ATTACHMENT 6

Expert Report

on the Chemical-Pharmaceutical

Documentation of

HUMET-R syrup

(physiologically essential macro and micro elements in chelate complex with humic acid)

made by
HUMET Trading, Research and Development Co.

Hungary, 2000

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EVALUATION

Introduction

This expert report is based on the Chemical, Pharmaceutical and Biological Documentation (Part II) for Humet-R syrup 300 ml made by Humet Trading, Research and Development Co., Budapest, Hungary in July 2000.

The sequence of information within this report is in conformity with the proposals of the "Notice to Applicants Concerning Marketing Authorisation of Medicinal Products for Human Use in the Member States of the European Community".

Humet-R syrup 300 ml developed by Humet Trading, Research and Development Co. is an OTC product, containing nine physiologically essential trace elements, following Mg, Fe, Zn, Mn, Cu, V, Co, Mo, and Se as active ingredients in stabile chelate complex formation with humic acid in suspension form. The finished product exists in 2 different immediate packaging materials (glass and plastic) with the same composition, filling volume and quality.

Humic acid used for producing Humet-R syrup 300 ml is a vegetable origin product manufactured by Humet Trading, Research and Development Co.

Part II A - COMPOSITION

Format No and Doc.Vol. No/P. No

Format 2B101A 2/003 to 005

A/1 Composition of the proprietary medicinal product:

Humet-R syrup 300 ml contains 2.25 g humic acid, 450 mg magnesium, 420 mg iron, 300 mg zinc, 90 mg manganese, 60 mg copper, 15 mg vanadium, 6 mg cobalt, 5.25 mg molybdenum and 3.75 mg selenium as active substances described in Part II C of this dossier.
The excipients are mainly orange syrup as flavouring and stabilising agent, and purified water as solvent. Dipotassium phosphate is necessary for the formation of chelate complexes.

A/2 Container:

The product is packed into brown glass bottle, or alternatively into brown, transparent polyethyleneterephthalate (PET) bottle, with polypropylene tamperproof cap and with a measuring device for easy dosing.

A/3 Clinical trial formula:

Clinical study was performed on Humet-R syrup 300 ml produced identically with registered formula.

A/4 Development pharmaceutics:

Format 2B102A
2/006 to 033

The principle of the choice of the composition was finding an efficient composition, which remained stable taking also the characteristic of peat extract into account.

The active substances are presented as stable water-soluble salt forms and humic acid with chelat forming capacity.
The dosage form chosen is familiar to patients.
Some solutions of different metal-salts showed incompatibility with each other's. Exact concentration and sequence of dissolving were established to bypass the precipitation or discolouring caused technological problem.

Excipients:
The orange syrup picked out of several fruit syrup is well known and safe, without interaction with the active substances. It is a natural origin substance (without synthetic colours, antioxidants and microbial preservatives) with sugar syrup given yellow colour and pleasant taste for product. It is suitable for increasing the viscosity of suspension prevented the sedimentation of the solid particles.

The individual mineral salts in solution require different pH value. The compatibility at the dissolving of the individual mineral salts is ensured by optimisation of preparation of the metal – humic acid chelate fractions in three steps, in optimal sequence and concentration.

The stability of the active substances in the solution is guaranteed by the formation of stabile chelate complexes in three steps.
The quality parameters found at release and on the control samples stored 16-30 months were compared. The investigations covered the physical-, chemical- and microbial stability completed by IR spectroscopic analyses of humic acid isolated from the syrup and AAS analyses of some elements. The samples tested did not change practically.

In the course of manufacturing process is ensured the homogeneity and the low microbial purity of product.
The formulation and manufacturing process chosen result in a stable product and reproducibility in process, which is justified by the results of the analytical routine tests, the real time and accelerated stability tests, too.

Format 2B103A
2/033 to 036

The compatibility between the plastic flacon and Humet-R syrup were studied by ICP-OES and IR spectroscopy method. Change could be found neither in the Humet-R syrup nor in the wall of PET flacon stored at 40°C during 6 months.

The in vivo bioavailability studies are discussed in the Clinical Documentation.

Part II B - METHOD OF PREPARATION

B/1 Manufacturing formula:

Format 2B104A/1
2/038

The manufacturing formula refers to the commercial batch scale.

B/2 Manufacturing process:

Format 2B104A/2
2/039 to 042

The brief description of the manufacturing process:
The active substances are separately dissolved in purified water and filtered. This step is followed by chelat forming from humic acid, dipotassium phosphate and metal-salts solutions with intensive mixing in three parts. The suspension is completed with orange syrup and purified water.
The further steps are filling by automatic dosage pump in laminar-flow box, ensuring the homogeneity by permanent stirring and the low microbial purity, and packaging.

