Evaluation of the Administrative, Chemical, Pharmaceutical and Bioavailability Data of a New Medicine Application

(Reformulation of the innovator product)

Evaluator: [redacted]
Initial Evaluation completed: 29/03/2005
Final Report completed: 19/10/2006

Product Details

Proprietary Name:

Eltroxin

Active substance:

Levothyroxine sodium

Dose Form:

Tablet

Potency:

50 mcg

100 mcg

Type of application:

Reformulation of the innovator product

Corresponding innovative product & strengths:

Eltroxin Tablets; 50 mcg, 100 mcg; GlaxoSmithKline; TT50-2593

Consent & market status of innovative product:

Approved under Section 21 for distribution in New Zealand on 31-12-1969 and currently marketed.

Therapeutic use:

ATC/BNF classification: Thyroid hormones

Brief summary of indications: Hypothyroidism

Administration & dosage:

Oral

Adults:

The initial daily dose is usually 50 to 100 mcg daily, preferably taken before breakfast, adjusted at three or four week intervals by 50 mcg increments until normal metabolism is steadily maintained. This may require doses of 100 to 200 mcg daily.

In patients over 50 years and those with cardiac disease, lower initial doses are recommended and during dose titration smaller dosage increments should be used.

Children:

For infants with congenital hypothyroidism, a suitable starting dose is 25 mcg daily, adjusted at two to four week intervals by 25 mcg increments until mild toxic symptoms appear. The dosage is then slightly reduced. The same dosing regimen applies to juvenile myxoedema, except that the starting dose for children older than one year may be 2.5 to 5 mcg / kg / day.

Refer to data sheet for further dosing details.

As an immediate release tablet, the dose uniformity and in-use stability of a divided dose unit has not been established.

Packaging & closure:

White opaque polypropylene bottles with tamper-evident, push-fit, white opaque, low density polyethylene (LDPE) closures.

Pack sizes:

50 mcg tablets: 1000 tablets per bottle

100 mcg tablets: 1000 tablets per bottle

Storage conditions:

At or below 25°C

Protect from light

NZ Sponsor:

GlaxoSmithKline (NZ) Ltd, 8th Floor, Quay Tower, Cnr Customs & Albert Streets, Auckland, New Zealand

Manufacturers & Packer:

Active ingredient manufacturer:

Sandoz GmbH, Schaftenau Plant, Biochemiestrasse 10, A-6336 Langkampfen, Tyrol, AUSTRIA

Finished product manufacturer:

GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY

Finished product testing site:

GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY

Finished product packer:

GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY

Associated Drug Master File:

TT60-239-31-10

Overseas approvals:

European Medicines Evaluation Agency (EMEA) – under assessment

1. **The applicant should comment on the status of the application that has been submitted to the EMEA.**

Overseas evaluation reports provided:

None provided

Administrative Data

NOTE:

This application is for the approval of a new formulation of the currently approved Eltroxin tablets that will be manufactured at a new manufacturing site. The new formulation has been approved in Denmark (Danish Medicines Agency) and Germany (BfArM). GSK is ceasing supply of the currently supplied formulation. Eltroxin is the Pharmac funded levothyroxine. No other levothyroxine is available in NZ at this time.

1. Product name

The proposed proprietary name for the product is identical to the name of the current formulation registered in New Zealand. This name is clear, unambiguous and not misleading in any way with regard to the nature, purpose, uses or effects of the product. The new formulation is intended to replace the old formulation; therefore both formulations will not be marketed concurrently. **The applicant should confirm how they intend to communicate the change in formulation to New Zealand health professionals.**

2. Labelling

The applicant must provide full-scale, label drafts (in colour) for both strengths of the reformulated products.

If the labels for the reformulated products are similar to the labels for the current New Zealand innovator products then the packaging for the reformulated products must be labelled with the words, "New Formulation", for an appropriate period of time to ensure that the different formulations are easily distinguishable.

3. Data Sheet

The following changes to the proposed data sheet are required:

The proposed data sheet does not describe the colour or dimensions of the tablets, or any markings on the tablets. **The datasheet must include a description of the colour and dimensions of the tablets and any markings on them as per the New Zealand medicines Regulations and Guidelines Volume 1.**

The innovator data sheet specifies contraindications; however the proposed data sheet does not specify contraindications. **The datasheet must specify contraindications as per the New Zealand Medicines Regulations and Guidelines Volume 1, or the applicant must justify why this is not necessary.**

It was unclear what the numbers next to the headings "Adults" and "Children" referred to in the "Clinical particulars" section. **The applicant should clarify what the numbers next to the headings "Adults" and "Children" refer to in the "Clinical particulars" section of the data sheet and explain what these numbers mean. The applicant should also review whether it is necessary to include these in the data sheet.**

A signed declaration relating to the proposed data sheet has not been submitted. **The applicant must submit a signed declaration relating to the proposed data sheet.**

An information leaflet is not to be supplied with the product.

4. GMP status of manufacturers and packers

The sponsor has provided the following evidence of Good Manufacturing Practice (GMP) compliance for the active ingredient manufacturing site and the finished product manufacturing, testing and packing sites:

- Sandoz GmbH, Schaftenau Plant, Biochemiestrasse 10, A-6336 Langkampfen, Tyrol, AUSTRIA: A Certificate of Suitability dated 12/04/2004 from the European Directorate for the Quality of Medicines with an accompanying letter of access has been submitted as evidence of GMP for this site.
- GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY: A certificate from the State Agency for Health and Occupational Safety of Land Schieswig-Holstein. This certificate expired on 31-05-2004.

The applicant must provide current evidence of GMP for GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY.

Assessment:

The administrative information is complete and meets all requirements except for the following:

2. **The applicant should confirm how they intend to communicate the change in formulation to New Zealand health professionals.**
3. **The applicant must provide full-scale, label drafts (in colour) for both strengths of the reformulated products.**
4. **If the labels for the reformulated products are similar to the labels for the current New Zealand innovator products then the packaging for the reformulated products must be labelled with the words, "New Formulation", for an appropriate period of time to ensure that the different formulations are easily distinguishable.**
5. **The datasheet must include a description of the colour and dimensions of the tablets and any markings on them as per the New Zealand Medicines Regulations and Guidelines Volume 1.**
6. **The datasheet must specify contraindications as per the New Zealand Medicines Regulations and Guidelines Volume 1, or the applicant must justify why this is not necessary.**
7. **The applicant should clarify what the numbers next to the headings "Adults" and "Children" refer to in the "Clinical particulars" section of the data sheet and explain what these numbers mean. The applicant should also review whether it is necessary to include these in the data sheet.**
8. **The applicant must submit a signed declaration relating to the proposed data sheet.**
9. **The applicant must provide evidence of GMP for GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY that has not expired.**

Module 3.2.S: Drug Substance

Brief description of active ingredient

The active ingredient is the subject of an EP monograph.

The form of the active ingredient is levothyroxine sodium and includes five waters of crystallisation. This exact formulation has been accurately entered into SMARTI. The active ingredient present in the proposed product is identical to the active ingredient present in the innovator product.

No evidence of active ingredient polymorphism has been noted in international pharmacopoeia or innovator product files. Therefore, specific controls for polymorphism in the active ingredient are considered unnecessary.

The active ingredient has a known solubility of 15 mg in 100 mL of water at 25 °C. It is soluble in mineral acids and solutions of alkali hydroxides and carbonates, more soluble in alcohol and only slightly soluble in chloroform or ether. Data presented in the application suggests that at 37 °C levothyroxine sodium has a solubility of 9.7 mcg / mL at pH 1.0, 0.8 mcg / mL at pH 4.5 and 2.1 mcg / mL at pH 6.8. These results indicate that levothyroxine sodium just fits into the highly soluble category according to FDA and WHO guidance. Given the solubility of the active ingredient and the proposed finished product dose form, control of active ingredient particle size is warranted. The finished product manufacturer purchases levothyroxine sodium pentahydrate from the active ingredient manufacturer in micronised form with a mean particle size of less than [redacted]

Manufacture and QC by supplier of bulk active substance

The active ingredient in the reformulated products is identical to the active ingredient in the New Zealand registered innovator products and is sourced from the same manufacturer.

An EDQM Certificate of Suitability (No. R1-CEP 1998-141-Rev 00) has been supplied in lieu of a DMF attesting to the quality of the supplier's active ingredient (refer to TT60-239-31-10).

A letter of access has been provided by the active ingredient manufacturer relating to this product.

The active ingredient is controlled to the most current version of the EP. In addition, tests for iodide content, related substances and residual solvents are performed. Specifications and methods for these tests are detailed in the EDQM Certificate of Suitability in the DMF.

The applicant should provide assurance that no significant changes have been made to the manufacturing process since the Certificate of Suitability was issued and that any conditions attached to the Certificate of Suitability will be complied with.

Quality control applied by finished product manufacturer

The application does not state the controls placed upon received batches of active ingredient by the finished product manufacturer. **The applicant should detail the controls placed upon received batches of active ingredient by the finished product manufacturer. Certificates of Analysis, issued by the finished product manufacturer, should be provided for three batches of active ingredient.**

Assessment:

The manufacture and quality control of the bulk active ingredient meet all of the relevant requirements and are acceptable except for the following:

10. **The applicant should provide assurance that no significant changes have been made to the manufacturing process since the Certificate of Suitability was issued and that any conditions attached to the Certificate of Suitability will be complied with.**
11. **The applicant should detail the controls placed upon received batches of active ingredient by the finished product manufacturer. Certificates of Analysis, issued by the finished product manufacturer, should be provided for three batches of active ingredient.**

Module 3.2.P: Drug Product

3.2.P.1 Description and Composition of the Drug Product

1. Composition of the product

A copy of the full formulations and the quality standards applied to the excipients as detailed in Module 3.2.P.1 of the dossier is attached to this report on the Medsafe file. The formulation details as recorded in Medsafe's SMARTI database are also included in the attached Therapeutic Product Database Report.

The products have been formulated as:

Table 1: Composition of the reformulated products

Component	Quantity (mg / tablet)		Function	Reference to Standard
	50 mcg Tablet	100 mcg Tablet		
Triturate:				
Levothyroxine sodium	0.05563 (equiv. to 50 mcg of anhydrous substance)	0.11126 (equiv. to 100 mcg of anhydrous substance)	Active	EP and Suppliers CoS
Microcystalline celluiose	[redacted]	[redacted]	Filler	EP
Other Components:				EP
Microcrystalline celluiose	[redacted]	[redacted]	Filler	EP
Pregelatinised maize starch 1500	[redacted]	[redacted]	Disintegrant / binder	EP
Talc	[redacted]	[redacted]	Glidant	EP
Colloidal anhydrous silica	[redacted]	[redacted]	Glidant / anti-adherent	EP
Magnesium stearate	[redacted]	[redacted]	Lubricant	EP
Total	[redacted]	[redacted]	-	-

The different strengths are direct scales and are distinguished by different sizes and markings. These are as follows:

The 50 mcg tablets are white, round, biconvex and 6 mm in diameter with GS 11E on one face and 50 on the other.

The 100 mcg tablets are white, round and biconvex and 8 mm in diameter with GS 21C on one face and 100 on the other.

Assessment:

The composition information provided is complete and meets all requirements.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug substance

The active ingredient is levothyroxine sodium pentahydrate (five associated waters of crystallisation). Excess or free water can promote degradation of levothyroxine sodium, however, five waters of crystallisation appear to result in increased stability. For these reasons moisture levels during processing and in the finished products are controlled within defined upper and lower limits.

3.2.P.2.1.2 Excipients

The major excipient in the products that are currently registered in NZ is lactose. It is thought that lactose promotes the degradation of levothyroxine sodium. Therefore, reformulating the products to be lactose-free was hoped to improve the stability of the finished products.

Due to the very low dose of levothyroxine sodium required in each tablet, a triturate is prepared with a higher concentration of levothyroxine [redacted] in microcrystalline cellulose to ensure blend uniformity. The triturate is later blended with the other excipients. Various substances were investigated as potential drug carriers in the triturate including mannitol, dibasic calcium phosphate anhydrous and four different grades of microcrystalline cellulose. Microcrystalline cellulose 101 was selected due to its compatibility with the active ingredient and mean particle size [redacted] facilitating good content uniformity).

Maize starch is included in the new formulation at a concentration allowing it to function as a binder and disintegrant. A low moisture grade of starch (maize starch 1500) was chosen to prevent degradation of the active ingredient in the finished products.

There are no obvious compatibility issues between the active ingredient and the excipients present in the finished product formulation.

Summary:

All excipients used in the finished product formulation are established pharmaceutical excipients.

3.2.P.2.2 Drug Product

Divided dose units

The tablets are not scored.

