European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT
FOR
Insulin Human Rapid Marvel

International Nonproprietary Name:
Soluble Insulin Injection

Procedure No. EMEA/H/C/845

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu. http://www.emea.europa.eu

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LIST OF ABBREVIATIONS

ADR	**ADVERSE DRUG REACTION**
AE	**ADVERSE EVENT**
AFSSAPS	**AGENCE FRANCAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE**
ANCOVA	**ANALYSIS OF COVARIANCE**
AUC	**AREA UNDER THE CURVE**
CHMP	**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE**
CI	**CONFIDENCE INTERVAL**
CRO	**CONTRACT RESEARCH ORGANISATION**
DNA	**DEOXYRIBONUCLEIC ACID**
DMF	**DRUG MASTER FILE**
GIR	**GLUCOSE INFUSION RATE**
FAS	**FULL ANALYSIS SET**
HBA1C	**GLYCOSYLATED HAEMOGLOBIN**
IGG	**IMMUNOGLOBULIN G**
I.V.	**INTRAVENOUS**
PD	**PHARMACODYNAMIC(S)**
PK	**PHARMACOKINETIC(S)**
PPS	**PER PROTOCOL SET**
RP-HPLC	**REVERSE PHASE HIGH PERFORMANCE LIQUID CHROMATOGRAPHY**
RMP	**RISK MANAGEMENT PLAN**
S.C.	**SUBCUTANEOUS**
SOP	**STANDARD OPERATING PROCEDURE**

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Rapporteurs consider that the application for Insulin Human Rapid Marvel, which is based on a claim of biosimilarity to Humulin® S, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section VI).

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies.

Quality aspects

Biosimilarity

- The applicant is directly responsible for the content of the dossier and should have provided all the data required for the submission. The paucity of data on general development, manufacture and control of both Drug Substance and Drug Product prevented proper assessment of this application.
- Information with regard to the EU Member State from which the reference medicinal products used in the Quality, Clinical and Pre-clinical parts of the dossier were obtained, has been omitted. It is unclear if the comparators used for biosimilarity are valid and only studies performed with a valid reference product can be considered. The acceptability of the Lilly human insulin, derived from Humulin Regular Lilly 100 batch Z33319 is questioned.
- Biosimilarity has not been established for Marvel Rapid Drug Substance or Drug Product from a Quality perspective. A full comparability study should be provided for the Drug Substance in accordance with the CHMP Guidelines. Biosimilarity of the finished product with the reference product Humulin S has not been addressed, as required, in terms of the formulation, specifications, stability.

Drug Substance

- The provided description of the fermentation and harvesting process is not detailed and contains incomplete information about the process.
- The description of the purification and modification process as provided in the dossier is not detailed and contains incomplete information about the process.
- The Applicant has not provided a complete dossier for Drug Substance process validation. This section of the dossier requires complete revision to address the range of batch sizes and include full data and study reports.
- The information (study design and report) on product related impurities/substances provided by the manufacturer is not sufficient to draw conclusions whether all impurities are detected and whether correct assignments are made for the identity of the impurities.
- The comparative investigation of related impurities/compounds in insulin Drug Substance and Lilly insulin is not sufficient to draw the conclusion that the purity of insulin Drug Substance is comparable to Lilly insulin.
- With the exception of unclear references to Ph Eur, USP or both, no information for DS release test methods is provided in module S-4.2. Full descriptions and validation reports of the key drug substance release tests are not provided.

Drug Product

- The dossier does not adequately address the two different presentations of Drug Product (Vials and cartridges).
- The validation data provided for the Drug Product is severely deficient in terms of the manufacturing process steps and the range of batch sizes proposed for each presentation.

- No assurance is provided regarding physical separation measures or cleaning validation procedures used to assure segregation between different products.
- Essential details of source, batch number, site and process of manufacture of Drug Substance used to manufacture Marvel's Insulin Rapid presented in the dossier are absent as are details of where these batches have been used in the clinical and pre-clinical studies.
- Stability data is inadequate and the material appropriateness of the material used unclear. The in-use stability studies for the Drug Product are also inadequate.
- No information has been provided in the dossier and the SPC/PL on the device intended for the cartridge including suitability testing.

Non Clinical aspects

- The claim of comparability of Marvel insulin to Humulin insulin cannot be considered as sufficiently justified based on the presented data.

Clinical aspects

- An adequate pharmacokinetic comparison to the reference product has not been carried out.
- The pharmacodynamic study did not demonstrate equivalent blood glucose-lowering effect to that of the reference product.
- The efficacy and safety data, which cannot be used to compensate for the failure of pharmacodynamic similarity, showed consistent trends in favour of the reference products.
- The immunogenicity of the Marvel insulin products has not been properly evaluated.

A product-specific GMP inspection and a GCP inspection are requested before license approval (details in section II.4).

II. EXECUTIVE SUMMARY

II.1 Problem statement

Diabetes mellitus is a well-established condition primarily defined by hyperglycaemia, giving rise to risk of vascular damage. It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications (retinopathy, nephropathy and neuropathy), increased risk of macrovascular complications (ischaemic heart disease, stroke, and peripheral vascular disease), and diminished quality of life.

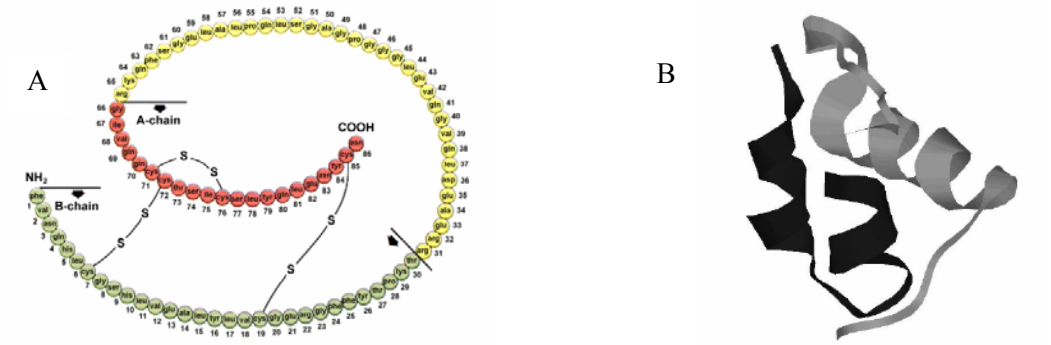
Diabetes mellitus exhibits wide geographic variation in incidence and prevalence. Recent estimates indicate there were 171 million people in the world with diabetes in the year 2000 and this is projected to increase to 366 million by 2030.

