design of clinical trials including statistical considerations and the number of patients needed should be related to the PK/PD parameters.

The biosimilar company says they have to come up with the numbers and give justification that this is satisfactory and then only EMA will review the application.

The MPA states that the biosimilar company must convince that their product is better than a placebo. Normally they demand that 50% of the activity should be retained. Then based on clinical judgment they have to decide on how much they are prepared to lose in the worst case, say 5%. Then the company can set up a study designed to show on the assumption that they are similar and the confidence interval between the reference and the biosimilar is no more than 5%. That determines how large the clinical trials should be.

## CLINICAL SAFETY AND PHARMACOVIGILANCE REQUIREMENTS

**1. What is the opinion on the pharmacovigilance plan for Insulin?**

The innovator company says that for Insulin, hypoglycemia and injection site reactions are the most common risk factors to be considered in their pharmacovigilance plan.

The biosimilar company adds that HbA1c can be used as a secondary point and the fact that patient can be on other medications having to be considered in the pharmacovigilance plan.

For the MPA, the main concern is immunogenicity. For the innovator product, they have uncertainties about cellular safety aspects, infections, autoimmune disorders and so they have a different pharmacovigilance plan. For biosimilars, it is unique as you are building on the established safety of the originator. For a biosimilar of an innovator product that has been on the market for at least 10 years, they already have a lot of information about its safety.

**2. Opinion on the Pre-licensing safety data requirements and the subjects required?**

The innovator company states that the number of patients should be based on the safety profile established for the innovator product.

The Biosimilar company believe that if they have 150/arm of the study, then that should be enough to give the required pre-licensing safety data.

The MPA believes that most if not all safety issues are related to the products pharmacological activity. The reference product may have a certain amount of neutralizing antibodies of importance that can cause loss of efficacy. Then, how much higher than that would be acceptable, decides in principle, the size of the safety database. They comment that other agencies look more on adverse event reporting. In many cases, the safety data base might be regarded as too small as they normally have no immunogenic problems with the reference product and also for the biosimilar product at the time of licensure. Therefore there is the need for pharmacovigilance program. The most well known problem is what happened with EPO where, probably due to minor change in the production of EPO, neutralizing antibodies were produced. In the case of EPO, the problem was much more pronounced as it will neutralize the endogenous EPO also. For other compounds like monoclonal antibodies, the consequence is only loss of activity, perhaps immunological reactions, but the consequences are not as far reaching as for endogenous proteins. So that also goes into the thinking when they decide it is appropriate to license a biosimilar product.

**3. Are there any additional/particular details to ensure traceability for biosimilars?**

The Innovator company says that the products should always have unique names and complete traceability should be ensured by careful reporting of product, including name of producer, and batch name.

**4. Is the risk of immunogenicity different in different therapeutic indications?**

The Innovator company answers yes because different patient populations may have different immune status. For some indications, the MPA says, the subjects might be on concomitant medication of drugs modulating the immune system and this should also be considered.

Questionnaires: [EMA guidelines on Biosimilar drugs- EMA & Biosimilar companies.](#)

The participants were CHMP members and biosimilar drug producing companies. 5 CHMP members and 3 biosimilar companies responded.

Almost all of the 5 CHMP members who responded think that the biosimilar guidelines are satisfactory and adequate or excellent. Member from Spain Dr. Sol Ruiz says “We are the ones who have developed the guidelines so, from our point of view, they are satisfactory so far and only they would need review as more experience is gained with the evaluation of more biosimilar products (as it is the case of the EPO guideline)”. Both Maltese member Dr. Patricia Vella Bonanno and Hungarian member Prof. János Borvendég, said the guidelines addressing quality requirements for biosimilar drugs with respect to biological activity is inadequate and need amendment. Prof. János Borvendég also thinks that the quality guidelines with respect to validation of analytical methods and the nonclinical and clinical guidelines are inadequate and need amendment.