The main control methods during manufacture comprise tests for technological parameters as revolutions per minute at stirring and filling mass predetermined test frequency and sample number.

The equipment and devices used are conventional in manufacturing of large volume solutions and suspensions.

B/3 Experimental data for the validation of the method of manufacture:

Format 2B105A

2/043 to 060

Widely used standard methods are applied in most of the manufacturing steps. The homogeneity of suspension is guaranteed by stirring continuously controlled. Dissolving of the active substances and steps of the chelate productions are critical for product quality. These processes are optimised and described in detail, clearly and exactly.

The suitability of manufacturing process was verified by a retrospective validation study on 33 consecutive batches produced between 11/97 and 03/98.

The reproducibility of the developed technology is demonstrated by monitoring of batch analyses.

The results of five representative elements tested by atomic absorption spectroscopy method show to batch-to-batch reproducibility and justify that the formulation selected and manufacturing process employed is satisfactory.

Part II C - CONTROL OF STARTING MATERIALS

C/1 Active substances:

Specifications and routine tests and description:

Mineral salts

Format 2B106A/1-5
2/063 to 099

Greater part salts form of minerals used as the source of each element can be founded in official monographs in Ph. Eur., BP or USP. The test methods and requirements of the two non official mineral salts, sodium metavanadate and cobalt sulphate are described in 'in-house' monographs prepared by Humet Trading, Research and Development Co.

These in-house' test methods and acceptance criteria are in agreement with monographs of other similar official monographs taking certificates of manufacturer into consideration. Validation studies are not included in the documentation.

The manufacturer certifies the mineral salts used for production of Humet-R syrup and their quality is accepted.

Humic acid

Format 2B106Aii/
Herbal/6-7
2/100 to 114

Humic acid used for producing Humet-R syrup 300 ml is manufactured by Humet Trading, Research and Development Co. Similar structural substances produced by alkaline extraction are termed as humic acid, which mark three fractions, namely humic acids, fulvic acid and humin. Humic acid in Humic acid extract is presented as potassium humate arisen from manufacturing procedure.

It is not described in a pharmacopoeia. Specifications and test methods of humic acid are prescribed in a Quality Test Specification document.

The parameters specified and tested on the all batches for release can be accepted based on the scientific data. The identity is determined by characteristic, which is typical for humic acid. The specifications of particle size, homogeneity and redispersibility and pH value are suitable for ensuring the constant physical-chemical quality of drug substance for manufacturing of finished product. The assay is determined based on content of dried substance. The purity tests are chosen well for a product origin of plant as mechanical-, microbial- and toxic metal (lead) purity, which are in line the current requirements.

Pesticide (chlorinated carbon hydrates) and toxic heavy metal (cadmium and lead) content have been investigated as skip testing. The results were far under the international limits.

There is not agricultural cultivation on the mine area of peat so it's permanent testing is not necessary.

Scientific data:

Humic acid extract is a standardised peat extract originated from a homogenous fen type, geologically young and slightly basic in Hungary around Lake Balaton. It contains grey and brown humic acids, fulvene acid, hymatomelane acids, humic acid fragment and different valence metals in chelat bound. The molecular mass of the humic acid components in the solution are 2 000 - 3 000 Daltons, and fulvic acid is 800 - 1 000 Daltons.

Format 2B107A/ Herbal
2/117 to 120
2/151 to 157

Their structural formula is characterised by the Hawroth scheme, which illustrates that diverse polypeptides, phenol carbonic acids are bound to the polynuclear heteroaromatic nucleus. The most important functional groups are -COOH, phenolic-OH, =NH, $-NH_2$, =C=O. In the nuclear structure di- and trihydroxyphenol rings and quinonoidal structure are detected. Also carbohydrate compounds are connected to the nucleus. The peculiar capacity for metal binding arises by the simultaneous presence of functional groups.
This structural formula is supported by elemental analysis and ash analysis of peat vehicle. The existence of the functional groups is justified by infrared spectroscopy. The metal components are determined by ICP-OES and AAS methods.

The γ-ray treatment for bacterial reduction was optimised because it can indicate certain changes, most likely decarboxylation and/or chain brake.

2/161-166

Manufacturing process:
After the screening the peat mined to the uniform size and discharging of plant remains the humic acid is extracted by dipotassium phosphate solution. The colloidal solution in required concentration and mechanical purity filled in stainless steal vessels under pressure of nitrogen gas is submitted to an optimised γ-ray treatment for bacterial reduction.