It is noted that the currently registered New Zealand products are scored. The products based on the new formulation are not capable of delivering all approved dose regimens (for example, doses for children, elderly and patients with cardiac disease). It is necessary that the reformulated products can be halved to ensure that the administration of all approved dose regimens is possible. **The applicant should confirm that the reformulated tablets can be halved and submit evidence of uniformity and stability of divided dose units.**

3.2.P.2.2.2, 2.2.3 Overages, Physicochemical and biological properties

There are no overages in the new formulation.

Dissolution characteristics of each strength of the reformulated product have been studied in five different media at four different pH values (see Table 2):

Table 2: Dissolution conditions for pharmaceutical development

pH	Medium	Volume of Medium (mL)	Paddle Speed (rpm)
1.0	0.1 M HCl	500	100
1.0	0.1 M HCl + 0.2 % sodium dodecyl sulphate	500	100
2.0*	0.01 M HCl + 0.2 % sodium dodecyl sulphate	500	50
4.5	Acetate buffer	500	100
6.8	0.05M phosphate buffer	500	100

*Conditions are those specified in USP monograph for levothyroxine sodium tablets

Dissolution of the reformulated tablets was slower in higher pH media (pH 4.5 and 6.8) where in some cases only 80 % of drug was released after 60 minutes.

Virtually complete release of the reformulated tablets was achieved in pH = 1 and pH = 2 (USP) medium. The addition of a surfactant (sodium dodecyl sulphate) into the dissolution medium prevents absorption of levothyroxine sodium from acid solutions onto surfaces, especially in filter units. In the absence of surfactant, typical losses of levothyroxine sodium were approximately 5 %.

It was found that the USP dissolution test method (0.01 M HCl + 0.2 % sodium dodecyl sulphate, volume 500 mL, paddle 50 rpm) was too discriminatory between different formulations of Eltroxin Tablets to be used for the bioequivalence study (see module 5.3). Commercial products that have proved to be clinically acceptable over many years appeared to be non-equivalent. Therefore, a [redacted] medium [redacted] + 0.2 % sodium dodecyl sulphate) and a [redacted] paddle speed [redacted] were selected for release specifications and comparative dissolution testing for the bioequivalence study. A medium volume of 500 mL was retained. Stability studies were already in progress using the conditions specified in the USP monograph and so were continued (see Table 3).

The applicant should explain why they chose not to use the USP dissolution method for release specification testing for the new products.

The applicant should justify the discriminatory nature of the dissolution method chosen for release specification testing, given that it uses a [redacted] medium and a [redacted] paddle speed than the current USP method.

Table 3: Summary comparison of dissolution conditions used for specification testing, comparative dissolution testing for the bioequivalence study and stability testing of reformulated Eltroxin Tablets

	In-house Method **(Specification testing and comparative dissolution testing for the bioequivalence study)**	**USP method** **(Stability testing)**
Apparatus	Paddle apparatus of the European Pharmacopoeia which is the same as the USP Apparatus 2	Paddle apparatus of the European Pharmacopoeia which is the same as the USP Apparatus 2
Dissolution medium	[redacted] + 0.2 % SDS	0.01 M HCl + 0.2 % SDS
Dissolution medium volume	500 ± 10 mL	500 ± 10 mL
Dissolution medium temperature	37.0 ± 0.5°C	37.0 ± 0.5°C
Number of tablets per vessel	1	1
Rotation speed	[redacted] ± 2 rpm	50 ± 2 rpm
Sampling time	45 minutes for a single point determination; 10, 20, 30, 45, 60 minutes for a profile	45 minutes for a single point determination; 10, 20, 30, 45, 60 minutes for a profile
Filter	30 mm diameter 0.45 µm regenerated cellulose membrane	30 mm diameter 0.45 µm regenerated cellulose membrane

The dissolution rate of the reformulated tablets was compared in each of the dissolution systems described in Table 3. Three batches of each strength were tested after storage for 18 months at 25°C / 60 % RH. The results are attached to this report and show that generally at the 45 minute time point the percentage of levothyroxine sodium released is similar in both media. **The applicant should state how many tablets were tested from each batch of the reformulated tablets for the dissolution rate comparison using the in-house method and the USP method.**

It was noted that the release specifications for the current NZ innovator products include compliance with the dissolution test specified in the USP 23 monograph for levothyroxine sodium tablets:

Method: Paddle (USP apparatus 2) at [redacted] ± 2 rpm in 500 mL of medium [redacted] at 37.5°C.

Specification: Q = 55 % at 80 minutes

This method is different to the in-house and current USP method, however, it does not allow discrimination between batch quality.

The excipients in the reformulated products are largely insoluble in aqueous media, so release of drug from the tablets is expected to be dependent on tablet disintegration followed by extraction of the active into solution. Disintegration is monitored as part of in-process controls during the manufacture of the reformulated products.

3.2.P.2.3 Manufacturing Process Development

[redacted] processes were considered for the manufacture of the reformulated finished products. Both methods were shown to produce tablets with acceptable and comparable physical parameters including: disintegration time, hardness,

friability, loss on drying, content uniformity and weight uniformity. The [redacted] method was chosen to avoid unnecessary exposure of the active ingredient to moisture.

3.2.P.2.4 Container Closure System

The proposed packaging is white opaque polypropylene bottles with tamper-evident, push-fit, white opaque LDPE caps.

The proposed packaging and pack sizes are appropriate for the product. There are no obvious compatibility or safety issues that need to be resolved.

The NZ Medicine regulations do not require the product to be packaged in a safety container.

3.2.P.2.5, 2.6 Microbiological Attributes and Compatibility

Microbial testing has been performed on two production scale batches of triturate and three production scale batches of the finished products (two batches of 50 mcg product and one batch of 100 mcg product). All of the batches tested had total viable aerobic counts of less than 5 cfu / g and absence of Escherichia coli from a 1 g sample was demonstrated. These results comply with EP standards for microbial quality of pharmacopoeial preparations.

Microbial testing during tablet stability studies has confirmed that the finished products remain in compliance with EP microbial standards throughout storage for up to 12 months at 25°C / 60 % RH or 30°C / 60 % RH.

Assessment:

The pharmaceutical development information provided is complete and meets all requirements except for the following:

12. The applicant should confirm that the reformulated tablets can be halved and submit evidence of uniformity and stability of divided dose units.

13. The applicant should explain why the USP dissolution method was not chosen for release specification testing of the new products.

14. The applicant should justify the discriminatory nature of the dissolution method chosen for release specification testing, given that it uses a [redacted] medium and a [redacted] paddle speed than the current USP method.

15. The applicant should state how many tablets were tested from each batch of the reformulated tablets for the dissolution rate comparison using the in-house method and the USP method.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturers

See page 2 of this report.

3.2.P.3.2 Batch Formula

The representative batch formula for levothyroxine sodium triturate is based on a commercial batch size of [redacted].

The representative batch formula for the final blend is based on a commercial batch size of [redacted] yielding [redacted] tablets of 50 mcg product or [redacted] tablets of 100 mcg product. The final blend batch size in production may be in the range of [redacted] depending on market demand. Each final blend batch may be used in portions to produce the required batch sizes of 50 mcg or 100 mcg tablets.

The batch and product formulae are consistent.

The quantity of triturate required for the formulation of a tablet batch is adjusted depending on assay results of the triturate after final blending.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

The products are manufactured by a [redacted] tableting process. The active ingredient is initially incorporated into a triturate with microcrystalline cellulose before it is blended in with the other excipients.

The main stages of the manufacturing process are:

Stage 1 - Triturate preparation:

[redacted]

Stage 2 - Tablet blend:

[redacted]

Stage 3 - Compression:

[redacted]

In-process controls include:

Stage 1

- Assay of levothyroxine sodium content in the triturate after final blending is complete (see intermediate product specifications). The assay result determines the amount of triturate required for formulation into a tablet batch according to the required tablet potency.

Stage 2

- Loss on drying of the final blend [redacted]

The applicant should explain what the [redacted] method is that is used for testing loss on drying of the final blend.

Stage 3

- Uniformity of weight (EP method) – 50 mcg tablet: [redacted] 100 mcg tablet: [redacted]
- Mean weight (n = 20) – 50 mcg tablet: [redacted]; 100 mcg tablet: [redacted]
- Disintegration (EP method) – Not more than [redacted]
- Crushing Strength (EP method) – Not less than [redacted]
- Friability (EP method) – Not more than [redacted]

3.2.P.3.4 Controls of Critical Steps and Intermediates

Specifications and routine tests for the triturate include:

- Appearance / description
- Identification of levothyroxine sodium by HPLC
- Assay of levothyroxine sodium content by HPLC

Batch analytical data was provided for two production scale batches of levothyroxine sodium triturate.

3.2.P.3.5 Process Validation and/or Evaluation

Details of the batches used for process validation are presented in Table 4:

Table 4: Details of the batches used for validation, stability and bioequivalence studies

	Tablet Strength					
	50 mcg tablet			100 mcg tablet		
Active ingredient batch number	78451014	78451015	78451014	78451014	78451015	78451014
Tablet blend batch number	0206	0205	0204	0204	0206	0205
Tablet batch number	0274	0275	0276	0271	0272	0273
Batch size (kg): Tablet blend Tablet	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scale	Production	Production	Production	Production	Production	Production
Date of Manufacture	November 2001	November 2001	November 2001	November 2001	November 2001	November 2001
Site of Manufacture	Glaxo Wellcome Gmbh, Bad Oldesloe, Germany	Glaxo Wellcome Gmbh, Bad Oldesloe, Germany	Glaxo Wellcome Gmbh, Bad Oldesloe, Germany	Glaxo Wellcome Gmbh, Bad Oldesloe, Germany	Glaxo Wellcome Gmbh, Bad Oldesloe, Germany	Glaxo Wellcome Gmbh, Bad Oldesloe, Germany
Use	Stability testing, Validation studies	Stability testing, Validation studies	Stability testing, Validation studies	Stability testing, Validation studies	Stability testing, Validation studies	Stability testing, Validation studies, Bioequivalence study

Acceptable process validation data was provided to demonstrate:

- Uniformity of levothyroxine sodium triturate
- Uniformity of tablet blend
- Content uniformity of the reformulated tablets (compliance with EP specifications was demonstrated)
- Stability of the active ingredient during tablet manufacture

- Compliance of the new finished products with the following in-process control specifications: uniformity of weight, crushing strength, disintegration and friability

The proposed manufacturing process is acceptable.

Assessment:

16. **The applicant should explain what the [redacted] method is that is used for testing loss on drying of the final blend.**

3.2.P.4 Control of Excipients

Specifications and test methods (3.2.P.4.1 – 4.4)

All of the excipients are purchased from commercial suppliers as complying with the current edition of the EP. The finished product manufacturer either tests the excipient for compliance with current EP specifications or accepts the product based on the suppliers' Certificate of Analysis and performs identity tests on receipt. When excipients are purchased from new suppliers, the finished product manufacturer tests the excipient for compliance with current EP specifications until reliability of supply is established.

These specifications are acceptable.

3.2.P.4.5 Excipients of Human or Animal Origin

The product contains no ingredients derived from animals or humans.

A TSE annex III status has been assigned to this product and entered into SMARTI.

3.2.P.5 Control of Drug Product

Release Specifications (3.2.P.5.1 and 3.2.P.5.6)

The finished products are controlled to the following release specifications:

- Appearance / description (in-house).
- Identification of levothyroxine sodium by HPLC and UV (in-house).
- Assay of levothyroxine sodium by HPLC (in-house).
- Uniformity of content by HPLC (in-house)
- Loss on drying (in-house) – drying to constant weight.
- Dissolution (in-house) – uses paddle (Apparatus 2 USP) at [redacted] in [redacted] medium [redacted] + 0.2 % sodium dodecyl sulphate) at 37°C. This method uses a [redacted] paddle speed and [redacted] medium than the method specified in the USP product monograph. As discussed in module 3.2.P.2.2.3, the applicant should justify the discriminatory nature of this dissolution method. It was unclear whether release limits for dissolution apply to individual units or to the mean of a particular number of units. **The applicant should confirm whether release limits for dissolution apply to individual units or to the mean of a particular number of units.**

Release specifications for the new products are similar to those of the New Zealand innovator products except for the following:

- The second identification test for the new products is a UV method instead of a TLC method.

- The following tests are performed as part of in-process controls for the new products: uniformity of weight, mean weight, disintegration, crushing strength and friability. These tests were included in release specifications for the innovator product.
- The New Zealand innovator product release specifications and the USP monograph for levothyroxine sodium tablets include limits for liothyronine sodium; however, liothyronine sodium limits are not included in the release specifications for the new formulation. Given that the active ingredient is controlled to specifications for liothyronine content and stability data show no significant increase in liothyronine content after storage of the triturate for 10 months at ambient warehouse conditions or throughout the complete tablet manufacturing process it is likely that this is acceptable. In addition, the shelf life impurity limit for liothyronine sodium is 1.0 % w/w (relative to levothyroxine sodium content). This is lower than the limit for liothyronine sodium of 2 % w/w (relative to levothyroxine sodium content) in the release specifications for the innovator product and the USP monograph for levothyroxine sodium tablets. The absence of a release specification for liothyronine content is satisfactorily justified.