It is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin. Insulin is produced by the beta cells of the islets of Langerhans located in the pancreas, and the absence, destruction, or other loss of these cells results in type 1 diabetes (insulin-dependent diabetes mellitus). Most children with diabetes have type 1 diabetes and a lifetime dependence on exogenous insulin. Type 2 diabetes (non–insulin-dependent diabetes mellitus) is the most common form of diabetes and a heterogeneous disorder. Most patients with type 2 diabetes have insulin resistance, and their beta cells lack the ability to overcome this resistance. Although this form of diabetes was previously uncommon in children, in some, countries 20% or more of new patients with diabetes in childhood and adolescence have type 2 diabetes, a change associated with increased rates of obesity. Other specific types are currently less common causes of diabetes mellitus, but are those in which the underlying defect or disease process can be identified in a relatively specific manner (e.g. other endocrine diseases, iatrogenic, cystic fibrosis). Finally, gestational diabetes is carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but has been previously unrecognized.

II.2 About the product

Insulin is a natural mammalian hormone which was successfully isolated in 1922 and has been used therapeutically shortly after that time when it was successfully prepared from animal pancreas in sufficient quantity and purity. In more recent years, the source of much of the insulin used for treatment in Europe has been prepared using recombinant DNA technology to be identical to human insulin or as an insulin analogue with very slight modification of the molecule to alter its speed or duration of action.

Schematic (A) and 3-D structure (B) (USP reference standard) of insulin.



Insulin consists of two polypeptide chains, A and B. The A chain has 21 amino acids; the B-chain has 30 amino acids. The chains are linked together through the disulphide bridges of the sulphur atoms of cystein.

Marvel LifeSciences Ltd has developed a new insulin product synthesised by recombinant DNA technology using *E. coli* cells specially transformed to express the human insulin gene as the source of the hormone, which is then extracted and purified as the final insulin crystals.

This new insulin, which has the identical chemical sequence and structure to human insulin, is prepared as three different formulations with different rates and durations of action, namely soluble insulin (Insulin Human Rapid Marvel), isophane insulin (Insulin Human Long Marvel), and a 30/70 mixture of the soluble and isophane insulins (Insulin Human 30/70 Mix Marvel), each having the pharmacotherapeutic ATC codes of A10AB01, A10AC01 and A10AD01, respectively.

The formulation is presented both in cartridges for injection subcutaneously using suitable injection pens and in 10 ml vials for injection using conventional insulin syringes and needles. It is noteworthy that no indication is given about the devices and needles that are compatible with the cartridges.

The indications sought for by the Applicant are exactly the same as those of the reference product Humulin® (see section II.3), namely "the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis and for the initial control of diabetes mellitus and diabetes mellitus in pregnancy".

II.3 The development programme

The legal basis for this application is a similar biological application (EC Directive 2001/83/EC as amended, Article 10 (4)). The reference medicinal product, which is authorised in the EU, is Humulin® 100 IU/ml solution for injection (S, I, M3); it is licensed in the UK and its Marketing Authorisation Holder is Eli Lilly and Co Ltd.

The Marvel Insulins have similar ingredients to the reference products qualitatively; however, there are quantitative differences in the level of preservatives. Protamine and zinc levels require to be determined specifically for the Marvel products in the case of the Long and 30/70 Mix formulations.

This is the first European application for a biosimilar insulin. The relevant CHMP Guidance includes the following:

- Guideline on Similar Biological Medicinal Products containing Biotechnology-derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005);
- Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substance:
    - Quality Issues (EMEA/CPMP/BWP/3207/00/Rev 1/2003);
    - Non-Clinical and Clinical Issues (EMEA/CPMP/3097/02/2003) and its Annex: Guidance on Similar Medicinal Products containing Recombinant Human Soluble Insulin (CHMP/BMWP/32775/2005).

Quality

This guidance has not been followed, since the guidelines clearly state that the comparability exercise for a similar biological medicinal product versus the reference product is an additional element to the normal requirements of the quality dossier and this should be dealt with separately when presenting the data. The Applicant have presented characterisation for a single batch of the recombinant insulin Drug Substance with an Eli Lilly insulin (<u>not</u> Humulin S 100IU/ml solution), the Ph Eur reference standard and two further insulins which are not relevant for a Biosimilarity exercise. This characterisation study is not sufficient since an extensive comparability exercise is required for a Biosimilar product, which should include several batches each of the Marvel insulin Drug Substance and the claimed comparator insulin (Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substance:

Quality Issues EMEA/CPMP/BWP/3207/00/ Rev 1). This guidance document was originally available in September 2001 and was updated in December 2003.

Non Clinical

The set of toxicity studies conducted were as required by guidance, but excluded assessment of immunogenicity and of kinetics, both points that guidance suggests should be assessed.

Clinical

According to the Guideline, the clinical studies required to demonstrate the comparability of two recombinant (soluble) insulin containing products are:

- a single dose cross-over pharmacokinetic study vs. the reference product using subcutaneous administration, preferably in patients with type I diabetes, including the determination of plasma glucose levels;
- a double-blind cross-over hyperinsulinaemic euglycaemic clamp study, where data on glucose infusion rate and serum insulin concentrations should be made available.

Provided that clinical comparability can be concluded from PK and PD data, there is no need for efficacy studies; however, no guidance is given about the criteria to be met in order to demonstrate comparability. Safety information essentially relates to the potential for immunogenicity, which has to be addressed with a 12-month clinical study, including a comparative phase of at least 6 months to be completed pre-approval, while the 12-month data can be presented as part of post-marketing commitment.

To support the claim of biosimilarity, the Applicant performed four clinical trials.

- Three pharmacodynamic (PD) studies using the euglycaemic clamp technique, one for each formulation, were conducted in 24 healthy volunteers. They were designed as randomised cross-over comparisons of the Marvel insulins with the equivalent insulins from the reference product (Humulin S, Humulin I and Humulin M3). Insulin concentrations measured in these studies have been used to address the pharmacokinetic requirements.
- A single efficacy and safety multicentre clinical study was conducted in both type 1 and type 2 diabetic patients to compare all three test formulations to the reference products; patients received either a flexible dose regimen of soluble and isophane insulins or a fixed dose combination of biphasic insulin. The study was initially planned as a double-blind, parallel group, comparative study lasting 6 months, and was further extended to 12 months as an open, unblinded, treatment study. Only results of the double-blind 6-month phase of the study have been submitted.