Format 2B108A/ Herbal
Format 2B109A/ Herbal
2/121 to 134

Quality control during manufacture:
The circumstances of mining of peat are a controlled process.
The peat prepared for extraction is qualified.

2/135 to 150

Analytical development & validation:

Chemical profile:
The peat mined from well-encircled area of moorish basin lain in Keszthely area, Zala county, Hungary is mainly calcium humat, which is black fine grained with fibre structure.
It is chemically not a homogeneous substance. Their composition is stated by different up to date method.
The peat contains 55-70 % of organic substances, 10-28 % inorganic substances and 15-18 % water.
The functional groups of organic substances are determined, which responsible for the metal binding and other characteristics.

Format 2B110A/ Herbal
2/137 to 148

Format 2B111A/ Herbal
2/151 to 157

Test methods for humic acid:
The test methods of peat extract are simple usual methods prescribed in national pharmacopoeia, so their validation is not necessary.
The microbial test and requirement is given by national pharmacopoeia. Though considering the minor divergence in this topic between the Hungarian Pharmacopoeia and European Pharmacopoeia the results of tests seem adequate.

Format 2B111A/
Herbal
2/100 to 114

Impurities:
Potential impurities, namely microbial contamination, pesticide residues, heavy metals, originate from the peat.
The extraction of humic acid is prepared by maceration with aqueous potassium pyrophosphate solution under controlled circumstances.
The microbial contamination is reduced by γ-ray treatment of the peat extract.
These impurities are specified and controlled in accordance with prescription of Ph. Eur.

Format 2B112A/
Herbal
2/158 to 166

Batch analysis:
The manufacturing firms are well known in this topic and certified the quality of all batches included the detailed purity test of each nine mineral salt. The release of mineral salt based on the certificates.
Some certificates are attached to the documentation.
The all-humic acid batches are qualified by quality description of Humet Trading, Research and Development Co. The documentation presents the analyses of five consecutive batches. The products comply with quality test specification, which justified the humic acid extract can be manufactured in the same, suitable quality.

Format 2B113A/
Herbal
2/167 to 207

C/2Excipients:

The purified water and dipotassium phosphate used for production of Humet-R syrup 300 ml are described in the current Ph. Eur. monographs.
The orange syrup is produced by Szobi Szörp Gyümölcsfeldolgozó Rt., Hungary. It contains neither synthetic colour materials, nor preservative, nor antioxidant. The firm and its products are qualified by OÉTI (National Institute of Food-Hygiene and Nutrition, Hungary).
The release of orange syrup based on the certificates of manufacturer. Certificates of Orange No. 3512 and Orange super concencentrate are attached to the documentation.

Format 2B114A
2/209 to 227
Format 2B115A
2/228 to 243

C/3 Immediate packaging:

Humet-R syrup 300 ml is packed in two alternative immediate packaging. One of them is brown glass container with assurance cap and other is brown transparent plastic (polyethyleneterephthalate, PET) bottle, with polypropylene tamperproof cap.
A polypropylene measuring device belongs to the packaging material for easy dosing.

Format 2B116A
2/245 to 282

The all-packaging materials meet the Ph. Eur.'s requirements, and comply with manufacturer's specification. The substance of PET bottle conforms to prescribed of Ministry of Health, Italy. Format 2B116A 2/245 to 282

The quality of immediate packaging materials is accepted on the basis of certification by manufacturing firms. Some certificate is enclosed to the documentation.

The interaction, namely leaching and sorption, between the immediate packaging and Humet-R syrup was justified by ICP-OES and IR spectroscopy test methods. 2/033 to 036

Part II D - CONTROL TESTS ON INTERMEDIATE PRODUCTS

No control tests on intermediate products are reported. Format 2B117A/1 2/283

Part II E - CONTROL TESTS ON THE FINISHED PRODUCT

The documentation of the finished product control includes the following parts:

- release specifications and acceptable limits of the finished product
- test methods
- validation study of ICP-OES method
- results of batch analyses.

E/1 Finished product specification and tests for release: Format 2B117A/2-3 2/286 to 312

The pharmaceutical dosage form is definitely characterised using the following test parameters: appearance, particular size of suspension, homogeneity and dispergating capacity, pH and mechanical purity taking into account the relevant requirements and test methods of Ph. Eur.

The identification of humic acid – metal chelat content is carried out by a pH dependent precipitation.

The trace elements are identified together with their assay determination.

The test methods for quantitative determination of active ingredients are ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometry) method. The acceptance limits prescribed in the specifications for release change among +5 and (-)15 percentile except the requirement for magnesium, which is +12 and (-)5, and. for selenium the highest one is +7 %. On the basis of results of five consecutive batches reported doesn't necessary of these wide limit.