Release specifications do not include testing for tetraiodothyroacetic acid (tetrac), 4-[(4-hydroxy-3,5-diiodophenyl)oxy]-3,5-diiodobenzoic acid (HDPhDB acid), unknown impurities or total impurities. However, stability studies performed on three production scale batches of each strength of the finished product stored at 25°C /60 % RH indicate that impurity levels comply with the following shelf life specifications:

Table 5: Shelf life specifications for impurities (excluding liothyronine sodium)

Impurity	Shelf life specification (%)
Tetrac	≤ 1
HDPhDB	≤ 2.5
Unknown impurities	≤ 1
Total impurities	≤ 6

The applicant should confirm the quantities of tetrac, HDPhDB, unknown impurities and total impurities that are contained in the NZ innovator products. Data from at least three batches of the NZ innovator product should be provided. If the New Zealand innovator products do contain tetrac and HDPhDB, the applicant should explain why Medsafe was not notified about these impurities previously.

Tablet dimensions are not included in the release specifications. **Release specifications should include testing for tablet dimensions.**

The applicant should confirm that all release specification tests are conducted on every batch. If there is reduced testing for some parameters, the reasons for this should be stated.

Expiry Specifications (3.2.P.5.1 and 3.2.P.5.6)

Shelf life and release specifications for the reformulated products are the same except for the following:

- The lower acceptance limit for the assay is reduced from 95 % to 90 % in the shelf life specifications.
- The upper limit for loss on drying is increased from 6 % to 6.5 % in the shelf life specifications.
- Shelf life specifications do not include a test for uniformity of content.

- Shelf life specifications include testing for impurities and microbial content (EP method).

It is unclear whether shelf life specifications for dissolution are based on the USP method or the method used for release testing of the reformulated products. **The applicant should confirm whether shelf life specifications for dissolution are based on the USP method or the method used for release testing of the reformulated products.**

Shelf life specifications include impurity limits for liothyronine sodium, tetraiodothyroacetic acid (tetrac), 4-[(4-hydroxy-3,5-diiodophenyl)oxy]-3,5-diiodobenzoic acid (HDPhDB acid), unspecified impurities and total impurities. Liothyronine sodium is considered to be a drug substance process impurity and a degradation product. Tetrac and HDPhDB are both degradation products. The shelf life impurity limits comply with ICH requirements based on a maximum daily dose of 300 µg except for the limit for HDPhDB acid (2.5 % w/w (relative to levothyroxine sodium content)), which is above the qualification threshold. To justify this limit, one batch of the 100 µg strength of a current innovator product was tested for HDPhDB acid content after storage for 18 and 24 months at 25°C / 60 % RH and 30°C / 60 % RH and 34 months at 25°C / 60 % RH. **The applicant should confirm which formulation (batch number: G03102) was used to justify HDPhDB acid shelf life specifications for the reformulated products and state what the shelf life of this product is and the name of the regulatory authority(s) that it is approved by.** The results showed that levels of HDPhDB acid up to 3 % w/w were present in the innovator batch tested after storage for 34 months. Stability studies demonstrated that both strengths of the reformulated tablets contain less than 2.5 % w/w (relative to levothyroxine sodium content) after storage at 25°C / 60 % RH for 24 months. The New Zealand innovator product specifications and pharmacopoeial monographs do not include limits for tetrac or HDPhDB acid.

The total impurity limit (excluding liothyronine sodium) in the shelf life specifications is 6 %. **Given that the limits for tetrac, HDPhDB and unknown impurities are 1 %, 2.5 % and 1 % respectively, the applicant must justify why the total impurity limit in the shelf life specifications is so high (6 %).**

Analytical Procedures: description and validation (3.2.P.5.2, 3.2.P.5.3)

The finished products are tested using in-house test methods.

Adequate validation data has been provided for the following in-house test methods:

- Assay of levothyroxine sodium content (HPLC) – The validation data provided shows that the HPLC assay method is specific, linear, accurate, precise, robust and suitable for testing tablets that contain 80 to 120% of the label claim for both strengths of the finished product.
- Content uniformity of levothyroxine sodium (HPLC) – The validation data provided shows that the HPLC method for content uniformity testing is specific, linear, accurate, precise and suitable for testing tablets that contain 70 to 130 % of the label claim for both strengths of the finished product.
- Drug-related impurity content (HPLC) – The validation data provided shows that the HPLC method for determining drug-related impurity content is specific, linear, accurate, precise, robust and suitable for quantifying impurities from limits of quantification up to specification limits. The impurity test method is capable of discriminating all of the required impurities listed in the innovator specifications and the BP and USP monographs for levothyroxine sodium tablets.
- Dissolution of the finished products (HPLC) - The validation data provided shows that the HPLC assay method used for the dissolution test method used for release specifications is specific, linear, accurate, precise and suitable for testing tablets that contain 50 to 150% of the label claim for both strengths of the finished product.

Batch Analyses (3.2.P.5.4)

Batch analyses were provided for three production scale batches of each strength of the finished product. For further batch details refer to Table 4.

All of the batches tested complied with release specifications except that the tablets were not imprinted and the UV identification test was not performed.

The applicant must submit signed Certificates of Analysis for three production scale batches of each strength of the finished product. It is expected that the Certificates of Analysis provided will provide evidence that the reformulated tablets comply with release specifications for tablet imprinting and the UV identification test.

Assessment:

17. **The applicant should confirm whether release limits for dissolution apply to individual units or to the mean of a particular number of units.**
18. **The applicant should confirm the quantities of tetrac, HDPhDB, unknown impurities and total impurities that are contained in the NZ innovator products. Data from at least three batches of the NZ innovator product should be provided. If the New Zealand innovator products do contain tetrac and HDPhDB, the applicant should explain why Medsafe was not notified about these impurities previously.**
19. **Release specifications should include testing for tablet dimensions.**
20. **The applicant should confirm that all release specification tests are conducted on every batch. If there is reduced testing for some parameters, the reasons for this should be stated.**
21. **The applicant should confirm whether shelf life specifications for dissolution are based on the USP method or the method used for release testing of the reformulated products.**
22. **The applicant should confirm which formulation (batch number: G03102) was used to justify HDPhDB acid shelf life specifications for the reformulated products and state what the shelf life of this product is and the name of the regulatory authority(s) that it is approved by.**
23. **Given that the limits for tetrac, HDPhDB and unknown impurities are 1 %, 2.5 % and 1 % respectively, the applicant must justify why the total impurity limit in the shelf life specifications is so high.**
24. **The applicant must submit signed Certificates of Analysis for three production scale batches of each strength of the finished product. It is expected that the Certificates of Analysis provided will provide evidence that the reformulated tablets comply with release specifications for tablet imprinting and the UV identification test.**

3.2.P.6 Reference Standards or Materials

The reference standards used in the testing methods for the new finished products are the same as those that have previously been used in the testing methods for the innovator products:

Levothyroxine acid (CAS Registry No. 51-48-9) is available commercially and as a Chemical Reference Substance of EP. A working standard material has been established by GlaxoSmithKline and the purity of the current batch by HPLC has been assigned as 96.0 % w/w for use in HPLC methods.

Liothyronine acid (CAS Registry No. 6893-02-3) is used in the resolution check for the HPLC determinations of assay, drug-related impurities, content uniformity and dissolution of the new finished products. It is available commercially and as a Chemical Reference Substance of EP. A working standard material has been established by GlaxoSmithKline and the purity of the current batch by HPLC has been assigned as 94.1 % w/w for use in HPLC methods.

3.2.P.7 Container Closure System

Description, suitability, quality control, delivery device

The proposed packaging is white opaque polypropylene bottles with tamper-evident, push-fit, white opaque LDPE caps.

The finished product manufacturer assesses the suitability of suppliers of packaging materials through a regular programme of formal GMP audits. Audits are performed before a supplier commences supply and at intervals throughout supply to check that standards are maintained.

The finished product manufacturer tests packaging materials on their receipt until reliability has been established. Upon confirmation of acceptable standards, a reduced testing regimen may be implemented where components are accepted on the supplier's Certificate of Analysis.

The polypropylene bottles and LDPE caps are tested for concordance with a representative IR spectrum, absence of critical defects and compliance with dimensional limits. **The applicant should provide signed Certificates of Analysis for the polypropylene bottles and LDPE caps.**

Both the polypropylene bottles and LDPE caps are suitable for contact with the finished products, and are certified by the suppliers to conform to the EC Directive 90/128/EEC for food contact. The colouring agent used in both these materials is titanium dioxide (E171).

Assessment:

25. The applicant should provide signed Certificates of Analysis for the polypropylene bottles and LDPE caps.

3.2.P.8 Stability

1. Active substance

The active ingredient is an established pharmaceutical substance; however, its degradation profile and stability have not been detailed in the DMF, innovator product dossier or application dossier.

The Certificate of Suitability provided does not specify an expiry or re-test period for the active ingredient. **The applicant should state the proposed shelf life and storage conditions for the active ingredient and provide stability data to support these.**

3.2.P.8.1 Stability Summary and Conclusion

The proposed shelf life for the triturate is 6 months when it is stored in the proposed packaging under warehouse conditions at up to 25°C.

The proposed shelf life for the unopened reformulated products is 24 months when stored at or below 25°C in the proposed packaging.

Further information must be provided for assessment before a conclusion can be made with regard to the shelf lives of the triturate and reformulated products (see assessment summaries).

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

Primary stability studies have been completed. Further stability testing under long term and intermediate conditions will be performed at the discretion of the product manufacturer.

The applicant should outline the on-going stability protocol for commercial batches of each strength of the reformulated products.

3.2.P.8.3 Stability Data

Triturate:

Stability data was provided for two batches of triturate stored in the proposed packaging for 10 months at ambient warehouse conditions (15-25°C / 40-60 % RH). **Given the hygroscopic nature of levothyroxine sodium and the poorly defined storage conditions in the informal stability study, the applicant should make a post-approval commitment to perform a formal stability study for three batches of the triturate stored in the proposed packaging for 6 months at 25°C / 60 % RH.**

Reformulated products:

Stability data up to 24 months for three production scale batches of each strength of the reformulated products are presented in the application.

All of the batches used for stability testing were manufactured in November 2001 and stability testing commenced in December 2001.

Stability testing was performed on batches of the reformulated products stored at 25 ± 2°C / RH 60% ± 5 % for 24 months, 30 ± 2°C / RH 60 ± 5 % for 24 months and 40 ± 2°C / RH 75 % ± 5 % for 6 months. Further testing was performed on the same batches after exposure to visible and UV light as per ICH guidance.

Details of the batches tested are provided in Tables 4 and 6.

Table 6: Stability batches and corresponding storage conditions

Strength	Batch No	Storage condition	Data to... (months)	Use	Batch size (kg)	Active material lot
50 mcg	0274	25 ± 2°C / RH 60 ± 5 %	24	Stability	[redacted]	78451014
		30 ± 2°C / RH 60 ± 5 %	24			
		40 ± 2°C / RH 75 ± 5 %	6			
	0275	25 ± 2°C / RH 60 ± 5 %	24	Stability	[redacted]	78451015
		30 ± 2°C / RH 60 ± 5 %	24			
		40 ± 2°C / RH 75 ± 5 %	6			
	0276	25 ± 2°C / RH 60 ± 5 %	24	Stability	[redacted]	78451014
		30 ± 2°C / RH 60 ± 5 %	24			
		40 ± 2°C / RH 75 ± 5 %	6			
100 mcg	0271	25 ± 2°C / RH 60 ± 5 %	24	Stability	[redacted]	78451014
		30 ± 2°C / RH 60 ± 5 %	24			
		40 ± 2°C / RH 75 ± 5 %	6			
	0272	25 ± 2°C / RH 60 ± 5 %	24	Stability	[redacted]	78451015
		30 ± 2°C / RH 60 ± 5 %	24			
		40 ± 2°C / RH 75 ± 5 %	6			
	0273	25 ± 2°C / RH 60 ± 5 %	24	Stability	[redacted]	78451014
		30 ± 2°C / RH 60 ± 5 %	24			
		40 ± 2°C / RH 75 ± 5 %	6			

Stability batches were tested for description, assay (levothyroxine sodium), drug-related impurities, loss on drying, dissolution, disintegration and microbial purity.

Sampling methods were not described and it was unclear how many tablets from each batch of reformulated product were tested as per the stability protocol. **The applicant should provide a description of sampling methods for the primary stability studies including confirmation of how many tablets were tested from each batch.**

No significant changes in description were observed during stability testing of either tablet strength. It was noted that the tablets tested were not imprinted.

Stability data showed decreases in assay over time for both product strengths, with accompanying increases in total degradation products (excluding liothyronine sodium). There were no significant increases in liothyronine sodium content throughout the 24 months studies performed at 25°C / 60 % RH and 30°C / 60 % RH. All mean assay and impurity results remained within shelf life specifications for 24 months when stored at 25°C / 60 % RH. Mean assay results for most of the batches tested in the stability studies did not meet assay specification limits after storage for 24 months at 30 ± 2°C / RH 60 ± 5 % and 6 months at 40 ± 2°C / RH 75 ± 5 %.