Dr. Patricia adds that there are too few MAA for biosimilars to adequately qualify if the guideline has been successful and so it is still premature to make such an assessment at this time. This view is also shared by her Romanian counterpart Dr. Robert Ancuceanu. Dr. Lyudmil Antonov of the Bulgarian Drug Agency also reveals that they have so far not received an application for a biosimilar product and so they have no experience on which to base their answers to my questionnaire. Dr. David Lyons of the Irish Medicines Board says “As a technical incompetent in the area I have been shocked at the reluctance of the technically competent to sign off, we know r-HGH is what it is and a bit more glycosylation here or there is vanishingly unlikely to make a difference yet this type of issue used as an excuse not to proceed. Perhaps the guidance was used to support this stance and may actually have acted as a hindrance. I suspect the situation was probably exacerbated by pressure from the innovatory industry.”

For biosimilar companies, Dr. **Karl Heinz Emmert**, Biotechnology Research & Development, Ratiopharm, Mythili Mamidanna, Media: Dr. Reddy’s Laboratories and Dr. Samir Sangitrao RAC (US), Head - Regulatory Affairs, Intas Biopharmaceuticals Ltd were responding to the questionnaire.

Both Ratiopharm and Intas says the biosimilar guidelines were inefficient in providing applicants with a ‘user guide’, showing where to find relevant scientific information in the various CHMP guidelines, in order to substantiate the claim of similarity. Ratiopharm and Dr. Reddy’s Laboratories both say the guidelines are inadequate in addressing non-clinical data: *in vitro* studies and clinical data: efficacy trials. Ratiopharm also thinks the biosimilar guidelines

are unsuccessful with regard to its fulfilling of its stated purposes to introduce the concept of similar biological medicinal products or to outline the basic principles to be applied as well as most aspects of nonclinical, clinical and immunogenicity guidelines.

Intas Biopharmaceuticals expects more from the guidelines addressing quality requirements for biosimilar drugs with respect to comparability exercise for quality, purity and impurities and specifications of the similar biological medicinal product. They say that few examples and listing of tests to be done under each category required to demonstrate similarity will help. For examples, aggregates impurities can be tested by SDS PAGE (gel electrophoresis), SEC HPLC (Size Exclusion Chromatography), Analytical ultracentrifuge, etc. Also, in case of Europe some of the molecules has monograph in European Pharmacopoeia. The specification / limits given in Pharmacopoeia are much wider than what regulatory agency expect. So if EMEA can give issue a guideline in what they are expecting for each product or class of product. It will be very helpful to industry. EMEA has already given guidance on non-clinical and clinical aspects so guidance on quality attributes and the limits that EMEA is expecting would give clear understanding and will also help for uniform standards for all the Biosimilars entering Europe.

#### What additional information needs to be added to improve the guidelines?

Dr. Reddy's Laboratories: interchangeability has to be addressed if the EMEA is really serious about smaller Generic companies producing these complex medicines...and the requirements for this has to be risk-based and cannot really be full-fledged trials.

Ratiopharm: Definition of clinical similarity and clinical requirements for MA.

Intas: Impurity characterization- Currently there is an available guideline on impurity characterization for pharmaceutical products. As pharmaceutical and biotech impurities vary a little bit, a guideline which will focus on biotech impurities and the characterization required for the same will be helpful. For e.g. at which % of impurity one needs to report the impurity, at which % one has to identify / characterize, etc.

All three companies needed to contact the EMEA for scientific and regulatory advice. Both Dr. Reddy's Laboratories and Intas rated the EMEA response as satisfactory or good, but

Ratiopharm rated the EMEA response to general guidelines on Biosimilars and on nonclinical and clinical issues to be poor. The reason they gave for the poor rating was the CHMP changed requirements between scientific advice granted to one company and final information asked from other companies for the same protein, thus approving products with very different data bases; e.g. products were approved although dose equivalence was not shown, bioequivalence to the reference product was not demonstrated and the safety data base was very limited.

#### General comments/propositions on how EMEA can improve on Biosimilars Regulation.

Dr. Reddy's Laboratories: With the FDA now on board with Biosimilars and Japan also considering the same, it is about time for the ICH to get involved and harmonize across regions.