The clinical development programme, some of which predates the Guidelines, is not consistent with the current regulatory requirements. The Applicant had started their development before the Annex document was issued and scientific advice had been sought from the National Authorities of three Member States: Finland, Sweden and The Netherlands. Although no great details have been given about these advices, the Applicant made a first amendment to the protocol of their clinical efficacy and safety trial to comply with the recommendations received and a second amendment to prolong the trial from 6 to 12 months after the Guideline was issued. The Applicant considered the analysis of efficacy of this clinical trial as pivotal in their application to demonstrate biosimilarity between its insulin Human Marvel products and the Humulin reference products. This approach is, however, not considered acceptable by the Rapporteurs. The sensitivity to detect differences between different insulin products is much higher for euglycemic clamp PK/PD studies than that of well-designed clinical efficacy trials, as indicated in the Guideline. Hence, the clinical efficacy data are considered to be only supportive to the performed PK/PD studies, whereas the safety data from this trial are considered as pivotal.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP
According to the Applicant, all product manufacture was conducted in compliance with the requirements of **GMP**.

Recombinant human insulin is manufactured by a Third Party

The facility at which the Drug product is manufactured has been inspected by the local regulatory agency in 2005. A product specific GMP inspection is requested however, due to the inadequacy of the dossier to address segregation between products manufactured at the shared contract facility and the use of data from a different product as a substitute for supporting data for this marketing authorisation application.

GLP
Preclinical safety studies were conducted at a facility in India. Inspection of these facilities by the GLP Inspectorate of the Netherlands was arranged and audit visits were conducted prior to and after the work described was conducted. Compliance was deemed satisfactory, although it should be noted that there was no specific audit of studies included in this application.

GCP
According to the Applicant, all clinical studies were conducted in accordance with the Declaration of Helsinki and in compliance with the requirements of **GCP**.

The PK/PD studies were performed by a contract clinical research organisation (CRO) with experience in the euglycaemic clamp technique (FARMOVS-PAREXEL, South Africa).

The efficacy and safety study (411-BK-03-01-0000) was coordinated by a CRO based in Germany, CCDRD AG, which is allegedly well experienced in such projects. There were 27 clinical centres (hospital or private practice) based in Germany (3), Poland (10), Bulgaria (7), and Serbia (7). The distribution of the randomised patients by country was: 234 in Poland, 153 in Bulgaria, 101 in Serbia, and 38 in Germany. The recruitment of the centres ranged from 2 to 78 patients. The four most important centres, which individually recruited more than 30 patients and overall 40% of the study population, were located in Poland (1), Bulgaria (2) and Serbia (1).

The study report does not give any clue about how and by whom the trial was monitored; moreover, no site audits were performed. Overall, the number of patients that dropped out and/or had major protocol deviations amounts to a substantial 18% of the randomised study population but this figure greatly varies depending on the centres, from 0 to 47%. Other concerns are frequent non-compliance with the sequential randomisation, a low reporting rate of adverse events (lower than expected for this patient population), and a discrepancy detected in the safety listings. For all these reasons, a GCP inspection of the CRO and/or the most important centre(s) is deemed appropriate.

II.5 General comments on the submitted dossier

There is a general consensus amongst all assessors that the overall quality of the dossier is very poor.

In particular, the traceability of the batches used in the **Drug Substance** part of the dossier is unclear, and the relationship between these and the Drug Product batches and the batches used in pre-clinical and clinical studies has not been provided. The majority of data for the Drug Substance is provided as

summary tables without the detailed supporting data or study reports. Similar inadequacies are also present in the **Drug Product** sections of the dossier. Full study reports are essential to allow proper assessment of this biosimilar insulin application. Data tables have been provided without sufficient discussion and no critical evaluation of the data has been presented. In addition, detailed information (such as batch number and country of origin) of the batches used in the comparability exercise (quality, non-clinical and clinical) is lacking. Since comparability to Humulin from the UK market should be demonstrated, information with regard to the origin of the reference products used is considered essential to conclude on the status of the data provided. *(Note: only studies performed with the reference product claimed can be considered as pivotal data).*

The description of studies in the **Non-Clinical** section of the dossier was brief, to the extent that no justification was provided for the relevance of the selected pharmacology studies for specifically characterising the degree of similarity between the originator and claimed biosimilar products. There was no discussion of the absence of immunogenicity and kinetic measures. Major objections were raised on these aspects.

The **Clinical** Overview is common for all three formulations and is a skeletal draft, like the Summaries of Clinical Efficacy (1 page plus the synopsis of the clinical trial) and Clinical Safety (22 lines). No critical evaluation has been presented, only definitive statements without justification. In addition, the format and content of the study report (411-BK-03-01-0000) are not acceptable. Indeed, the body of the report contains a minimum amount of information and a very small number of summary tables; this leaves the Assessors with the sole option of searching volumes of appendices and building summary tables of their own to conduct their evaluation. More importantly, a detailed analysis of critical data, such as insulin doses or immunogenicity, is simply missing.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Biosimilarity

The regulatory and scientific basis for a biosimilar application should be a side-by-side comparability exercise with an EU reference product. The Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/05) explicitly requires (in section 5.1) that: "*Comparability of the similar biological medicinal product with the chosen reference product should be addressed for both the medicinal product and the active substance in the medicinal product*." However, the dossier does not contain a side-by-side comparison of each presentation of Marvel's drug product with the reference drug product Humulin S. In section 1.5.2 ('specific requirements') of Module 1 only summary data which are presented with regard to comparability. It is also noted that the suitability of Humuline Regular Lilly 100 batch Z33319 as a comparator product (Quality, Clinical and Pre-clinical) is questioned as it is unclear whether this batch was obtained in the EU.

The comparability exercise on the level of the drug substance consists of a comparison of impurity profile by HPLC of insulins from several sources. The Applicant submitted data derived from the following batches: Marvel's drug substance; Lilly human insulin; USP insulin human RS; EP Insulin (human); From the viewpoint of a comparability exercise, the data from EP, USP are not meaningful. Consequently this data cannot be considered valid. Furthermore, information on purification/pretreatment of the insulin drug substance is lacking. A more detailed description of the data, especially demonstrating the validity of the purification/pre-treatment, is asked for and should be submitted.

From a quality point of view, biosimilarity has not been established for the drug products either. This is of particular importance for the Long and Mixed 30/70 product as the formulation is designed to directly determine the time-action characteristics of there modified release preparations. A full comparability study should be provided for each finished product with the respective reference products based on scientific data. This should include a side-by-side comparison of each presentation with the respective reference products, Humulin S, Humulin I and Humulin M3 (vials and cartridges). Biosimilarity should be demonstrated in terms of the formulation, specifications, stability and delivery (for the cartridges). Comparability data of the critical excipient protamine have not been submitted.

The Applicant should submit a satisfactory side-by-side comparison exercise for both drug substance and finished products in line with current Guidance. Robustness of the comparability exercise, e.g. by including data from more than one batch of both Marvel's insulin and reference product, has not been addressed. Biological data, confirming the biological activity *in vitro*, were not found in the quality part of the dossier.

A separate section, in addition to Drug Substance and Drug Product characterisation sections, would be expected.