Data on samples stored at 25°C / 60 % RH show a small amount of degradation for which mass balance is not completely demonstrated. The applicant suggests that this may be attributed to the complex degradation patterns of levothyroxine sodium, which involve

deiodination and deamination, as iodine-based fragments are unlikely to be detected by the HPLC method.

The dissolution test method used for the stability studies is different to the test used for release specifications as discussed in Module 3.2.P.2. Method validation was provided for the dissolution test method used for stability testing and adequate specificity, linearity, range, accuracy and precision was demonstrated. A trend towards a decrease in dissolution rate was observed for both strengths of the reformulated product after storage at 25°C / 60 % RH for 24 months and was more significant for the 50 µg product. All results were within specification after storage at 25°C / 60 % RH for 24 months. It was noted that some dissolution results for one batch of the 50 µg product (Batch No. 0274) fell below specification after 12 and 18 months of storage at 25°C / 60 % RH. **The applicant should discuss these results and if possible provide an explanation.**

Results of loss on drying and disintegration tests showed variability with some trends towards increased loss on drying and disintegration times respectively beyond the 12 month time point and under high humidity conditions. All mean results remained within specification.

Microbial content was within EP specifications for all batches of the reformulated products tested after 24 months storage at 25°C / 60 % RH and 30°C / 60 % RH.

Data are presented following short-term storage of three batches of each strength of the reformulated product, packaged in the proposed packaging in a light cabinet under ICH conditions. Small decreases in assay, with accompanying increases in degradation products were observed along with decreases in dissolution and increases in disintegration time. All mean batch results remained within specification after light exposure. These results indicate that the following storage instructions are appropriate: Protect from light.

Stability in-use

Stability of the reformulated tablets has been investigated after repeated opening and closing of the container throughout a 100-day period, to simulate daily use. Results showed a decrease in assay (levothyroxine sodium) and a small increase in degradation products after the 100-day period. There was also an increase in loss on drying. All results remained within shelf life specifications.

Assessment:

The stability data meet all requirements except for the following:

26. **The applicant should state the proposed shelf life and storage conditions for the active ingredient and provide stability data to support these.**
27. **The applicant should outline the on-going stability protocol for commercial batches of each strength of the reformulated products.**
28. **Given the hygroscopic nature of levothyroxine sodium and the poorly defined storage conditions in the informal stability study, the applicant should make a post-approval commitment to perform a formal stability study for three batches of the triturate stored in the proposed packaging for 6 months at 25°C / 60 % RH.**
29. **The applicant should provide a description of sampling methods for the primary stability studies including confirmation of how many tablets were tested from each batch.**
30. **It was noted that some dissolution results for one batch of the 50 µg product (batch number 0274) fell below specification after 12 and 18 months of storage at 25°C / 60 % RH. The applicant should discuss these results and if possible provide an explanation.**

Module 5.3: Biopharmaceutical Data

Summary of published pharmacokinetic data for the innovator product

Sources of published data:	The innovator product data sheet Martindale's *The Complete Drug Reference* Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th edition Thomson MICROMEDEX 1974 - 2005
Rate of absorption:	Typical T_{max} is approximately 2 to 4 hrs (variable)
Extent of absorption:	Absolute bioavailability is about 50-80 % (variable)
Typical C_{max}	Typical C_{max} after a specific dose is variable
Metabolism:	Approximately 41% is metabolised by deiodination to the active metabolite tri-iodothyronine (liothyronine, T3) and about 38% to inactive reverse tri-iodothyronine (reverse T3), both of which undergo further deiodination to inactive metabolites. About 21% is metabolised via other pathways, such as: deamination and decarboxylation to tetraiodothyroacetic acid (tetrac), conjugation in the liver and excretion in the bile. Levothyroxine is reported to undergo enterohepatic recycling and excretion in the faeces.
Route of elimination:	Approximately 50 % of thyroxine is eliminated in the faeces and approximately 50 % of a dose of thyroxine is excreted in the urine.
Rate of elimination:	The terminal elimination half-life is about 6-8 days in euthyroid subjects; it is prolonged in hypothyroidism and reduced in hyperthyroidism.
Active entities:	thyroxine (T4) triiodothyronine (T3)
Dose-response proportionality:	Measurement of C_{max}, AUC and T_{max} after the administration of therapeutic doses (50-200 mcg) is difficult due to endogenous concentrations of T4.
Effects of food:	Following oral administration, the absorption of thyroxine is incomplete and variable especially when taken with food. The amount absorbed increases during fasting conditions.
Is this a narrow therapeutic index medicine?	Yes (see FDA Guidance for Industry 2000: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.) The Health Canada Therapeutic Products Directorate Expert Committee on Bioavailability and Bioequivalence consider levothyroxine to be a critical dose drug rather than a narrow therapeutic index drug. They recommend that current bioequivalence standards for narrow therapeutic index drugs should be applied to levothyroxine until such time as bioequivalence criteria for critical dose drugs are defined.

Comparative bioavailability data submitted with the application

Study	Title
RES11116	An open-label, single-centre, fasting, single dose, randomised, two-treatment, two-sequence crossover design study in healthy male and female volunteers to assess the bioequivalence of two ELTROXIN formulations

Summary and Assessment of Bioequivalence Study RES11116

1. Administrative information and compliance with GCRP

Summary:

Study Reference: RES11116

Date of trial: Initiation date: 17 December 2002

Completion date: 26 February 2003

Sites for trial: *Clinical:*
PAREXEL GmbH
Institute of Clinical Pharmacology
Klinikum Westend, Haus 18
Spandauer Damm 130
D-14050 Berlin, Germany

Clinical Investigator:
G. Golor, MD, PhD
PAREXEL GmbH
Institute of Clinical Pharmacology
Klinikum Westend, Haus 18
Spandauer Damm 130
D-14050 Berlin, Germany

Assays:
W & T Laboratory
Turmstrabe 21
10559 Berlin
Germany

Adverse events: All adverse events were of mild to moderate intensity. Adverse events considered treatment-related by the investigator occurred more frequently after the administration of the reformulated product (10 adverse events in 8 of 36 subjects) than after the reference product (3 adverse events in 3 of 36 subjects) and are detailed in Table 7:

Table 7: Drug-Related Adverse Events

		Treatment:	
Adverse Event	Total*	Reference Product	Reformulated Product
Headache	6	2	5
Malaise & Fatigue	2	1	1
Sweating	2	0	2
Diarrhoea	1	0	1
Abdominal Discomfort & Pain	1	0	1
Number of adverse events	12	3	10
Number of subjects with adverse events	9	3	8
Number of subjects exposed	36	36	36

* Adverse events that were ongoing over both treatment periods were counted for each treatment period, but only once in the total column.

No adverse event persisted beyond the end of the study. No serious adverse event or death was observed during the study and no subject was withdrawn from treatment due to an adverse event.

The study was conducted in accordance with the requirements of Good Clinical Practice, German Drug Law, the Declaration of Helsinki and with Independent Ethics Committee approval (Chamber of Physicians, Berlin).

Assessment:

The administrative information provided is complete and meets all requirements.

2. Formulations compared and quality control

Summary:

Reference product: [Formulation A]	Current European formulation of Eltroxin 100 mcg Tablets **(not the NZ formulation)**
Batch Number:	2707
Mean assay:	95.0 % of label claim (by UV)
Content uniformity:	Complies with requirements of BP (range 91.1 – 97.0 % of label claim)
Source of batch used:	GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY
Source of reference product available in NZ:	GlaxoSmithKline, 7333 Mississauga Road North, Mississauga, Ontario L5N 6L4, CANADA

Evidence that reference formulation was the same as that marketed in NZ:

The reference product (European formulation) is not the same as that marketed in NZ. The NZ Regulatory Guidelines for Medicines, 2001 require that a biostudy is submitted comparing the new products with the current NZ innovator products. **The applicant should justify why they have submitted a biostudy comparing the new products with the European innovator products and not the NZ innovator products.**

The current European products share many common excipients with the current NZ products but differ in qualitative and quantitative composition. The European formulations include sodium citrate, which is absent from the NZ formulations. The European formulations and the NZ formulations are not direct scales. Details of the composition of these formulations are shown in Tables 8 and 9.

Table 8: Formulation details of the 50 mcg strength of the newly formulated, NZ innovator and European innovator products

Ingredient	New formulation 50 mcg mg / tablet	NZ innovator 50 mcg mg / tablet	European innovator 50 mcg mg / tablet
Levothyroxine sodium	0.05563	0.056	0.056
Microcrystalline cellulose	[redacted]	-	-
Lactose monohydrate	-	[redacted]	[redacted]
Maize starch	[redacted]	[redacted]	[redacted]
Sodium citrate	-	-	[redacted]
Acacia powder, spray-dried	-	[redacted]	[redacted]
Talc	[redacted]	-	-
Silica, colloidal anhydrous	[redacted]	-	-
Magnesium stearate	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 9: Formulation details of the 100 mcg strength of the newly formulated, NZ innovator, and European innovator products

Ingredient	New formulation 100 mcg mg / tablet	NZ innovator 100 mcg mg / tablet	European innovator 100 mcg mg / tablet
Levothyroxine sodium	0.11126	0.112	0.112
Microcrystalline cellulose	[redacted]	-	-
Lactose monohydrate	-	[redacted]	[redacted]
Maize starch	[redacted]	[redacted]	[redacted]
Sodium citrate	-	-	[redacted]
Acacia powder, spray-dried	-	[redacted]	[redacted]
Talc	[redacted]	-	-
Silica, colloidal anhydrous	[redacted]	-	-
Magnesium stearate	[redacted]	[redacted]	[redacted]
Opadry yellow LB282	-	[redacted]	-
Total	[redacted]	[redacted]	[redacted]

Comparison of dissolution profiles of the reference product (European formulation) and the innovator products marketed in NZ:	The Certificate of Analysis for the reference product (European formulation) does not include a specification for dissolution testing. **The applicant should confirm whether the reference product is controlled to dissolution specifications prior to distribution and if so, provide details of these specifications.** Dissolution profiles for three full-scale production batches of each strength of the European and NZ products were compared at pH 1 (0.1 M HCl without surfactant), 4.5 (acetate buffer (USP)) and 6.8 (0.05 M phosphate buffer (USP)). The method used a paddle (USP apparatus 2) at 100 rpm in 500 mL of medium. The temperature of the dissolution system was not stated. Twelve tablets from each batch were tested and the mean results are presented in graphs attached to this report. The results indicate that dissolution profiles for the European products and the NZ products are similar in the above dissolution systems. **The applicant should justify the discriminatory nature of the dissolution comparison performed in pH 1 medium without surfactant comparing the European and NZ innovator products. The applicant should also justify why the in-house dissolution method used for release specification testing was not used to compare the European and NZ innovator products.** Similarity calculations using similarity factor f2 were presented comparing the dissolution profiles (refer to FDA guidance for dissolution testing), however, these could not be interpreted due to lack of information supporting their validity. In order for these calculations to be valid, at least two data points must be less than or equal to 85 % and no more than one data point should be above 85 %. If more than one data point above 85 % is used, false similarities may be concluded. In addition, if mean data is used, the % coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %. **The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparisons of the European and NZ innovator products.** **The applicant should confirm what the temperature of the dissolution system was for the comparison of dissolution systems for the European and the NZ products.**
Trial product: [Formulation B]	Reformulated Eltroxin Tablets
Batch Number:	0273
Batch size:	[redacted] (equivalent to full production scale)
Mean assay:	101.0 % of label claim (by HPLC)
Content uniformity:	Complies with requirements of EP (range 94.0 – 108.2 % of label claim)
Comparative dissolution system:	Medium: [redacted] + 0.2 % sodium dodecyl sulphate Paddle apparatus (equivalent to Apparatus 2 of USP) at [redacted] Time intervals: 5, 15, 30, 45, 60 and 80 minutes Monitoring by HPLC

Results:	See attachments for details. The results indicate that dissolution profiles of the European reference product and the reformulated 100 mcg tablets are similar in the above dissolution system. The similarity factor f2 was calculated to compare the dissolution profiles; however, this could not be interpreted due to lack of information as discussed previously in this report. **The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products.** **The applicant should provide further dissolution profile comparisons for the 100 mcg reference (European formulation) and test products (new formulation) across the pH range (for example, media with a pH of 4.5 and 6.8).** **Further dissolution profile comparisons should be provided for the 50 mcg tablets (European formulation versus reformulated tablets) using the proposed in-house dissolution test method and across the pH range.** As discussed earlier in this report the applicant should provide evidence to show that the in-house dissolution test procedure described above is capable of discriminating batches that have the required in vivo absorption characteristics from batches that do not.
Are the different strengths of the reference and trial products direct scales?	Reference product: No Trial product: Yes **The applicant should justify why they have not submitted a biostudy comparing both strengths of the new products with both strengths of the reference products given that the reference products are not direct scales.**