Ratiopharm: To define clearly what is required for MAA instead of frequently changing requirements.

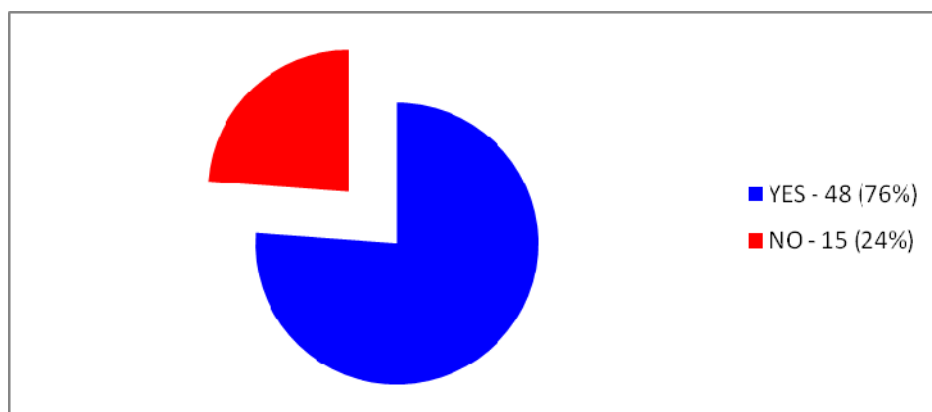
Intas: EMEA, FDA and other regulatory agency should recognize the comparability data obtained from reference product obtained from any one region (US/EU). They should not ask for repeat of quality comparability with reference product from each region.

#### Questionnaire on opinion of Specialist Doctors regarding Biosimilars

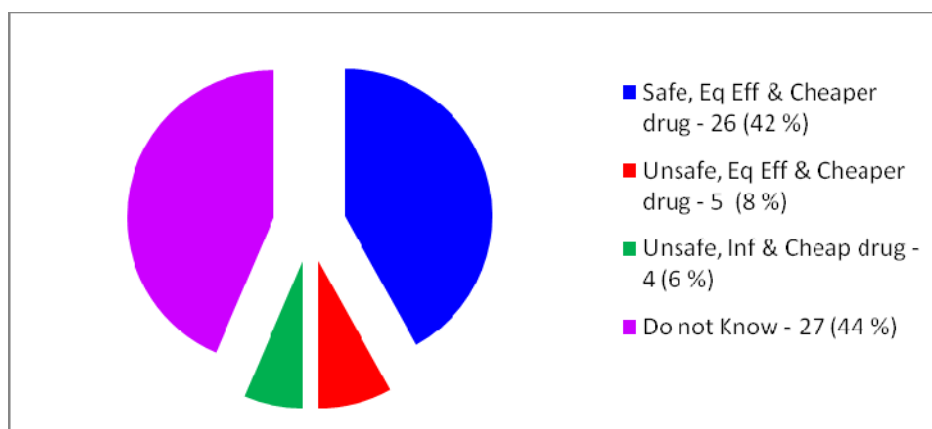
The participants are nephrologists, endocrine and diabetes specialists and oncology specialists from all over the world.

Number of participants: **335** & Number of respondents: **63**

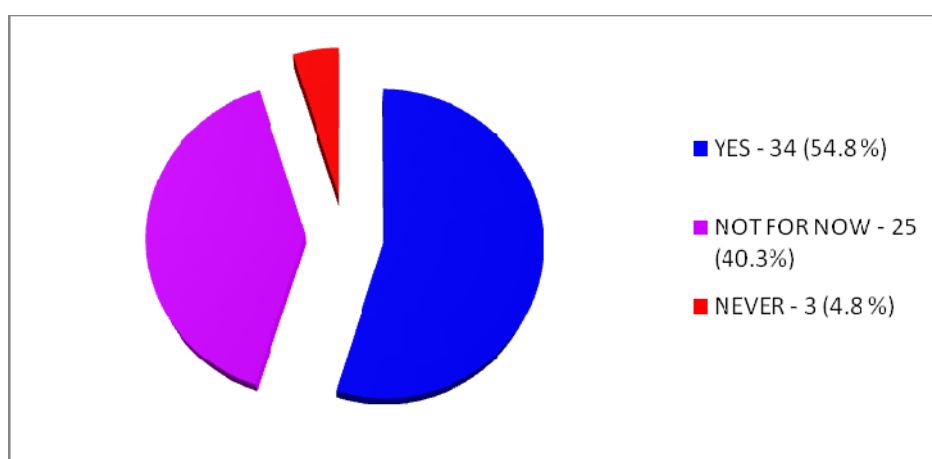
#### 1. Are you aware of Generic Biotechnology drugs/Similar Biological medicinal products/Biosimilars? *Total response: 63*