Drug substance

The drug substance is recombinant human insulin. The molecular formula of recombinant human insulin is: $C_{257}H_{383}N_{65}O_{77}S_6$ and MW of 5808 D. Insulin consists of two polypeptide chains, chain A (21 amino acids) and chain B (30 amino acids), linked by a disulfide bridge. Insulin Drug substance is produced by fermentation in an *E.coli* K-12 derived strain, followed by purification.

The drug substance is manufactured by a Third Party

The manufacturing process consists of several fermentation, harvest and purification steps.

The provided description of the fermentation and recovery/purification process is not detailed and contains incomplete information about the process. Fermentation controls, the limits set and their justification are not or barely addressed. All critical process parameters and action limits should be added to each step. For the purification process details are lacking for in-process controls and action limits (tolerance limits), pH adjustments, titres, chromatographic media and processes, splitting/pooling steps, holding times/storage times, all potential intermediates and their justification. Since the process is by no means 'fixed' in the dossier, major objections have been raised on the descriptions of the DS manufacturing.

The information provided on the process validation for the fermentation and the purification processes, including the removal of process related impurities, is too limited and insufficient for assessment of the performance, robustness and consistency of the process. Relevant details are lacking, including filter and column materials used during downstream processing. Full validation data in accordance with the guideline ICH M4Q should be supplied.

Although a number of critical steps and parameters of both the fermentation/harvesting process and the purification/modification process are mentioned, the supporting information is incomplete and therefore cannot be assessed.

In order to demonstrate biosimilarity, analytical data should be provided for multiple representative batches of the Drug Substance in addition to characterisation.The Drug Substance itself should be fully characterised for multiple representative batches as well as the additional requirements for a biosimilar medicinal product. Some characterisation data was presented in the dossier. A single batch was compared to recombinant human insulin isolated from a reference product (Humulin Regular Lilly 100, batch Z33319 EU sourcing unconfirmed) and three reference human insulins (USP Insulin human RS, Ph Eur human insulin. It has not been demonstrated that this batch is fully representative for the current commercial production process. Characterisation studies included amino acid analysis, amino acid sequence, circular dichroism, X-ray crystallography, Iso Electric Focusing (IEF), SDS-PAGE, ^{1}H-NMR (1D) spectra, Fourier Transform Infrared Spectroscopy (FT-IR) and no significant differences were found between the tested recombinant human insulins.

The impurity profile of the recombinant human insulin Drug substance was compared with the same reference drug substances. The comparative investigation of related impurities/compounds is not sufficient to draw the conclusion that the purity of insulin Drug Substance is comparable to Lilly insulin. Insufficient batches of insulin Drug Substance have been studied and the validity of the insulin Drug Substance (including whether it is a representative batch) and the Lilly comparator have not been established.

Batch release data of three drug substance batches. All three batches comply with the specifications, although from the date of manufacture these batches could not have been used in validation, characterisation or for the manufacture of the Drug Product batches used in pre-clinical or clinical studies. No batch traceability is given in the dossier.

Stability data have been provided of 4 initial batches stored up to 60 months at -70^{o}C or -20^{o}C, and up to 6 months at 2^{o}C to 8^{o}C. In addition data of 4 regular production batches were provided, one up to 48 months, two up to 24 months and one up to 12 months the fermentation batch size of five batches is not given in the dossier, and should be provided as yet. Slight trends of degradation (increase of RP-HPLC impurities) were visible at all tested temperature, but all values remained clearly within the specifications.

Drug product

For the Drug Product, the Applicant cites the respective Ph Eur monographs, however many aspects of the dossier does not address the additional requirements essential for MA approval.

The Drug Product manufacturing site is in EU. Data from another Insulin product which is also made at this site but from a different insulin Drug Substance, has been used throughout the dossier. This data cannot be considered as directly supporting the Marvel products and such background data should be presented in an appendix. Assurance of product segregation and adequacy of the cleaning procedures between the Marvel product and all other products at the manufacturing site has not been provided. There is no clear correlation between the lots of Drug Substance and the lots of Drug Product presented in the dossiers.

The validation data provided for Marvel Rapid is significantly deficient. All key manufacturing steps require to be validated and in-process controls justified.

The specifications and batch analysis data give rise to several objections. The exact insulin drug substance batches (source of drug substance, batch numbers) used for manufacturing all drug product batches should be given. In addition, information should be provided for which purpose (clinical studies, stability studies, process validation, etc.) the batches have been used. A clear overview of all batches of Marvel Insulin Rapid produced should be submitted.

The cartridge is intended for administration by a reusable device. The dose delivery properties from the cartridge when using a recommended device have not been addressed in the dossier.

In summary, there are major deficiencies throughout the dossier regarding the Drug Product. The formulation development sections are inadequate. None of the manufacturing process steps have been properly validated and the in-process controls have consequently not been verified as satisfactory. Minimal information has been supplied regarding the analytical procedures and the Human Insulin Reference Standards, for which the source, specifications and qualification procedures have not been provided. Some data from a different insulin product has been used to support batch release and stability data. As stated above, there is no discussion of biosimilarity with Humulin S for the Drug Product. In addition, the lack of traceability of the Batches of Drug Substance, used to manufacture the Drug Product lots, presented in the dossier are of particular concern.

Overall Summary

The entire Quality dossier for Insulin Marvel Rapid is of extremely poor quality. Required information (e.g. a comparability exercise) is lacking. Other information on key sections such a manufacturing process validation, development pharmaceutics, characterisation, specifications, batch data and stability are incomplete, unclear and inadequately presented. Some information had to be deduced from other parts of the dossier and data from other products manufactured using a different insulin drug substance are used as a substitute for the Marvel product. Complete information specific to the two presentations (cartridges and vials) pertaining to manufacture, specifications and stability have not been included.

A significant numbers of major objections have been identified, which preclude a marketing authorisation. Major objections and other concerns are outlined in the proposed list of questions.

The Applicant should therefore submit a completely revised and updated dossier.

III.2 Non clinical aspects

Pharmacology

In accordance with regulatory guidance, the Applicant presented *in vitro* pharmacology data to support its claim of similarity between its insulin products and its chosen comparator product, Humulin. Different *in vitro* biological assays were used to compare effects of each insulin preparation on cellular signalling. No *in vivo* pharmacology studies were conducted, which is in accordance with guidance (such studies with insulin are considered not sufficiently sensitive to detect any non-equivalence not identified by *in vitro* assays). Weaknesses in the description of why the tests were chosen, the methods used and the interpretation of results mean that the apparent conclusion of no difference between the two brands has not been proved. The Applicant should be required to represent its pharmacology data in sufficient detail as regards to justification of the suitability of the tests made, to details of the methodological description and to interpretation of the results, to prove satisfactorily that pharmacological equivalence of the two insulins has been shown and to eliminate the possibility that the two brands appear similar because of limitations of the experimental methods to detect a difference.