Assessment:

The product, quality control and in vitro comparative information provided is complete and meets all requirements except for the following:

31. **The applicant should justify why they have submitted a biostudy comparing the new products with the European innovator products and not the NZ innovator products.**
32. **The applicant should confirm whether the reference product is controlled to dissolution specifications prior to distribution and, if so, provide details of these specifications.**
33. **The applicant should justify the discriminatory nature of the comparative dissolution test performed in pH 1 medium without surfactant between the European and NZ innovator products. The applicant should also justify why the in-house dissolution method used for release specification testing was not used to compare the European and NZ innovator products.**
34. **The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparisons of the European and NZ innovator products.**

35. **The applicant should confirm the temperature of the dissolution system used to compare the European and the NZ products.**
36. **The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products.**
37. **The applicant should provide further dissolution profile comparisons for the 100 mcg reference (European formulation) and test products (new formulation) at pH 4.5 and 6.8.**
38. **Dissolution profile comparisons should be provided for the 50 mcg tablets (European formulation versus reformulated tablets) using the proposed in-house dissolution test method and across the pH range.**
39. **The applicant should justify the absence of a biostudy comparing both strengths of the new products with both strengths of the reference products given that the reference products are not direct scales.**

3. Study design

Summary:

Design:	Open-label, single-centre, single dose, randomised, two-treatment, two-sequence crossover design
Fasting/Non-fasting subjects	Fasted **Given that the absorption of levothyroxine is altered when it is administered with food, the applicant should justify why it is not necessary to perform a biostudy in non-fasting subjects.**
Fasting period:	Pre-dose: 10 hrs Post-dose: 4 hrs Subjects were allowed water up to one hour pre dose and after one hour post dose
Dose administered:	600 µg (6 x 100 mcg tablets swallowed whole without chewing)
Liquids that accompanied dose:	240 mL of water at room temperature
Time of day when dose administered:	8:30 to 10 am
Times and nature of meals and snacks consumed on study days:	Standardised low fibre meals at 4 and 10 hours, and a snack 14 hours following the morning dose.
Limitations applied to subjects' diet and medication during trial period:	No alcohol or xanthine-containing products were permitted for 24 hours prior to dosing until collection of the final blood sample during each period. No smoking or use of nicotine-containing products (including nicotine patches) was permitted while subjects were in the Clinical Pharmacology Unit. No grapefruit or grapefruit juice was permitted within seven days prior to the first dose of study medication until collection of the final blood sample during each period.

	Medicines known to interfere with levothyroxine pharmacokinetics were not permitted for at least seven days prior to dosing and throughout the study unless approved by the Investigator and GSK. Subjects currently taking regular medicines (or a course of medication including herbal remedies or vitamin supplements), whether prescribed or not were excluded from the study. Over the counter preparations were not permitted for 48 hours before each study day until the end of the study period. No subject was taking any regular medication prior to the study. 8 subjects received concomitant medications during the study. 3 subjects took 5 concomitant medications during the reference product treatment period and 5 subjects received 5 concomitant medications during the reformulated product treatment period. Drugs administered during treatment periods of the study were: paracetamol (po), lincomycin (po), ibuprofen (po), acetylsalicylic acid (po) and dexpanthenol ointment (topical). Acetylsalicylic acid (aspirin) and paracetamol were most commonly administered. Salicylates interfere with the protein binding of levothyroxine, therefore, the timing of salicylate use was examined to assess any effect on pharmacokinetic parameters. Only subject no. 7 had salicylate use within the 48-hour period of intensive pharmacokinetic sampling, which resulted in no apparent effect on this subject's pharmacokinetic parameters.
Limitations on subjects' posture and physical activity on study days:	Subjects remained upright or semi-recumbent for 4 hours after dosing and refrained from serious exercise for 24 hours prior to dosing and during the sample collection period.
Period between dosing phases:	37-39 days
Subjects entered in study (No and sex):	Total: 36 Group 1: 14 males + 4 females = 18 Group 2: 7 males + 11 females = 18
Subjects that completed the study:	Group 1: All subjects Group 2: All subjects
Age range:	20-40 years
Weight range:	BMI of 19.3-26.2 kg/m^2; body weight 50-75 kg (females), 55-80 kg (males)
Ethnicity:	35 caucasian / white and one of "other" origin (not further specified)
Subject withdrawals (if any) and reasons:	No subjects withdrew from the study
Were withdrawn subjects replaced?	Not applicable (no subjects were withdrawn)
Plasma/serum sampling times:	Pre-dose at 0.5, 0.25 and 0 hours and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24 and 48 hours post-dose
Significant deviations from the sampling protocol:	There were no significant deviations from the sampling protocol

Closeness of actual and nominal times:	The following deviations from the sampling protocol were considered acceptable: Up to 5 minutes for measurements scheduled up to 4h after dosing Up to 15 minutes for measurements scheduled from 4 h to 24h after dosing Up to 1 hour for measurements scheduled 24h after dosing Up to 2 hours for measurements scheduled 48h after dosing or later
Significant deviations from the study protocol:	There were no significant deviations from the study protocol

Assessment:

The study design information provided is complete and meets all requirements except for the following:

40. Given that the absorption of levothyroxine is altered when it is administered with food, the applicant should justify why it is not necessary to perform a biostudy in non-fasting subjects.

4. Assay procedure and pre-study validation

Summary:

Fluids analysed:	Serum
Entities assayed (unchanged drug and/or metabolites):	Levothyroxine (T4) – both total and free Triiodothyronine (T3) – both total and free Thyroid stimulating hormone (TSH)
Assay method:	Abbott AXSYM microparticle enzyme immunoassay (MEIA)
Preparation of samples for analysis:	Free levothyroxine (FT4): undiluted serum Total levothyroxine (TT4): diluted serum (1:2 up to 1:4) Free triiodothyronine (FT3): undiluted serum Total triiodothyronine (TT3): diluted serum (1:2 up to 1:4) Thyroid stimulating hormone (TSH): diluted serum (1:2 up to 1:16) Sample stability was confirmed for at least one day when stored in a refrigerator between 2 and 8 °C. The freeze-thaw stability of the samples was confirmed for at least one cycle at –20 °C.
Internal standard used in assay procedure:	Not detailed
Claimed MQC:	Free levothyroxine (FT4): assay sensitivity of 5.15 pmol / L Total levothyroxine (TT4): assay sensitivity of 13.50 nmol / L Free triiodothyronine (FT3): assay sensitivity of 1.69 pmol / L Total triiodothyronine (TT3): assay sensitivity of 0.50 pmol / L Thyroid stimulating hormone (TSH): assay sensitivity of 0.06 mU / L

Validation:

Intra-assay precision was determined using four control samples of pooled serum samples. Six replicate assays were performed on each control sample for each of the five bioanalytical parameters: FT4, TT4, FT3, TT3 and TSH.

Lyphocheck control samples, with low and high analyte concentrations, were assayed in replicates of six to confirm the accuracy of each of the methods.

Results:

Free levothyroxine (FT4):

Intra-assay precision (% CV) ranged from 3.13 % to 4.78 %

Accuracy: percentage bias from the target value of 4.08 % for the higher concentration level. The calculated percentage bias for the lower concentration level was 17.02 %; however the target concentration level was below the functional sensitivity of the assay.

Linearity of dilution could not be investigated since the equilibrium of free and linked hormones is impaired by dilution.

Total levothyroxine (TT4):

Intra-assay precision (% CV) ranged from 1.76 % to 2.34 %

Accuracy: percentage bias from the target value of 7.90 % for the higher concentration level and 11.65 % for the lower concentration level.

Linearity: percentage recoveries were 96.1 % to 127.0 % for dilutions of 1:2 and 1:4.

Free triiodothyronine (FT3):

Intra-assay precision (% CV) ranged from 4.53 % to 12.04 %

Accuracy: percentage bias from the target value of 1.78 % for the higher concentration level and 6.67 % for the lower concentration level.

Linearity of dilution could not be investigated since the equilibrium of free and linked hormones is impaired by dilution.

Total triiodothyronine (TT3):

Intra-assay precision (% CV) ranged from 5.15 % to 8.37 %

Accuracy: percentage bias from the target value of 4.94 % for the higher concentration level and 4.23 % for the lower concentration level.

Linearity: percentage recoveries were 96.0 % to 125.5 % for dilutions of 1:2 and 1:4.

Thyroid stimulating hormone (TSH):

Intra-assay precision (% CV) ranged from 2.96 % to 6.55 %

Accuracy: percentage bias from the target value of 2.80 % for the higher concentration level and 16.3 % for the lower concentration level.

Linearity: percentage recoveries were 83.5 % to 99.4 % for dilutions of 1:2 up to 1:16 (dilutions up to 1:16 could be performed without loss of validity as long as the expected values were above the functional sensitivity of the assay).

Assessment:

The assay procedure and validation information provided is complete and meets all requirements except for the following:

41. **The applicant should provide full details of the biostudy assay methods that were used including details of the internal standards.**

42. **The applicant should confirm that the validation data were generated at the site used for assaying the actual study samples.**

43. **Validation reports should be provided from W & T Laboratory to demonstrate that the assay methods used to measure both total and free levothyroxine and tri-iodothyronine are validated for specificity, linearity, precision, accuracy, recovery and stability.**

5. Quality control of sample assays

Summary:

Concentrations of daily calibration standards:	Not detailed
Investigators' criteria for accepting assay results:	Not detailed
Concentration of QC (seeded control) samples:	Not detailed

Assessment:

44. **Quality control information relating to the sample assays should be provided including concentrations of daily calibration standards, the criteria for accepting assay results and the concentration of QC (seeded control) samples.**

6. Pharmacokinetic parameters and statistical analysis

Pharmacokinetic parameters and statistical analyses were calculated / performed as per FDA Guidance for Industry (Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing, December 2000):

- AUC_{0-t}, C_{max} and T_{max} were calculated for total T4 and total T3.
- Analysis of variance was performed for both log-transformed AUC_{0-t} and C_{max}.
- Geometric means and 90 % confidence intervals of the geometric mean ratio (test / reference) in AUC_{0-t} and C_{max} were presented as evidence of bioavailability.

In addition, pharmacokinetic parameters (AUC_{0-t}, C_{max} and T_{max}) were calculated and statistical analyses were performed for free T4 and free T3.

As per current FDA guidance, serum profiles and pharmacokinetic measures were presented without adjustment for baseline endogenous T4 concentrations. It should be noted that the Expert Advisory Committee on Bioavailability and Bioequivalence from the Therapeutic Products Directorate, Health Canada, decided, in a teleconference on the 16th of April 2003, that total T4, without a baseline correction, is an insensitive measure for bioequivalence analysis. Blakesley V et al, 2004 discuss methods of correction for endogenous T4 concentrations in bioequivalence studies and conclude that studies that do not adjust for endogenous T4 may result in two products being declared bioequivalent when they differ significantly in potency.

The applicant should provide pharmacokinetic parameters and statistical analyses based on the results adjusted for baseline endogenous T4 concentrations or justify why this is not necessary.

Summary of results:

A copy of the tabulated results and the investigators' statistical analyses of the data from the study report are included with the attachments. The reported data (mean ± SD) are summarised below.