**2. What is your opinion regarding a Biosimilar drug? Total response: 62**



**3. Are you willing to prescribe any Biosimilar drug if it is possible to do so?**



**4. Please state the reasons why you will or will not prescribe any Biosimilar drug.**

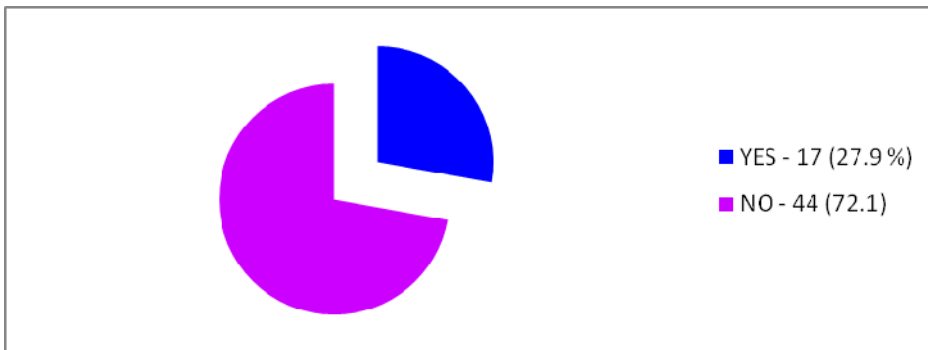
Total response: 58

Some doctors are willing to prescribe biosimilars if they are proven to be safe, effective and more cost-effective. Some look for information on antibody formation, data regarding the manufacturing methods (e.g. mode of synthesis and purification) and even the reputation of the company. In Sweden, a doctor thinks they are obliged to do so as the pharmacy will switch to the cheaper drugs anyway. Also in Sweden, most of their epoetin is given in-hospital and so the negotiated price by Stockholm County Council will be important.

One doctor says that as with most new drugs, they usually try with a few patients suitable for the product and as more experience of the drug evolves they can expand the use if there is a clear economic benefit while others simply say “Why not” as they are similar by definition and patients who require the biosimilar drug and benefit from it should be prescribed the drug.

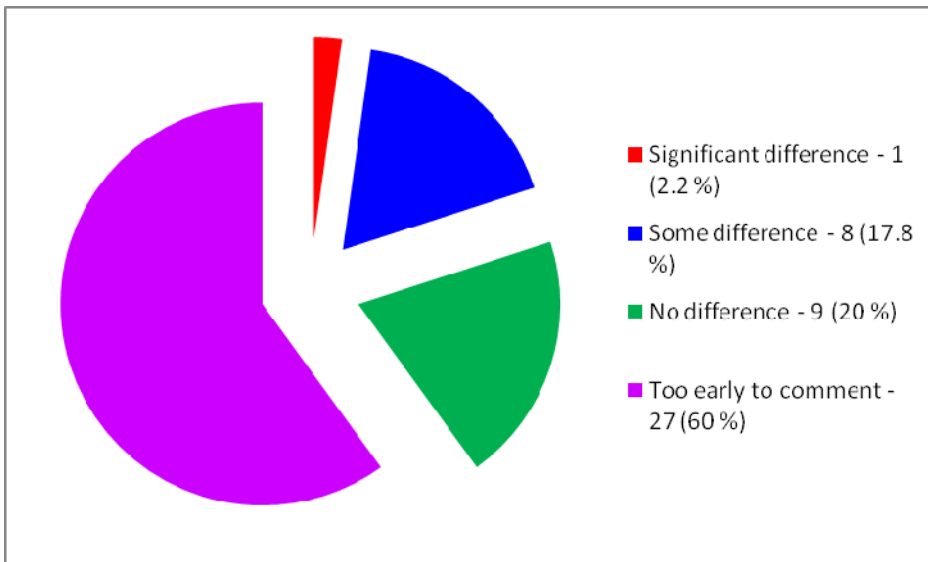
The doctors who are not willing to prescribe biosimilars think it is better to use the originator drug with which they have experience as they are unsure of the safety, dosage, efficacy and cost-effectiveness of the biosimilar drugs. They say they do not have sufficient knowledge about biosimilars, there is lack of documentation and they want to wait for more information about the potential risks. Some say a biosimilar drug is not always equally effective, unsafe and inferior and others say “I trust drugs that are proven to be safe and effective in clinical trials” and “I respect the original developer and clinical data they collect”.