Pharmacokinetics

No pharmacokinetic studies were undertaken. This is in accordance with regulatory guidance on development of biosimilar insulins.

Toxicology

General toxicity was studied in a single dose study and in a 28 day repeated-dose studies in rats using the subcutaneous administration. Local tolerance was also assessed in rabbits using subcutaneous administration. Study designs were comparative in nature and no meaningful differences in toxicity were found. The Applicant concluded equivalence has been shown in the preclinical data set. However, although there was measurement of blood glucose to a very a limited extent (with no difference between products found in degree of hypoglycaemia) there was no assessment of kinetics of insulin and no assessment of immunogenicity in the preclinical studies: the latter was studied in patients. The Applicant should be asked to justify deviation from guidance in respect of absence of kinetics, which was not addressed in the Non-clinical Overview. No data were provided for assessment of genotoxicity, carcinogenicity, or reproductive toxicity, nor for other types of toxicity. This is in accordance with guidance and is acceptable.

III.3 Clinical aspects

Pharmacokinetics

No specific pharmacokinetic study was conducted. The Applicant used the insulin concentrations measured in the pharmacodynamic study to address the pharmacokinetic requirements; these data are presented in the pharmacodynamics section.

This approach is not in line with the CHMP Guidance, which recommends a single dose cross-over pharmacokinetic study of the test product vs. the reference product using subcutaneous administration, preferably in patients with type I diabetes, and including the determination of plasma glucose levels.

Pharmacodynamics

Method

A pharmacodynamic study using the euglycaemic clamp technique was conducted in 24 healthy male volunteers. This was designed as a single-dose (0.2 IU/kg body weight of insulin injected subcutaneously) randomised cross-over comparison with the reference product Humulin S. In the euglycaemic clamp technique, glucose is infused continuously at a rate sufficient to counter the hypoglycaemic action of the injected insulin dose and the total amount administered provides an indication of its pharmacodynamic activity.

The primary objective of the study was the assessment of pharmacodynamic endpoints, and so the primary endpoint was the area under the curve (AUC) of the glucose infusion rate (GIR) between 0h (time of insulin injection) and the end of clamp. Other classical endpoints were various fractional areas under the GIR curve, onset of action, maximum rise in GIR, time to maximum rise in GIR, time to early and late half-maximum GIR. Serial blood samples were taken for the measurement of serum insulin and C-peptide, allowing for the estimation of exogenous insulin concentration.

In the absence of specific guidance on comparability criteria, the Applicant applied the classical acceptance interval of 80-125% for the mean AUCs ratio of both PD and PK data and for the maximum rise in GIR. The acceptance interval was widened to 70-143% for the insulin maximum concentration and this was justified by high intra-individual variability of the serum insulin.

Overall, the study design is in line with the CHMP Guidance. However, the quality of the experiment appears in several ways questionable (unblinded trial, no suppression of endogenous insulin, no criteria for a successful clamp performance). Furthermore, the Applicant did not justify the choice of the classical bioequivalence acceptance interval for PD and PK AUCs in the specific context of biosimilar insulins. In addition, the justification for widening the limits of the interval for the maximum insulin concentration is not acceptable.

Results

The mean PK and PD curves are presented in Figures 1 & 2.

The total AUCs for both PK and PD data were considered equivalent due to confidence intervals (CI) included within the 80%-125% limits.

However, early AUCs (up to 2 hours post-dose) were significantly higher for the test insulin with 95% confidence intervals excluding the point of 100%. The mean maximum exogenous insulin concentration for the test product was 16% higher than for the reference; its 95% CI was not included within the 80%-125% interval but it was included within the widened acceptance interval according to the Applicant, who concluded to bioequivalence. The elimination half-life and mean residence time were significantly shorter for the test insulin than for Humulin S. A possible explanation or justification why this would be acceptable was not provided by the Applicant. In addition, taking into account the observed difference in elimination half-life and the fact that the volume of distribution was similar, the clearance of both insulins might not be comparable. These parameters should have been calculated and discussed by the Applicant, as requested in the Guideline. Finally, the total exposure should have been considered to provide evidence that the products were comparable. Hence, $AUC_{0-\infty}$ should have been included in the pharmacokinetic data analysis.

Whereas the early insulin AUCs would still be considered bioequivalent (95% CI at 1 hour: 103%-124%), the early GIR AUCs would not (95% CI at 1 hour: 100%-145%); the mean GIR AUC for the test product was 22% higher at 1 hour than for the reference. As for the maximum GIR, it could be considered as equivalent (95% CI: 93%-120%).

Conclusion

There was a good correlation between PK and PD data. However, while the overall PK and PD were comparable using the acceptance criteria of classical bioequivalence, the profiles were significantly

different: the test insulin was absorbed and eliminated faster than the reference, which resulted in a higher early but somewhat shorter effect on blood glucose. That the test insulin could potentially induce a blood glucose-lowering effect 45% higher than Humulin S within the first hour of the subcutaneous injection is not considered clinically acceptable for biosimilar products. In clinical practice, this would preclude any potential switching from Humulin S to the test insulin due to possible harmful consequence to the patient (risk of hypoglycaemia).

In view of the disappointing results of the PD studies in general, the Applicant did not use them to support the claim of biosimilarity between the test and reference insulins, but proposed to rely on the results of a clinical efficacy and safety study in diabetic patients. However, this strategy is not acceptable because it is evident that clinical endpoints being less sensitive, it cannot compensate for the failure to show pharmacodynamic similarity.