Table 9: Pharmacokinetic parameters calculated by the investigators for Study RES11116

Free Unchanged drug (FT4):			
	T_{max} (h)	**C_{max}** (pmol/L)	**AUC_t** (pmol.h/L)
Treatment			
A: (Reference)	2.2 ± 1.2	26.2 ± 3.5	930 ± 101
B: (Test product)	2.6 ± 1.3	24.8 ± 3.7	907 ± 105
Statistical analysis:	***(median diff.)***	***(ratio)***	***(ratio)***
B/A: *Estimate*		*95 %*	*97 %*
90 % CI		*91-98 %*	*95-100 %*
Total Unchanged drug (TT4):			
	T_{max} (h)	**C_{max}** (nmol/L)	**AUC_t** (nmol.h/L)
Treatment			
A: (Reference)	2.5 ± 1.9	181.4 ± 39.4	6624 ± 1393
B: (Test product)	3.0 ± 1.7	170.5 ± 37.7	6487 ± 1292
Statistical analysis:	***(median diff.)***	***(ratio)***	***(ratio)***
B/A: *Estimate*		*94 %*	*98 %*
90 % CI		*91-97 %*	*96-101 %*
Free Metabolite (FT3):			
	T_{max} (h)	**C_{max}** (pmol/L)	**AUC_t** (pmol.h/L)
Treatment			
A: (Reference)	12.3 ± 17.2	4.9 ± 0.6	203 ± 21.0
B: (Test product)	9.5 ± 14.8	5.0 ± 0.6	202 ± 18.0
Statistical analysis	***(median diff.)***	***(ratio)***	***(ratio)***
B/A: *Estimate*		*101 %*	*100 %*
90 % CI		*97-106 %*	*97-103 %*
Total Metabolite (TT3):			
	T_{max} (h)	**C_{max}** (nmol/L)	**AUC_t** (nmol.h/L)
Treatment			
A: (Reference)	16.0 ± 18.3	1.6 ± 0.2	66 ± 10
B: (Test product)	16.5 ± 19.1	1.6 ± 0.2	65 ± 8
Statistical analysis	***(median diff.)***	***(ratio)***	***(ratio)***
B/A: *Estimate*		*102 %*	*99 %*
90 % CI		*96-108 %*	*94-104 %*

Table 10: A comparison of the investigators' pharmacokinetic parameters versus recalculated parameters for study RES11116

	T_{max} (h)	T_{max} (h)	C_{max} (nmol/L)	C_{max} (nmol/L)	AUC_t (nmol.h/L)	AUC_t (nmol.h/L)
Total Unchanged drug (TT4):						
Treatment						
A: (Reference)	2.5 ± 1.9	2.53 ± 1.88	181.4 ± 39.4	181.42 ± 39.35	6624 ± 1393	6623.87 ± 1392.98
B: (Test product)	3.0 ± 1.7	3.02 ± 1.72	170.5 ± 37.7	170.46 ± 37.74	6487 ± 1292	6487.45 ± 1291.95
Statistical analysis:		***(median diff.)***	***(ratio)***	***(ratio)***	***(ratio)***	***(ratio)***
B/A: Estimate		*0.5*	*94 %*	*93.9 %*	*98 %*	*98.1 %*
90% CI		*0.00 to 1.00*	*91-97 %*	*90.7-97.3 %*	*96-101 %*	*95.7-100.6 %*
Normalised estimate				***88.3 %***		***92.3 %***
Normalised 90% CI				***85.3-91.5 %***		***90.0-94.6 %***
Power				***100 %***		***100 %***
Total Metabolite (TT3):						
	T_{max} (h)	T_{max} (h)	C_{max} (nmol/L)	C_{max} (nmol/L)	AUC_t (nmol.h/L)	AUC_t (nmol.h/L)
Treatment						
A: (Reference)	16.0 ± 18.3	16 ± 18.28	1.6 ± 0.2	1.58 ± 0.24	66 ± 10	65.64 ± 10.26
B: (Test product)	16.5 ± 19.1	16.45 ± 19.08	1.6 ± 0.2	1.6 ± 0.22	65 ± 8	64.81 ± 8.37
Statistical analysis:		***(median diff.)***	***(ratio)***	***(ratio)***	***(ratio)***	***(ratio)***
B/A: Estimate		*0*	*102 %*	*101.9 %*	*99 %*	*99.2 %*
90% CI		*-5.79 to 7.75*	*96-108 %*	*96.4-107.8 %*	*94-104 %*	*94.3-104.3 %*
Normalised estimate				***95.9 %***		***93.3 %***
Normalised 90% CI				***90.6-101.4 %***		***88.7-98.1 %***
Power				***100 %***		***100 %***

Key: ☐ Investigators' calculated pharmacokinetic parameters

▒ Recalculated pharmacokinetic parameters

* Normalised estimates and 90 % confidence intervals were calculated as there is a 6.3 % difference in potency between the reference product and the test product.

Determination of pharmacokinetic parameters

Check calculations have been carried out using 6 randomly selected data for total levothyroxine (T4) and total tri-iodothyronine (liothyronine; T4) results (the resultant spreadsheets are attached to this report on the Medsafe file). The results are in satisfactory agreement with those reported by the investigators and therefore, the investigators' remaining

calculations, having been carried out in the same manner, may reasonably be assumed to be correct.

Statistical analysis

Check statistical calculations have been carried out (the resultant spreadsheets are attached to this report on the Medsafe file). The results are in satisfactory agreement with those reported by the investigators and therefore, the investigators' remaining analyses of other pharmacokinetic parameters, having been carried out in the same manner, may reasonably be assumed to be correct. (A comparison of the supplied and recalculated pharmacokinetic values is provided in the table above).

Assessment:

45. **The applicant should provide pharmacokinetic parameters and statistical analyses based on the results adjusted for baseline endogenous T4 concentrations, or justify why this is not necessary.**

7. Overall assessment of this bioequivalence study

General

The study report submitted does not include all of the required information.

The following information needs to be supplied before the evaluation can be completed:

The applicant should justify why they have submitted a biostudy comparing the new products with the European innovator products and not the NZ innovator products.

The applicant should confirm whether the reference product is controlled to dissolution specifications prior to distribution and, if so, provide details of these specifications.

The applicant should justify the discriminatory nature of the comparative dissolution test performed in pH 1 medium without surfactant between the European and NZ innovator products. The applicant should also justify why the in-house dissolution method used for release specification testing was not used to compare the European and NZ innovator products.

The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparisons of the European and NZ innovator products.

The applicant should confirm the temperature of the dissolution system used to compare the European and the NZ products.

The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products.

The applicant should provide further dissolution profile comparisons for the 100 mcg reference (European formulation) and test products (new formulation) at pH of 4.5 and 6.8.

Dissolution profile comparisons should be provided for the 50 mcg tablets (European formulation versus reformulated tablets) using the proposed in-house dissolution test method [redacted] and at pH 4.5 and 6.8.

The applicant should justify the absence of a biostudy comparing both strengths of the new products with both strengths of the reference products given that the reference products are not direct scales.

Given that the absorption of levothyroxine is altered when it is administered with food, the applicant should justify why it is not necessary to perform a biostudy in non-fasting subjects.

The applicant should provide full details of the biostudy assay methods that were used including details of the internal standards.

The applicant should confirm that the validation data were generated at the site used for assaying the actual study samples.

Validation data (including raw results) should be provided from W & T Laboratory to demonstrate that the assay methods used to measure both total and free levothyroxine and tri-iodothyronine are validated for specificity, linearity, precision, accuracy, recovery and stability.

Quality control information relating to the sample assays should be provided including concentrations of daily calibration standards, the criteria for accepting assay results and the concentration of QC (seeded control) samples.

The applicant should provide pharmacokinetic parameters and statistical analyses based on the results adjusted for baseline endogenous T4 concentrations, or justify why this is not necessary.

Medicines compared
The reference medicine was not the same formulation as the innovator/market leader product in New Zealand.

Study design
The study design was appropriate for the medicines concerned. The number of subjects afforded adequate statistical power. The appropriate entities were monitored.

Sampling times were appropriate and adequate to yield reliable pharmacokinetic data.

Assay methodology and quality control
The assay procedure has not been adequately developed and validated. In-study assay quality control data are not provided.

Pharmacokinetic parameters
Re-calculated pharmacokinetic parameters are in satisfactory agreement with those reported by the investigators indicating that the reported data have been calculated correctly.

Statistical analysis
The statistical analyses of the data carried out by the investigators are appropriate. Check calculations have yielded results that are in satisfactory agreement with those reported by the investigators.

Consistency of results with published data for reference product
The results of the biostudy are consistent with the published data for the reference medicine.

Bioequivalence
This bioequivalence study compared the 100 mcg strength of the reformulated products with the 100 µg strength of the European products. The European products differ in formulation to the New Zealand products and neither are direct scales. The applicant submitted dissolution data to demonstrate comparability between the New Zealand and European products; however dissolution comparability does not necessarily equal clinical comparability.

In summary, this application has been submitted for approval under the Intermediate Risk Stream, however, the biostudy provided does not meet Medsafe Intermediate Risk Stream criteria for demonstration of bioequivalence as the reference product used is not the New Zealand innovator product. Therefore, further information is required as detailed below:

46. Please provide either a bioequivalence study comparing the reformulated products and the New Zealand innovator products, or a bioequivalence study comparing the European innovator products and the New Zealand innovator products. Alternatively, clinical data supporting the safety and efficacy of the European formulation, or the new formulation should be submitted via the High Risk Medicine Stream.

IV. Clinical Data

Not applicable.

References

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 2000 Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 1997 Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms.

Therapeutic Products Directorate, Health Product and Food Branch, Health Canada – Expert Advisory Committee on Bioavailability and Bioequivalence. Record of Proceedings from a teleconference on April 16, 2003.

Blakesley V, Awni W, Locke C, Ludden T, Granneman GR, Braverman LE 2004 Are Bioequivalence Studies of Levothyroxine Sodium Formulations in Euthyroid Volunteers Reliable? Thyroid Vol 14, Number 3, pages 191-200.

Summary of Initial Assessment

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product have been assessed. The data have been checked for compliance with Medsafe's requirements for new intermediate risk medicines and in accordance with the pharmacopoeial standards and ICH, CPMP and FDA technical guidelines adopted by Medsafe (see *New Zealand Regulatory Guidelines for Medicines Volume 1*).

The application and the supporting data as originally submitted were found to meet most, but not all, requirements. A number of significant deficiencies were identified. These deficiencies are detailed above under the relevant headings and are listed in summary form below:

Product details:

1. **The applicant should comment on the status of the application that has been submitted to the EMEA.**

Administrative:

2. **The applicant should confirm how they intend to communicate the change in formulation to New Zealand health professionals.**
3. **The applicant must provide full-scale, label drafts (in colour) for both strengths of the reformulated products.**
4. **If the labels for the reformulated products are similar to the labels for the current New Zealand innovator products then the packaging for the reformulated products must be labelled with the words, "New Formulation", for an appropriate period of time to ensure that the different formulations are easily distinguishable.**
5. **The datasheet must include a description of the colour and dimensions of the tablets and any markings on them as per the New Zealand Medicines Regulations and Guidelines Volume 1.**
6. **The datasheet must specify contraindications as per the New Zealand Medicines Regulations and Guidelines Volume 1, or the applicant must justify why this is not necessary.**
7. **The applicant should clarify what the numbers next to the headings "Adults" and "Children" refer to in the "Clinical particulars" section of the data sheet and explain what these numbers mean. The applicant should also review whether it is necessary to include these in the data sheet.**
8. **The applicant must submit a signed declaration relating to the proposed data sheet.**
9. **The applicant must provide evidence of GMP for GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY that has not expired.**

Drug substance:

10. The applicant should provide assurance that no significant changes have been made to the manufacturing process since the Certificate of Suitability was issued and that any conditions attached to the Certificate of Suitability will be complied with.
11. The applicant should detail the controls placed upon received batches of active ingredient by the finished product manufacturer. Certificates of Analysis, issued by the finished product manufacturer, should be provided for three batches of active ingredient.

Drug product:

12. The applicant should confirm that the reformulated tablets can be halved and submit evidence of uniformity and stability of divided dose units.
13. The applicant should explain why the USP dissolution method was not chosen for release specification testing of the new products.
14. The applicant should justify the discriminatory nature of the dissolution method chosen for release specification testing, given that it uses a [redacted] medium and a [redacted] paddle speed than the current USP method.
15. The applicant should state how many tablets were tested from each batch of the reformulated tablets for the dissolution rate comparison using the in-house method and the USP method.
16. The applicant should explain what the [redacted] method is that is used for testing loss on drying of the final blend.
17. The applicant should confirm whether release limits for dissolution apply to individual units or to the mean of a particular number of units.
18. The applicant should confirm the quantities of tetrac, HDPhDB, unknown impurities and total impurities that are contained in the NZ innovator products. Data from at least three batches of the NZ innovator product should be provided. If the New Zealand innovator products do contain tetrac and HDPhDB, the applicant should explain why Medsafe was not notified about these impurities previously.
19. Release specifications should include testing for tablet dimensions.
20. The applicant should confirm that all release specification tests are conducted on every batch. If there is reduced testing for some parameters, the reasons for this should be stated.
21. The applicant should confirm whether shelf life specifications for dissolution are based on the USP method or the method used for release testing of the reformulated products.
22. The applicant should confirm which formulation (batch number: G03102) was used to justify HDPhDB acid shelf life specifications for the reformulated products and state what the shelf life of this product is and the name of the regulatory authority(s) that it is approved by.
23. Given that the limits for tetrac, HDPhDB and unknown impurities are 1 %, 2.5 % and 1 % respectively, the applicant must justify why the total impurity limit in the shelf life specifications is so high.
24. The applicant must submit signed Certificates of Analysis for three production scale batches of each strength of the finished product. It is expected that the

Certificates of Analysis provided will provide evidence that the reformulated tablets comply with release specifications for tablet imprinting and the UV identification test.

25. The applicant should provide signed Certificates of Analysis for the polypropylene bottles and LDPE caps.

Stability:

26. The applicant should state the proposed shelf life and storage conditions for the active ingredient and provide stability data to support these.
27. The applicant should outline the on-going stability protocol for commercial batches of each strength of the reformulated products.
28. Given the hygroscopic nature of levothyroxine sodium and the poorly defined storage conditions in the informal stability study, the applicant should make a post-approval commitment to perform a formal stability study for three batches of the triturate stored in the proposed packaging for 6 months at 25°C / 60 % RH.
29. The applicant should provide a description of sampling methods for the primary stability studies including confirmation of how many tablets were tested from each batch.
30. It was noted that some dissolution results for one batch of the 50 mcg product (batch number 0274) fell below specification after 12 and 18 months of storage at 25°C / 60 % RH. The applicant should discuss these results and if possible provide an explanation.