**5. Have you ever prescribed a Biosimilar drug? Total response :61**



**6. Have you observed any clinical differences between Innovative drugs & Biosimilar drugs?**

Total response: 45



**7. Are you willing to prescribe a biosimilar human soluble Insulin if it is possible?**

Total response: 60. 35 Respondents said YES while 25 said NO

**8. Please justify the reasons for your answer to the above question. Total response: 57**

The doctors say that if the biosimilar insulin is sufficiently documented and safety tested then it is in their interest to prescribe cheaper products and reduce medication costs. They think insulin is an easy molecule to make and test and are willing to prescribe if it has same efficacy as porcine insulin or biological insulin. They believe biosimilar insulins would do the same job as existing branded human insulins

In contrast some doctors say they trust more original insulins. Some say insulin has to be “BioEqual and not BioSimilar”. Others do not have sufficient knowledge about biosimilar insulins. One doctor commented that biosimilar insulins may have a better pricing but then their equipment to give insulin must be as good as those for the original insulins. Some even say that patients in their country do not pay for their insulin and their government can pay for the original human insulin.

**Telephone Interview: Dental and Pharmaceutical Benefits Agency**

**(Tandvårds- och läkemedelsförmånsverket- TLV)**

**By Niklas Hedberg, Medical Investigator.**

**1. Who pays for expensive biotechnology drugs like Insulin, EPO, HGH, G-CSF, in Sweden?**

In general, co-payment by patients is about 20% of the entire cost of the drugs. For more expensive drugs it decreases and for this group of drugs it might be as low as 2-3%, exact figures can be found but is not available at the TLV. The rest is paid by the County councils through the National Government Funding.

**2. Does the scheme cover all patients who need biotechnology drugs or only those who need immediate medical care?**

The scheme covers all patients who need biotechnology drugs. There can be restrictions on some indications, but currently there are no such restrictions on any biotechnology drugs.

**3. What will be the TLV attitude towards Biosimilar drugs/ Generic Biologic drugs? Will it be welcomed like the Generics?**

Yes, the biosimilar drugs are welcomed by TLV. The assessment will be simple as long as they have a lower cost than the innovator drugs.

**4. Are there any Biosimilar drugs covered in the TLV pharmaceutical reimbursement.**

Yes there are.

**5. Are there any Original Innovator drugs which were previously not covered by the pharmaceutical reimbursement system but their biosimilar version is included.**

The TLV is not aware of any Biosimilars drug/company that did this and thinks this is unlikely as it will prove to be very difficult for them, even though there are no legal hindrances for this. If a Biosimilar company apply for a drug whose Reference drug is not included in the Pharmaceutical reimbursement system, the company will then have to provide full medical documentation and health economic documentation to prove their drug is efficient and cost-effective.