Figure 1: PK soluble insulin

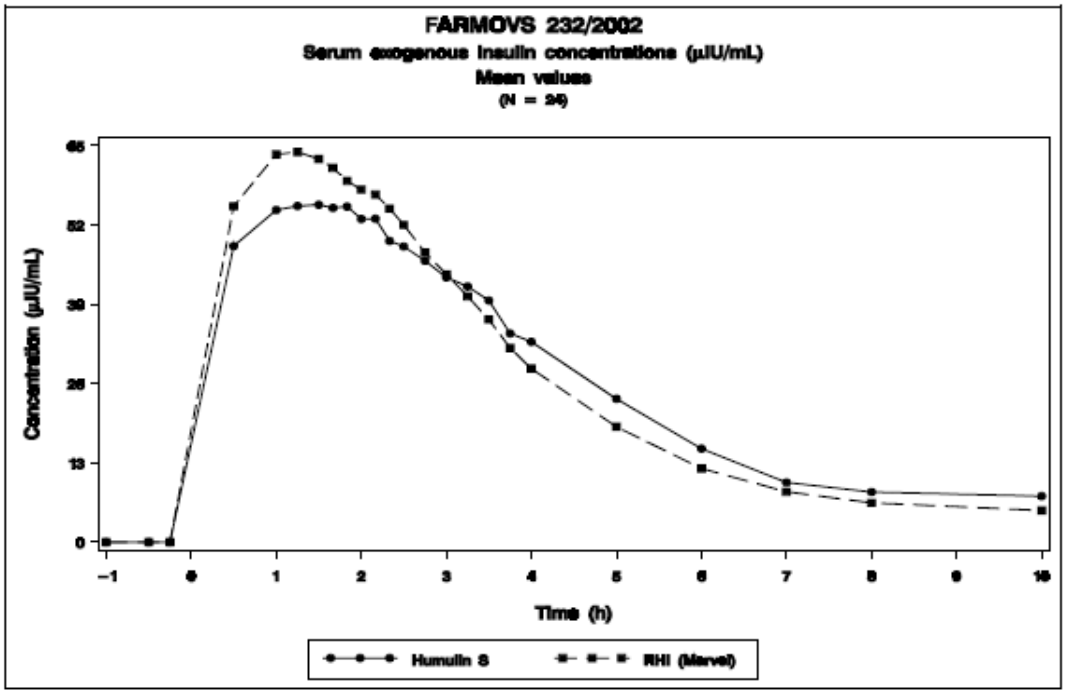
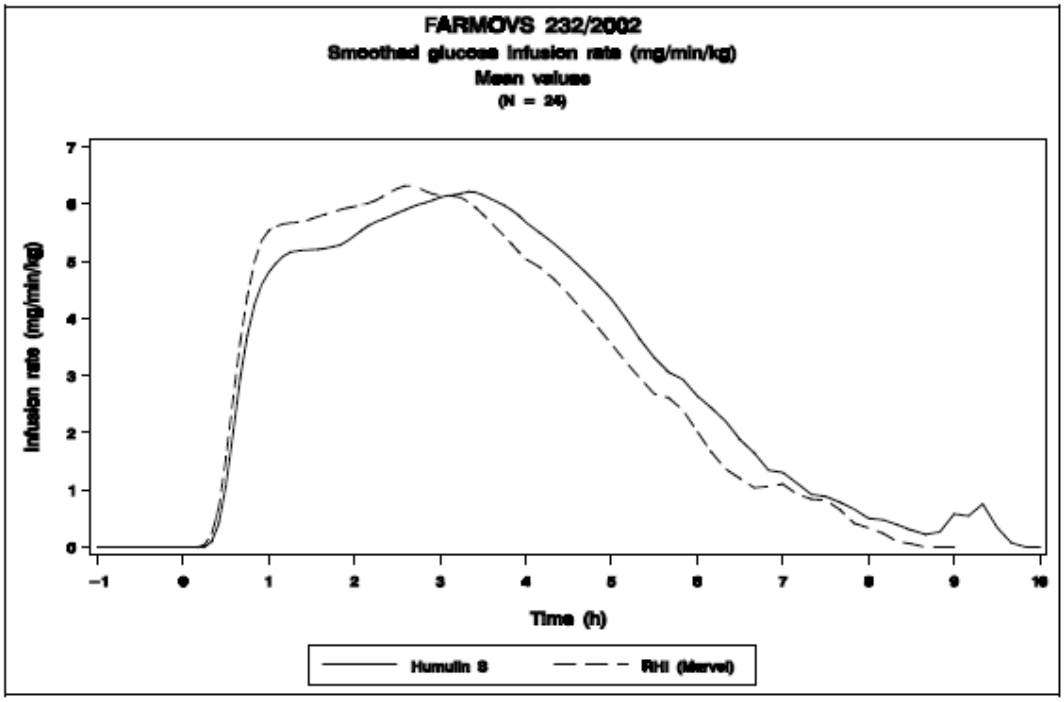


Figure 2: PD soluble insulin


FARMOVS 232/2002
Smoothed glucose infusion rate (mg/min/kg)
Mean values
(N = 24)
Infusion rate (mg/min/kg)
0
1
2
3
4
5
6
7
−1
0
1
2
3
4
5
6
7
8
9
10
Time (h)
Humulin S
RHI (Marvel)

Clinical efficacy

The objective of the efficacy and safety trial (Study 411-BK-03-01-0000) was "to prove the equivalence of a test formulation containing human recombinant insulin to a reference product of the same type (Humulin®) for the treatment of diabetes". It was conducted in both type 1 and type 2 diabetic patients to compare all three test formulations to the reference products in the same trial; patients received either a flexible dose regimen of soluble and isophane insulins or a fixed dose combination of biphasic insulin.

Method

The primary endpoint was the glycosylated haemoglobin (HbA1c) measured after 24 weeks of treatment. Secondary efficacy endpoints were HbA1c measured after 12 weeks, the incidence and severity of hypoglycaemia, the parameters of an 8-point blood glucose profile, and changes in bodyweight. The main safety endpoints were the treatment-emergent AEs, the local tolerability, and the development of IgG antibodies to insulin.

Patients of both genders, aged 18-75 years, were suffering from type 1 or type 2 diabetes mellitus for at least 24 months and under treatment with either a free combination of soluble and isophane insulins or a fixed combination (30/70) of biphasic insulin for at least 6 months. They continued the treatment with the type of regimen (free combination or biphasic insulin) that they were receiving before the beginning of the trial.

It was planned that 480 patients would be randomised into the trial. The randomisation was stratified into 4 strata according to the type of combination (fixed or free) and the type of diabetes (1 or 2). This was designed as an equivalence trial using an equivalence margin of 0.6% on HbA1c measured at 24 weeks. Two populations were defined for the analysis of efficacy data. The full analysis set (FAS) included all randomised patients who received study medication and for whom HbA1c data were available at week 12 and/or 24. The per-protocol set (PPS) included all patients in the FAS who were treated for the full 24 weeks and had no major protocol violations. The primary analysis was done on the PPS, as the aim of the trial was to demonstrate equivalence.

As already pointed out, the resort to an efficacy trial to compensate for the failure of showing pharmacodynamic similarity is not endorsed. Moreover, the equivalence margin chosen by the Applicant for HbA1c is considered too wide and unacceptable. The definition of FAS is not the preferred one either; ideally, all patients that were randomised and treated should have been included. Finally, while each formulation has to be shown biosimilar to the corresponding reference insulin, the design of the trial would only allow for the comparison of the biphasic formulations since the two others are administered in combination.