Biopharmaceutical data:

31. The applicant should justify why they have submitted a biostudy comparing the new products with the European innovator products and not the NZ innovator products.
32. The applicant should confirm whether the reference product is controlled to dissolution specifications prior to distribution and, if so, provide details of these specifications.
33. The applicant should justify the discriminatory nature of the comparative dissolution test performed in pH 1 medium without surfactant between the European and NZ innovator products. The applicant should also justify why the in-house dissolution method used for release specification testing was not used to compare the European and NZ innovator products.
34. The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparisons of the European and NZ innovator products.
35. The applicant should confirm the temperature of the dissolution system used to compare the European and the NZ products.
36. The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products.
37. The applicant should provide further dissolution profile comparisons for the 100 mcg reference (European formulation) and test products (new formulation) at pH 4.5 and 6.8.

38. Dissolution profile comparisons should be provided for the 50 mcg tablets (European formulation versus reformulated tablets) using the proposed in-house dissolution test method [redacted] and pH 4.5 and 6.8.
39. The applicant should justify the absence of a biostudy comparing both strengths of the new products with both strengths of the reference products given that the reference products are not direct scales.
40. Given that the absorption of levothyroxine is altered when it is administered with food, the applicant should justify why it is not necessary to perform a biostudy in non-fasting subjects.
41. The applicant should provide full details of the biostudy assay methods that were used, including details of the internal standards.
42. The applicant should confirm that the validation data were generated at the site used for assaying the actual study samples.
43. Validation reports should be provided from W & T Laboratory to demonstrate that the assay methods used to measure both total and free levothyroxine and tri-iodothyronine are validated for specificity, linearity, precision, accuracy, recovery and stability.
44. Quality control information relating to the sample assays should be provided including concentrations of daily calibration standards, the criteria for accepting assay results and the concentration of QC (seeded control) samples.
45. The applicant should provide pharmacokinetic parameters and statistical analyses based on the results adjusted for baseline endogenous T4 concentrations, or justify why this is not necessary.
46. This application has been submitted for approval under the Intermediate Risk Stream. However, the biostudy provided does not meet Medsafe Intermediate Risk Stream criteria for demonstration of bioequivalence, as the reference product used is not the New Zealand innovator product. Therefore, further information is required as detailed below:

    Please provide either a bioequivalence study comparing the reformulated products and the New Zealand innovator products, or a bioequivalence study comparing the European innovator products and the New Zealand innovator products. Alternatively, clinical data supporting the safety and efficacy of the European formulation, or the new formulation should be submitted via the High Risk Medicine Stream.

The sponsor was requested by letter dated 29/03/2005 to address these issues.

Resolution of Issues

Evaluator: Jacqui Watt

Sponsor's responses to issues raised in the initial assessment

The sponsor responded to the request for further information on 19/10/2005.

The responses received and the evaluator's assessment of the responses is as follows:

Product details:

1. **The applicant should comment on the status of the application that has been submitted to the EMEA.**

The proposed new formulation was approved in Germany in July 2005. Approval is still pending in Denmark and The Netherlands.

Administrative:

2. **The applicant should confirm how they intend to communicate the change in formulation to New Zealand health professionals.**

The applicant states that New Zealand health professionals will be notified of the change in Eltroxin formulation via a notification letter.

3. **The applicant must provide full-scale, label drafts (in colour) for both strengths of the reformulated products.**

No change to the labelling is proposed for either strength of the finished product. The proposed artwork is that which is currently supplied, as submitted to Medsafe with the Self-Assessable CMN dated 24/05/2004. This is acceptable.

4. **If the labels for the reformulated products are similar to the labels for the current New Zealand innovator products then the packaging for the reformulated products must be labelled with the words, "New Formulation", for an appropriate period of time to ensure that the different formulations are easily distinguishable.**

GlaxoSmithKline believe it is not necessary to add the words "New Formulation" to the packaging artwork for the reformulated product for the following reasons:

- This is not a requirement of the New Zealand Medicines Regulations and Guidelines.
- New Zealand health professionals will be notified of the change in formulation of Eltroxin tablets via a specific notification letter.

This is acceptable.

The reformulated tablets and the currently approved tablets are distinguishable by appearance as detailed below:

Currently approved tablets:

50 mcg: small white, biconvex tablets, engraved "50" over a bisecting breakline.

100 mcg: small yellow, biconvex tablets, engraved "100" over a bisecting breakline.

Reformulated tablets:

50 mcg: white to off-white, round, biconvex tablets, imprinted with GS 11E on one face and 50 on the other.

100 mcg: white to off-white, round, biconvex tablets, imprinted with GS 21C on one face and 100 on the other.

5. **The datasheet must include a description of the colour and dimensions of the tablets and any markings on them as per the New Zealand Medicines Regulations and Guidelines Volume 1.**

A description of the colour and dimensions of the tablets, as well as markings has been added to the Presentation section of the data sheet. This is acceptable.

6. **The datasheet must specify contraindications as per the New Zealand Medicines Regulations and Guidelines Volume 1, or the applicant must justify why this is not necessary.**

The draft data sheet has been revised to comply with the requirements for data sheet content and structure, as per the New Zealand Medicines Regulations and Guidelines Volume 1. Contraindications are now specified. This is acceptable.

7. **The applicant should clarify what the numbers next to the headings "Adults" and "Children" refer to in the "Clinical particulars" section of the data sheet and explain what these numbers mean. The applicant should also review whether it is necessary to include these in the data sheet.**

The numbers refer to clinical study references in the Global Core Text for the product. They were mistakenly transferred into the New Zealand data sheet, and have been removed in the revised data sheet. This is acceptable.

8. **The applicant must submit a signed declaration relating to the proposed data sheet.**

A signed declaration relating to the proposed data sheet has not been provided. It is acceptable for this to be submitted to the data sheet coordinator with the proposed data sheet after approval of this product is published in the New Zealand Gazette.

9. **The applicant must provide evidence of GMP for GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY that has not expired.**

A GMP Preclearance letter from the Therapeutic Goods Administration (TGA) Australia, dated 11/08/2004 has been provided for GlaxoWellcome GmbH & Co, Industriestasse 32-36, 23843 Bad Oldesloe, GERMANY. The letter remains current until 31/05/2007. This is acceptable.

Drug substance:

10. The applicant should provide assurance that no significant changes have been made to the manufacturing process since the Certificate of Suitability was issued and that any conditions attached to the Certificate of Suitability will be complied with.

GlaxoSmithKline have confirmed that no significant changes have been made to the manufacturing process of levothyroxine sodium since the issue of the Certificate of Suitability. Assurance has also been provided that all conditions attached to the Certificate of Suitability will be complied with. This is acceptable.

11. The applicant should detail the controls placed upon received batches of active ingredient by the finished product manufacturer. Certificates of Analysis, issued by the finished product manufacturer, should be provided for three batches of active ingredient.

The finished product manufacturer routinely performs identity and specific rotation testing on batches of levothyroxine sodium. Batches of active ingredient are approved for manufacture of the finished products based on the results detailed in the Certificate of Analysis from the supplier.

Generally Medsafe would also expect the finished product manufacturer to routinely test each batch of active ingredient for assay and related substances. ***The finished product manufacturer should routinely test each batch of active ingredient for assay and related substances as well as identity and specific rotation.***

Evidence should be provided to support the acceptability of reduced testing of the active ingredient by the finished product manufacturer. Such evidence may include but not be limited to information regarding any auditing of the active ingredient manufacturer that is performed by the finished product manufacturer, GMP certification for the active ingredient manufacturing site and Certificates of Analysis issued by the finished product manufacturer for batches of active ingredient.

Certificates of Analysis issued by the finished product manufacturer for three batches of the finished product have been provided. However, these detail results transposed from the supplier's Certificate of Analysis and are not representative of testing performed by the finished product manufacturer. ***Certificates of Analysis issued by the finished product manufacturer for three batches of active ingredient representative of testing performed at the finished product manufacturing site should be provided.***

Drug product:

12. The applicant should confirm that the reformulated tablets can be halved and submit evidence of uniformity and stability of divided dose units.

The reformulated tablets are not scored and not intended to be halved. The following statement has been included in the revised data sheet: "Due to a lack of data to support the use of crushing tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow tablets." ***It is recommended that this statement is amended to read, "Due to a lack of data to support the use of crushing or halving tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow whole tablets."***

Given that the registered dose for some patients is 25 mcg, the dosage instructions in the data sheet have been revised as summarised in Table 1.

Table 1: Summary of revised dosage instructions in the proposed data sheet.

Statement in current data sheet	Revised statement
Where there is cardiac disease, 25 mcg daily, or 50 mcg on alternate days, is more suitable. In this condition the daily dosage may be increased by 25 mcg at intervals of perhaps four weeks.	Where there is cardiac disease, 25 mcg given as 50 mcg on alternate days, is more suitable. In this condition the daily dosage may be slowly increased by 25 mcg increments (given as 50 mcg on alternate days) at intervals of perhaps four weeks.
For infants with congenital hypothyroidism a suitable starting dose is 25 mcg thyroxine sodium daily, with increments of 25 mcg every two to four weeks until mild toxic symptoms appear.	For infants with congenital hypothyroidism a starting dose is 25 mcg thyroxine sodium given as 50 mcg every other day is advisable. This may be slowly increased by increments of 25 mcg (given as 50 mcg on alternate days) every two to four weeks until optimal response is achieved. This dosing regimen is illustrated in Table 2.
The same dosing regimen applies to juvenile myxoedema, except that the starting dose in children older than one year may be 2.5 to 5 mcg / kg / day.	The same dosing regimen applies to juvenile myxoedema, except that the starting dose in children older than one year may be 2.5 to 5 mcg / kg / day. The calculated daily dose equivalent should be rounded to the nearest 25 mcg to determine the actual prescribed dose.

Table 2 (copied from the proposed data sheet)

Daily dosing	Dosing regimen
25 microgram	One 50 microgram tablet on alternate days
50 microgram	One 50 microgram tablet daily
75 microgram	One 50 microgram tablet daily and one 50 mcg tablet on alternate days
100 microgram	One 100 microgram tablet daily
125 microgram	One 100 microgram tablet daily and one 50 microgram tablet on alternate days

The following justification for the revised dosage instructions has been provided:

- The pharmacokinetic profile of thyroxine includes a long plasma half-life (approximately 7 days), a low turnover rate (10 % per day) and a period of 4 to 6 weeks before steady state levels are achieved (Waldestein 1997, Wiersinga 2001).
- In studies where alternate dosing regimens have been evaluated, serum levels of thyroxine, triiodothyronine and thyroid stimulating hormone were generally maintained in patients treated once- or twice weekly compared with daily dosing (Grebe 1997, Taylor 1994, Roher 1979, Bauhofer 1976).

The above changes have been discussed with [redacted] and are considered to be acceptable.

13. The applicant should explain why the USP dissolution method was not chosen for release specification testing of the new products.

As discussed in the initial evaluation report, several different dissolution media and paddle speeds, including those specified in the USP (Test 1), were investigated during development of the testing method for the reformulated tablets. Dissolution testing was performed on the batches of Eltroxin tablets that were used in the bioequivalence study. The results generated using USP conditions indicated that the two bioequivalence batches were not sufficiently equivalent, as the f2 value was 40 (below the similarity acceptance criteria of 50). However, the results of the bioequivalence study indicate that the two formulations are bioequivalent.

The applicant states that the results demonstrate that the USP dissolution conditions may be too discriminatory for Eltroxin tablets. For example, if USP conditions were used as part of release testing, it may result in batches failing to meet the required specification, yet still providing acceptable in vivo characteristics.

This explanation is acceptable.

14. The applicant should justify the discriminatory nature of the dissolution method chosen for release specification testing, given that it uses a [redacted] medium and a [redacted] paddle speed than the current USP method.

To demonstrate the discriminatory nature of the proposed dissolution test method, results from testing batches of Eltroxin tablets manufactured using low and high compression pressures were compared. The results are presented in Tables 3 and 4. The results show rapid release of the active ingredient from the low compression tablets, which meet the dissolution specification (Q = 70 after 45 minutes) after 10 minutes. Much slower release of levothyroxine sodium was observed for the high compression tablets, which failed to meet the required dissolution specification. These results indicate that the dissolution test method proposed for use at release and expiry is capable of discriminating between tablets of varying hardness.

A comparison of the results for the batches used in the bioequivalence study was also provided and is presented in Table 5. These results show that dissolution rates for the reference and test products are similar in the dissolution system proposed for release and expiry testing of the finished products.

Table 3: Comparison of dissolution rates for reformulated 50 mcg tablets manufactured using low and high compression pressures.