**6. How the cost-effectiveness principle is applied to biosimilars and are there any special requirements or principles when you consider an application from a biosimilar drug?**

Formally, the Biosimilar drugs are considered by the same criterion as their Reference drugs but in practice, it is much easier for the Biosimilar drugs. The Reference drug has to provide documentation to prove its Efficacy and Cost utility analysis. On the other hand, since the Biosimilar drug has the same efficacy as the Reference drug, the technique they use to argue about the cost-effectiveness principle is cost minimisation and price comparison. This off course is valid as long as they have a lower cost than their reference drug.

**Swedish Association of Local Authorities and Regions (Sveriges Kommuner och Landsting- SKL) Email Interview by Agneta Rönn  
Manager, Section for Statistics, Economy and Governance Division.**

They say that they have not compiled statistics on biosimilars yet.

1. The Stockholm County Council is responsible for buying the drugs and it is them who make the savings with biosimilars.

2. Biosimilars are more difficult to get compliance than the generics, because the price differences are less. There are rumours that the products are not that equivalent and that in some cases where the drugs are purchased by placing order, the originals can become cheaper.

However, biosimilars are invaluable and have an important place. They will have more important role in the future to create competition in the biotech drug market. We have not quantified any

data yet and are at the beginning of the development and at the present, do not have much savings.

#### 4. DISCUSSION & ANALYSIS

Understanding and critically evaluating the EMEA guidelines on Biosimilar products is of crucial importance as we need to facilitate their entry into the market. Original biotechnology drugs are highly expensive. Therefore Biosimilars are of immense value to us in face of spiralling health care expenses and the current global financial crisis (1). But the biosimilars should not be given a free rein as well. They should be carefully assessed keeping in mind, the safety of humans and efficacy of the drugs. The importance of Biosimilars in the future is further highlighted by the fact that several innovator companies already have generic units or are moving to acquire them (4).

The EMEA cannot write a cook book explaining what companies should do for biosimilars. It is up to the companies to decide based on the principles put forward in the guidelines and discussions with the EMEA. From a quality point of view, it is more challenging to do a biosimilar than an original drug because the biosimilar companies not only need to develop their own product but also show that it is comparable to the originator. There is misconception in the community including doctors about biosimilars as drugs having a full opening into the market with limited clinical data. But the fact is, unless they have a sound basis in pharmaceutical development and comparability, they have no chance at all for approval. There are also apprehensions that Biosimilar companies do not have any possibility to investigate complications or reactions to their product like their big Innovator counterparts. This was evident in the talk with the MPA and the survey of the specialist doctors. A large majority of them expressed willingness to prescribe biosimilar drugs amid caution and apprehension but very few have actually started prescribing them. A biosimilar cannot be made in a backyard like a generic. It needs a lot of investment and therefore the savings are less. But for expensive biotechnology drugs, even a 20% rebate is still significant. This supported by the results from the interviews with the Swedish MPA, TLV and SKL suggesting that Biosimilar drugs are very much welcome as long as they are approved by EMEA and cheaper than the innovator.

Looking at the biosimilars market, it is a surprise that there is not yet a biosimilar Insulin. It is a largely used protein and fairly simple to manufacture. Reasons are likely that it is a reasonably cheap product and the companies usually have a wide portfolio of soluble insulin, analogues and medical devices. Besides analogues are also gaining in popularity. The amount of money made from Insulin will be much less compared to HGH or EPO. There are also the efficacy and immunogenicity issues (6). According to the information given by Sanofi-aventis of Sweden, Recombinant Human Soluble Insulin has a market share of only 14.1 % while other insulins hold 85.9%. It might be for these reasons; companies were slow to start on the Insulins compared to other biosimilar products.

For a company to apply for MAA of a Biosimilar, the company should apply directly to the EMA as biosimilar drugs are generally biotechnology products. Their application will be discussed by the CHMP which will then appoint a Rapporteur and a Co-Rapporteur country who will conduct the assessments. The other members are allowed to comment on their decision and then there is a majority decision in the end on whether the product is acceptable or not (6). The various parts of the guidelines are outsourced to working parties under the CHMP - The Biotech Working Party (BWP) for the quality issues, The Safety Working Party (SWP) for preclinical issues, The Efficacy Working Party (EWP) for the clinical part. Moreover, ad hoc working parties have participated in both writing the over-arching guideline as well as the product specific guidelines (insulins, growth hormones, EPO, G-CSF etc.) (3).