Results

Out of 628 patients screened, the randomised population included a total of 526 patients, 243 with type 1 diabetes and 283 with type 2 diabetes; 265 received the test insulins and 261 received Humulin. There were more patient drop-outs and/or major protocol deviations in the test group than in the reference group. As a result, 86% of patients were included in the PPS for the Humulin group, and only 78% for the test insulins. This 8% difference reaches statistical significance. Regarding the drop-outs (12% vs. 7%), the difference was attributable to patient's request, non compliance, and adverse drug reactions, all reasons possibly related to a worse tolerability.

The distribution of the treatment combination (free or fixed) is shown in Table 1.

Table 1 Distribution of the treatment combinations (FAS)

	Test	Ref		Test	Ref		Total
Free			*Biphasic*				
Type 1	106	103	Type 1	17	17		243
Type 2	38	39	Type 2	104	102		283
Total	144	142	**Total**	121	119		526

The only information available about the insulin doses is a single table showing the mean daily dose over the whole treatment period; in addition, the doses of the biphasic formulation have been split between their regular (30%) and NPH (70%) contents and pooled with the respective insulins. This analysis is highly insufficient; a proper statistical analysis should have been performed in order to support equivalence of the doses with a pre-defined and justified acceptance interval for the CIs. Indeed, if the doses administered are not equivalent, it is not possible to conclude that similarity of the products has been established even if the endpoint analysis shows similarity.

The results on the primary endpoint are shown in Table 2. They are fairly consistent across the sub-groups with substantial trends favouring Humulin except for the free combination in type 2 diabetes. As already mentioned, the conclusion of similarity based on a CI < 0.6% is not acceptable; none of the CIs would be contained within a ±0.3% interval, which is considered more appropriate.

Table 2 HbA1C (%) at 24 weeks

	Adjusted mean*			
PPS	Test	Humulin	Difference	95% CI
Type 1 – Fixed	8.43	8.16	0.28	(-0.54, 1.09)
Type 1 – Free	8.53	8.30	0.22	(-0.15, 0.60)
Total Type 1	8.51	8.29	0.22	(-0.12, 0.56)
Type 2 – Fixed	7.73	7.52	0.21	(-0.04, 0.47)
Type 2 - Free	7.33	7.68	-0.35	(-0.85, 0.15)
Total Type 2	7.65	7.56	0.09	(-0.15, 0.32)

**From ANCOVA adjusting for screening value*

In addition, while both treatments improved HbA1c by a similar amount from screening to week 12, the test insulins performed less well between weeks 12 and 24. Whereas HbA1c continued to decrease or was stabilized under treatment with Humulin, it tended to increase again in patients with both types of diabetes treated with the biphasic test formulation. This raises some questions about the long-term maintenance of effect of the test product.

Conclusion

The efficacy data collected in the 411-BK-03-01-0000 trial do not support the claim of biosimilarity of the test and reference insulins.

Clinical safety

The main safety data are provided by the 411-BK-03-01-0000 trial in diabetic patients over the first 6 months (double-blind phase).

As already mentioned, the reporting rate of AEs was unexpectedly low, especially in the population of patients with type 2 diabetes. Nevertheless, there were twice as many patients with type 1 diabetes who reported AEs when treated with the test insulins in comparison with the reference insulins (24% vs. 12%). In patients with type 2 diabetes, the rates were more comparable and in favour of the test products (25%

vs. 31%). ADRs were very few; those related to poor glycaemic control seemed to be roughly equivalent in both treatment groups. The assessment of local tolerability was done by the patient and the investigator using a scale of 0 to 5. Although the differences were marginal, they were all in favour of the reference products. Treatment discontinuations due to ADR also showed a trend in favour of the reference insulins.

Finally, immunogenicity data are very limited. The percentages of patients who developed new antibodies over the first 24 weeks were as follows:

- Type 1 diabetes: 21.9% (test) vs. 14.0% (reference)
- Type 2 diabetes: 10.7% (test) vs. 12.5% (reference)

The Applicant failed to provide a full evaluation of the immunogenicity of the tests insulins as required in the CHMP Guideline on biosimilar insulins. In particular, the strategy used for assessing immunogenicity was not described, nor was the assay and its validation. The selection of the patient population, excluding naive patients and children, was not justified. The analysis of IgG titres over time was limited to patients developing new antibodies. Finally, no comprehensive analysis of the impact of the antibodies on efficacy and safety data had been planned.

Conclusion

The safety data presented from the 411-BK-03-01-0000 trial are deficient and do not support the claim of biosimilarity of the test and reference insulins.

Pharmacovigilance system

A Summary of Pharmacovigilance has been provided with a statement signed by the Applicant and the qualified person responsible for pharmacovigilance, indicating that the Applicant has the services of a qualified person for pharmacovigilance and the necessary means for notification of any adverse reaction occurring either in the community or in a third country.

The Pharmacovigilance system as described by the Applicant does not fulfil the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union. The Pharmacovigilance system has the following deficiencies: a summary Curriculum Vitae and job description of the QPPV, a description of the back-up procedure to apply in the absence of the QPPV, all documented procedures, a statement regarding the compliance of the systems with the internationally agreed standards for electronic submission of adverse reaction reports, and a copy of the registration of the QPPV, with the EudraVigilance system and identification of the process used for electronic reporting to Competent Authorities.

Provided that the deficiencies are rectified prior to the Applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The Applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Risk Management Plan

The Risk Management Plan (RMP) submitted by the Applicant does not comply with the EMEA Guideline on Risk Management Systems for Medicinal Products for Human use and is insufficient to support the present application. The Interface between EU-RMP and EudraVigilance has not been provided as Marvel Life Sciences are currently not registered with Eudravigilance, although registration will be obtained. It is unacceptable that Marvel Life Sciences are not currently registered with EudraVigilance.

Safety Specification
The Applicant should resubmit the RMP in the form of the EU template to provide a summary of information on the subjects specifically studied in the clinical trial programme and amend the epidemiology of the indication to type 1 diabetes and type 2 diabetes requiring insulin therapy (rather than all type 2 diabetics). The Applicant did not identify important identified or potential risks (including with other medicinal products, food and other substances) or missing information. No class effects were identified.

Pharmacovigilance Plan
The Applicant should commit to follow up spontaneous reports of poor glycaemic control, hypoglycaemia, hyperglycaemia and related events to establish whether patients have recently changed from Humulin to Insulins Marvel.

Risk Minimisation measures
The Applicant's justification for not requiring additional risk minimisation activities is supported.

Post marketing Surveillance Programme
In addition to routine pharmacovigilance activities the RMP proposed by the Applicant includes a registry study in the first country to market the products. The Applicant should provide a copy of the protocol for the registry study.

IV. ORPHAN MEDICINAL PRODUCTS

Not applicable.