The test for microbial purity is required as biological purity test.

The arsenic and lead (1.5 mg/300 ml), and aluminium (30 mg/300 ml) are limited as heavy metal purity investigated together with elements by ICP-OES method.

From inactive ingredients the identity of sugars are described.

E/2 Scientific data:

Format 2B118A/1
2/313 to 320

Inductive coupled plasma optical emission spectrometry (ICP-OES) method was applied for assay of elements.

Their specificity, linearity, accuracy and robustness were investigated in the validation study.

Batch analysis:

Format 2B118A/2-3
2/321 to 331

The results of the analysis on five consecutive commercial size batches demonstrate that the parameters tested, which comply with the relevant specifications, fulfil the requirements, set in the finished product specification at release.
The results of analysed batches show the required reproducibility of the manufacturing process for Humet-R syrup 300 ml.

Part II F - STABILITY

F/1 Stability tests on active substance:

Format 2B119A
2/334

Special stability test on the salts form of the minerals is not performed since all of them used as source of elements are well known stable inorganic compounds and their qualities are documented by the manufacturer.

The stability test of humic acid extract according to ICH stability guideline is not included in the file.
The storage conditions are proposed under pressure of nitrogen in airtight stainless steal cans, as final packaging, stored in refrigerator (5±3°C) for 6 months.

This short-term shelf life can be accepted by reason of well-closed final packaging and on the basis of IR spectra prepared in development phase.

F/2 Stability tests on the finished product:

Format 2B120A
2/335 to 373

The documentation of stability studies on the finished product includes the following parts:

- Stability study according to ICH stability guideline
- Stability of the Humet-R syrup after the first opening

Stability study according to ICH stability guideline

Format 2B120A/1-3
2/337 to 345

3 commercial size batches in the both alternative final packaging in which the product is intended to be marketed (glass container and PET bottle) were investigated according to ICH stability guideline.

Format 2B120A/1-3
2/337 to 345

The parameters studied (appearance, change of mass, mechanical impurities, not soluble particles, homogeneity, pH, microbial purity, lead content, metal content and degradation products of humic acid) are indicators of product quality, which are affected by storage.

The analytical methods are partly the same as those used at release. The changes in IR spectra of Humet-R syrup give information about degradation of humic acid.

Stability after the first opening

The pharmaceutical and microbial properties were investigated on two commercial batches ensured similar circumstances as in the treatment period at patients.

Format 2B120A/4-10
2/346 to 370

Results of stability study:
The results of real time and accelerated stability test on all of the 3 batches till now show that the pharmaceutical properties have not changed. The weight loss of product packed in PET flacon was less than 1.0 %.

The content of individual metals did not show significant and tendentious changes during the storage.

The humic acid did not decompose significantly. The microbial purity of product meets the pharmacopoeial requirements.

The stability of Humet-R syrup after the first opening is conforms to requirements for the treatment period.

During stability tests performed no changes were observed either in the physical or in the chemical and microbial characteristics that would refer to the instability of the product.
So based on the real time and accelerated stability test finished till now on six batches and 2 months testing after first opening on two batches, it can be established that the Humet-R syrup is stable.

All batches were tested in both alternative packaging materials and the compatibility of PET flacon to product was studied, so the results of parameters observed support the suitability of packaging.

Format 2B120A/11-12
2/372

Proposed shelf life & storage conditions:

The proposed shelf life of Humet-R syrup 300 ml is two years in both packaging when the product is stored at room temperature (between 15 and 25°C) protected from light.

The product may be administered during 1 months after first opening stored in refrigerator.

Conclusion

Humet-R syrup is an OTC product, containing physiologically essential trace elements, presented in chelat bound with humic acid, as active substances in an orange flavouring suspension form packaging brown glass or plastic bottle.

Up-to-date manufacturing processes in the desired quality produce Humet-R syrup, as well as one of the active substances, humic acid.

Batch analysis data on humic acid and finished product demonstrate that the manufacturing processes chosen result in consistent quality, which complies with the specifications.

The specifications are in accordance with the manufacturing methods and cover all critical parameters.

Notwithstanding the analytical methods used are not fully validated based on the current EC and ICH guidelines they comply with the scientific state of the art.

The stability data justify the recommended storage conditions for the finished product, and the real time data support the proposed shelf-life period.

Summarising:

On the basis of the Chemical, Pharmaceutical and Biological Documentation and the above argumentation I am convinced that despite negligible deficiencies in the dossier Humet-R syrup 300 ml produced by Humet Trading, Research and Development Co. is an effective, safe, stabile, up-to-date OTC product contained macro- and microelement in chelat-complex formation with humic acid.