The ICH has the responsibility of taking up the issue of Biosimilars and harmonising the guidelines. This would go a long way in reducing the costs of biotech drugs.

The EMA guidelines are still in its nascence and it might be premature to make an assessment now. But from all the data that had been collected so far, it is pretty clear that EMA has a job in hand in revising the present guidelines and forming additional product-specific guidelines as more and more generics as well as innovator companies delve in to the biosimilars market.

Insulin is probably the most well characterized product and fairly easy to show comparability. It has reliable surrogate markers and it is fairly well concentrated in the final product. Therefore it is not difficult to do chemical testing and structural analysis on the active substance or the

finished product (6). Therefore Insulin in particular should be encouraged into the biotech market provided they satisfy the entire EMA criterion for human safety and efficacy.

**Future Studies:** Future studies can focus on comparative study of pharmacovigilance reports of Biosimilars and their respective Innovator drugs. As more and more experience is gained from biosimilar products, their safety and efficacy profiles will become clearer. Doctors and patient groups can be involved to assess the safety and efficacy of biosimilars and compare them to innovator drugs. Patient groups can be assessed on their treatment satisfaction quotient for the biosimilar products. Doctors will be able to assess the safety and efficacy using primary and secondary endpoints. As more and more companies enter into the biosimilars field, the CHMP members will gain more experience and better insight into the various challenges they will face. A future study with the CHMP members to pool the information they have gathered over time will further enhance the understanding of how to approach these complex biosimilar products and ensure better management of the safety and efficacy issues.

## 5. REFERENCES

1. European Generic medicines Association (EGA) [Online]  
Biosimilar Medicines | FAQ, Frequently Asked Questions about Biosimilar Medicines  
<http://www.egagenerics.com/FAQ-biosimilars.htm> [Accessed: 3 March 2009].
2. Italian Biotechnology Directory, Global biotech overview 2008 [Online]  
[http://www.biodirectory.it/show\\_section.php?sectionId=111302](http://www.biodirectory.it/show_section.php?sectionId=111302)  
[Accessed: 10 December 2008].
3. Jens Ersbøll MD, CHMP member, Chief Medical Officer, Danish Medicines Agency - Email response on March 26, 2009.
4. Pfizer, Aurobindo in Deal to Sell Generic Drugs  
Pfizer, India's Aurobindo in deal to license and sell dozens of generic prescription drugs  
By Linda A. Johnson AP Business Writer  
Trenton, N.J. March 3, 2009 (AP) [Online] [Accessed 15 March 2009]  
<http://abcnews.go.com/Business/wireStory?id=6994762>
5. Susan Aldridge, 01 June 2007.  
Why biosimilars are not true generics. [Online]. Pharmaceutical Technology Europe  
(<http://www.ptemag.com/pharmtecheurope/Biopharmaceuticals/Why-biosimilars-are-not-true-generics/ArticleStandard/Article/detail/435320>). [Accessed 5 September 2008].
6. Swedish Medical Products Agency Interview on 2nd April, 2009.
7. wp – 4th April 2006 © Biopro Baden-Württemberg GmbH [Online].  
(<http://www.bio-pro.de/en/region/ulm/magazin/02081/index.html>)  
[Accessed: 6 September 2008].

5. APPENDIX

**Interview List and Timetable**

| <b>Date</b>    | <b>Contact person</b>             |
|----------------|-----------------------------------|
| March 12, 2009 | Niklas Hedberg                    |
| March 13, 2009 | Agneta Rönn                       |
| March 23, 2009 | Dr. Inger Mollerup                |
| March 24, 2009 | Marianne Tallavaara               |
| April 2, 2009  | Mats Welin & Ann Johnsson         |
| April 2, 2009  | Mikael Andersson & Bertil Jonsson |
| April 9, 2009  | Bharat Mahajan                    |
| April 13, 2009 | A.V.Sriram                        |