V. BENEFIT RISK ASSESSMENT

This application for a recombinant human insulin is the first in the EU based on a claim of biosimilarity to an approved product (Humulin® from Eli Lilly). CHMP Guidance has been issued for biotechnology-derived proteins in general and for soluble insulin in particular (non-clinical and clinical issues). Therefore, the primary purpose of this assessment is not the characterisation of the benefit/risk profile of the product as such but the qualitative and quantitative evaluation of the similarity of the product to the reference chosen by the Applicant.

Overall, there is a lack of adequate information regarding comparability of the **Drug Substance** and **Drug Product** with Humulin S, which precludes any conclusion regarding biosimilarity. In addition, there are many serious deficiencies in the Quality part of the dossier including a lack of validation data for the manufacturing processes for both Drug Substance and Drug Product. There is a lack of traceability raising questions regarding which Drug Substance batches have been used for manufacture of the Drug Product used to support the Quality part of the dossier as well as to perform the pre-clinical and clinical studies.

There was no evidence of a difference between the products in the **non-clinical data**, as presented. However, for the pharmacological data, the Applicant has not established that its selected tests and the manner the experiments were designed and conducted is such that, had differences between products been present, these would have been detected. For toxicity data, again, no apparent difference between products was detected, but the Applicant did not assess comparative kinetics or immunogenicity and the absence of these data are not justified.

As far as the **clinical aspects** are concerned, the pivotal information needed to demonstrate the efficacy component of biosimilarity is to be derived from PK/PD studies. Provided that clinical comparability can

be concluded from these PK and PD data, there is no need for efficacy studies. However, there is a need to confirm similarity based on the immunogenicity of the product, which has to be addressed with a 12-month clinical study; data from the last 6 months of this study may be submitted as a post-approval commitment.

The PD study provided in this dossier showed that the test soluble insulin was absorbed significantly faster and had a significantly higher effect (potentially up to 45%) on blood glucose within the first hour of the subcutaneous injection as compared with Humulin S. Therefore, the two insulins cannot be considered as biosimilar; in clinical practice, it would not be safe to switch from one product to the other without potential dose adjustment.

In an attempt to compensate for these unsatisfactory results, the Applicant has proposed to rely on clinical efficacy data in diabetic patients, using HbA1c after 6 months of treatment as the primary endpoint. This strategy is not endorsed because this parameter is not sensitive enough to be used in the context of biosimilar products. In addition, the equivalence margin selected by the Applicant is much too wide and no analysis was planned to demonstrate that the doses administered were sufficiently identical. Finally, the test soluble insulin was given in combination with another test insulin (isophane formulation), which precludes any conclusion on the specific characteristics of the soluble insulin.

Eventually, the clinical study results demonstrated that the compliance was worse with the test insulins whereas HbA1c results tended to be more favourable with the reference insulins. In addition, the immunogenicity data, which are highly deficient, do not appear to support biosimilarity either. Overall, the clinical data submitted show that the test soluble insulin is not similar to Humulin S.

In conclusion, quality data do not support biosimilarity due to serious deficiencies in the dossier submitted. Non-clinical data require additional arguments to be presented from the Applicant with regard to whether biosimilarity can be accepted. Finally, clinical data show that Insulin Human Rapid Marvel is not similar to Humulin S. Therefore, the claim of biosimilarity cannot be endorsed and the Rapporteurs recommend refusal of marketing authorisation.

VI. LIST OF QUESTIONS

Deleted list of questions.

FOLLOW-UP MEASURES

Deleted follow-up measures.

VII. RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VII.1 Conditions for the marketing authorisation

Should the claim of biosimilarity be accepted, the content of the product information would essentially be the same as that of Humulin (or very similar). Since this is currently not the case and in view of the major objections, it is premature to propose any changes to the product information (SPC, PL, labelling).

A further review of Finished Product Specifications and limits should be submitted when a sufficient number of batches of each presentation have been produced.

Updated stability data for the Drug Substance and Finished Product should be submitted when available.

If not submitted before marketing authorisation, the 12-month immunogenicity data should be provided as a post-marketing commitment.

VII.2 Summary of Product Characteristics (SPC)

It is premature to propose any changes to the SPC. However, it should be specific for each formulation/presentation.

VII.3 Labelling

It is premature to propose any changes to the labelling.

VII.4 Package Leaflet (PL)

It is premature to propose any changes to the PL. However, the PL should be specific for each formulation/presentation; in addition, it should be compliant with the latest update of the QRD template. Finally, the results of the user consultation should be addressed.

User consultation

The patient information leaflet has been evaluated via a PL user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC (as amended). However, it is unclear by whom this study has been performed. Furthermore, only a summary of the patient consultation has been provided by the Applicant with the applications for the 3 insulin containing medicinal products.

From the summary, it becomes clear that the test was diagnostic. This is acceptable since this kind of test is the most useful and consists of:

- asking users to carry out the tasks they would normally carry out when using the leaflet.
- observing and recording what they do
- noting how they describe what they do
- probing to find out whether they can use the information they read appropriately
- noting what they say about the leaflet

Design/conduct of study
The objective of the study was to ensure that the information contained in the PL could be located by 90% of the participants of which at least 90% could show that this information was understood.

Only a summary of the patient consultation has been provided by the Applicant. An initial pilot interview was conducted with 2 subjects to identify potential problems with the questionnaire and the test method before the start of formal study. The formal testing process was subsequently started and consisted of an initial sample of 10 patients followed by a further sample of 10 patients. The Applicant's acceptance criteria for identification of suitable patients ensured that the study sample was reflective of populations who are likely to rely on the leaflet. The age range of participants and mix of social grades was satisfactory.

Each panel member was asked to answer the questions and their answers were recorded as well as how they located the information. The questionnaire covered all sections of the PL and did not follow the layout of the PL. Model answers were not provided in the summary of the test report. The questionnaire is considered acceptable to test participant's ability to identify and understand the information provided in the PL. In addition, participants were also given an opportunity to make general comments on use of the PL and its readability.

Results
Only a summary of results was provided in percentages for the 20 subjects included in the study. The results demonstrate that in general the proposed PL complies with standard acceptance criteria (90% of participants were able to find the information requested in the PL, of who 90% can show that they understand it). Only, one question relating to side effects did not meet the acceptance criteria. Since individual data are lacking due to the omission of the full study report, it is unclear whether the leaflet could be improved in this regard.

Conclusion
Only a summary of the patient consultation has been provided by the Applicant with the applications for the 3 insulin containing medicinal products. This is not considered acceptable. A full test report should be provided by the Applicant. In general, the summary indicates that the results demonstrate that subjects representative for the target group for this product are able to identify and comprehend key (safety) message. The results are considered supportive of the proposed PL. However, at present no further conclusions can be drawn since the underlying data are lacking.