Crushing Strength (kP)	Levothyroxine sodium released (%)					
	Time (min)	10	20	30	45	60
2.8	Mean (n=6)	93	95	95	95	96
	Range	90 - 96	91 – 99	92 – 101	92 – 100	93 – 102
	RSD	2.4	2.7	3.0	2.9	3.5
9.3	Mean (n=6)	25	41	51	63	72
	Range	18 – 32	31 – 53	39 – 66	49 – 80	59 – 87
	RSD	24.0	20.4	23.6	21.5	17.4

Table 4: Comparison of dissolution rates for reformulated 100 mcg tablets manufactured using low and high compression pressures.

Crushing Strength (kP)	Levothyroxine sodium released (%)					
	Time (min)	10	20	30	45	60
3.7	Mean (n=6)	93	96	97	98	99
	Range	89 - 96	90 – 100	90 – 103	89 – 107	89 – 113
	RSD	2.9	4.3	4.7	6.1	8.3
11.1	Mean (n=6)	23	39	51	64	72
	Range	17 – 33	28 – 51	38 – 68	51 – 80	61 – 87
	RSD	26.3	21.1	21.1	16.5	13.1

Table 5: Comparison of dissolution rates for the batches used in the bioequivalence study.

Formulation	Levothyroxine sodium released (%)					
	Time (min)	10	15	30	45	60
European (100 mcg) Batch 2707 Crushing strength – 4.8 kP	Mean (n=12)	41.3	94.2	96.4	95.5	97.2
	Range	35.2 – 50.0	90.2 – 98.0	90.2 – 99.2	84.5 – 98.7	94.9 – 99.7
	RSD	5.5	3.0	2.5	3.8	1.8
Reformulated (100 mcg) Batch 0273 Crushing strength – 6.4 kP	Mean (n=12)	52.4	79.2	92.2	95.8	96.6
	Range	41.0 – 57.5	69.5 – 84.7	88.1 – 95.3	93.0 – 98.7	93.3 – 99.4
	RSD	5.9	5.1	2.6	1.8	1.9

14. The applicant should state how many tablets were tested from each batch of the reformulated tablets for the dissolution rate comparison using the in-house method and the USP method.

As per USP requirements, six tablets were tested from the first stage of dissolution (S_1). If the first stage of dissolution failed, the second stage of dissolution was performed (S_2) and another six tablets were tested. All batches of reformulated tablets used for the dissolution rate comparison of the in-house and USP method met the specification at the first stage (S1), except for batch 0274. Batch 0274 failed the first stage of dissolution testing therefore twelve tablets were tested for this batch. This is acceptable.

15. The applicant should explain what the [redacted] method is that is used for testing loss on drying of the final blend.

The applicant has confirmed that the [redacted] method used for testing loss on drying of the final blend utilises a commercially available balance. A sample of tablet blend is placed on the weighing scale and the test is performed at 105°C for [redacted] (drying period). The loss on drying is automatically calculated and displayed by the apparatus. This is acceptable.

16. The applicant should confirm whether release limits for dissolution apply to individual units or to the mean of a particular number of units.

The applicant has confirmed that the release limits for dissolution apply to individual units, as per USP requirements. The acceptance criteria are presented in Table 6 and are acceptable.

Table 6: Dissolution Acceptance Criteria

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5 % (Q = 70 %)
S_2	6	Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q – 15 % (Q = 70 %)

17. The applicant should confirm the quantities of tetrac, HDPhDB, unknown impurities and total impurities that are contained in the NZ innovator products. Data from at least three batches of the NZ innovator product should be provided. If the New Zealand innovator products do contain tetrac and HDPhDB, the applicant should explain why Medsafe was not notified about these impurities previously.

The following information has been provided regarding the detection of tetrac and HDPhDB:

During the reformulation of Eltroxin tablets, the analytical methods were reviewed and further analytical development took place as required. The enhanced HPLC methodology used to determine drug related impurity content in the reformulated tablets enables better resolution of peaks, leading to the identification of peaks for tetrac and HDPhDB acid, which had not been previously seen using the old methodology.

Following identification of tetrac and HDPhDB acid, batches of current Eltroxin tablets were tested to determine the levels of these impurities. The analytical methods have been developed and validated for testing the proposed Eltroxin formulation; however the company consider the methods to be suitable for comparative analysis of the old and proposed Eltroxin products.

Current Eltroxin tablets contain both tetrac and HDPhDB acid. The results of impurity testing for the current tablets using the revised HPLC methodology are presented in Tables 7 and 8.

Table 7: Drug related impurities in the current New Zealand Eltroxin 50 mcg formulation after 3 years storage (room temperature).

Sample ID	Impurity content			
	Tetrac (%)	HDPhDB acid (%)	Total unknown impurities (%)	Total impurities (%)
Batch 2H511 Manufactured: August 2002	0.86	0.56	3.07	4.49
Batch 2G427 Manufactured: July 2002	0.81	0.58	2.83	4.22
Batch 2F529 Manufactured: July 2002	0.82	0.54	3.92	5.28

Table 8: Drug related impurities in the current New Zealand Eltroxin 100 mcg formulation after 3 years storage (room temperature).

Sample ID	Impurity content			
	Tetrac (%)	HDPhDB acid (%)	Total unknown impurities (%)	Total impurities (%)
Batch 2G487 Manufactured: July 2002	0.89	0.55	3.15	4.59
Batch 2G406 Manufactured: July 2002	0.80	0.56	2.65	4.01
Batch 2E486 Manufactured: July 2002	0.82	0.57	2.27	3.66

The results support the acceptability of the proposed shelf-life specifications for the finished product including tetrac NMT 1 % and total impurities NMT 5 %. The proposed shelf-life specification for HDPhDB is discussed in Question 22.

18. Release specifications should include testing for tablet dimensions.

Given that tablet dimensions are controlled to some degree during compression by the dies and punches of the tabletting machinery and in-process controls include uniformity of weight, it is not necessary for the release specifications to include limits for tablet dimensions.

The tablet dimensions have been provided for information only:

50 mcg

Diameter: 6.0 – 6.2 mm

Height: 2.7 – 3.2 mm

100mcg

Diameter: 8.0 – 8.2 mm

Height: 3.2 – 3.7 mm

19. The applicant should confirm that all release specification tests are conducted on every batch. If there is reduced testing for some parameters, the reasons for this should be stated.

GlaxoSmithKline have confirmed that all release specification tests are performed on all batches of the finished product at release.

20. The applicant should confirm whether shelf life specifications for dissolution are based on the USP method or the method used for release testing of the reformulated products.

GlaxoSmithKline have confirmed that the proposed dissolution method for stability testing is the same as that applied at the time of release. This is acceptable.

21. The applicant should confirm which formulation (batch number: G03102) was used to justify HDPhDB acid shelf life specifications for the reformulated products and state what the shelf life of this product is and the name of the regulatory authority(s) that it is approved by.

Eltroxin 100 mcg batch number G03102 was manufactured using the current European formulation as manufactured by GlaxoSmithKline at Poznan, Poland and Bad Oldesloe, Germany. This formulation is registered for marketing in Holland, Denmark, Poland, the Czech Republic and Lithuania. Details of the European formulation are attached to the initial evaluation report.

HDPhDB acid content of the current European 100 mcg formulation (batch G03102) is summarised in Table 10.

Table 10: HDPhDB acid content of the current European Eltroxin 100 mcg formulation

Batch	Storage time (months)	Storage conditions	HDPhDB acid content (% w/w relative to levothyroxine sodium content)
G03102	18	25°C/60% RH	1.6
		30°C/60% RH	2.0
	24	25°C/60% RH	2.4
		30°C/60% RH	3.0
	34	25°C/60% RH	3.0

The shelf-life for the current European tablets is 36 months. The applicant states that safe and efficacious use of the European formulation has been demonstrated over many years of clinical usage, representing millions of patient years of exposure since 1962 (e.g. approximately 1.9 million patient years of exposure to Eltroxin worldwide during 1997 and 1998, based on available sales volume data and assuming a standard daily dose of levothyroxine sodium of 100 mcg).

The company also state that the structure of HDPhDB acid has been analysed using the DEREK (Deductive Estimation of Risk for Existing Knowledge) SAR application, which is an industry accepted standard for the *in silico* prediction of genotoxic liability. The analysis revealed no structural features that would give cause for concern with regards to potential for genotoxicity.

A comparison of HDPhDB acid content for various batches of the current New Zealand innovator, the European innovator and the reformulated tablets is provided in Table 11.

Further evidence is required to support the proposed shelf-life specification for HDPhDB acid for the following reasons:

- The reformulated tablets contain significantly more HDPhDB acid than the current New Zealand innovator products.
- Data from only one batch of the European product has been provided to support the acceptability of the proposed shelf-life specification for HDPhDB acid.

Further evidence should be provided to support the proposed shelf-life specification for HDPhDB (NMT 2.5 %). Such evidence may include but not be limited to safety / toxicological data relating to batch G03102 of the European innovator product and further impurity data for two batches of the 100 mcg strength of the European innovator product and three batches of the 50 mcg strength of the European innovator product.

Table 11: HDPhDB content of Eltroxin tablets

Product	Strength	Batch Number	Storage details	HDPhDB content (%)
Current New Zealand innovator product	50 mcg	2H511 (Manufactured 08/2002)	36 months at room temperature	0.56
		2G427 (Manufactured 07/2002)	36 months at room temperature	0.58
		2F528 (Manufactured 07/2002)	36 months at room temperature	0.54
	100 mcg	2G487 (Manufactured 07/2002)	36 months at room temperature	0.55
		2G406 (Manufactured 07/2002)	36 months at room temperature	0.56
		2E486 (Manufactured 07/2002)	36 months at room temperature	0.57
European innovator product	100 mcg	G03102	34 months at 25°C / 60 % RH	3.0
Reformulated products	50 mcg	0276 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
		0275 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
		0274 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
	100 mcg	0273 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.2
		0272 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.2
		0271 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.3

22. Given that the limits for tetrac, HDPhDB and unknown impurities are 1 %, 2.5 % and 1 % respectively, the applicant must justify why the total impurity limit in the shelf life specifications is so high.

After reviewing the stability profile for the reformulated tablets after storage for 24 months, the company has revised the shelf-life specification for total impurities from NMT 6 % to NMT 5 %. Based on the impurity results provided for the current New Zealand products the proposed shelf-life specification for total impurities of NMT 5 % is acceptable. It is noted that a specification for total impurities is not included in the currently approved release and expiry specifications for the New Zealand innovator product.

23. The applicant must submit signed Certificates of Analysis for three production scale batches of each strength of the finished product. It is expected that the Certificates of Analysis provided will provide evidence that the reformulated tablets comply with release specifications for tablet imprinting and the UV identification test.

Certificates of analysis have not been provided for either strength of the finished product. The applicant has provided assurance that Certificates of Analysis (including release data for tablet imprinting and the UV identification test) will be provided when they become available at the time of next manufacture.

The applicant should explain why Certificates of Analysis were not issued for batches 0274, 0275, 0276, 0271, 0272 and 0273 of the reformulated products.

24. The applicant should provide signed Certificates of Analysis for the polypropylene bottles and LDPE caps.

Certificates of Analysis have been provided for the polypropylene bottles and LDPE caps and are acceptable.

<u>Stability:</u>

25. The applicant should state the proposed shelf life and storage conditions for the active ingredient and provide stability data to support these.

The applicant has confirmed that a retest period of 24 months is applied to levothyroxine sodium when stored at temperatures up to 25°C, and protected from light and moisture. Based on the stability data provided this is acceptable.

26. The applicant should outline the on-going stability protocol for commercial batches of each strength of the reformulated products.

A copy of the stability testing protocol has been provided. However, details of the number of batches that will be placed on post-approval stability studies have not been provided. ***The applicant should commit to placing at least one production scale batch of each strength of the finished product annually on stability trials.***

27. Given the hygroscopic nature of levothyroxine sodium and the poorly defined storage conditions in the informal stability study, the applicant should make a post-approval commitment to perform a formal stability study for three batches of the triturate stored in the proposed packaging for 6 months at 25°C / 60 % RH.

GlaxoSmithKline have made a commitment to perform a formal stability study for three batches of the levothyroxine sodium triturate stored in the proposed packaging for 6 months at 25°C / 60 % RH.

28. The applicant should provide a description of sampling methods for the primary stability studies including confirmation of how many tablets were tested from each batch.

Details of the sampling methods used for the primary stability studies have been provided and are acceptable.

29. It was noted that some dissolution results for one batch of the 50 µg product (batch number 0274) fell below specification after 12 and 18 months of storage at 25°C / 60 % RH. The applicant should discuss these results and if possible provide an explanation.

The applicant has confirmed that some low dissolution results for individual tablets from batch 0274 were recorded at Stage 1 of testing after storage for 12 and 18 months at 25°C / 60 % RH. Further testing demonstrated that the tablets complied with USP acceptance criteria at Stage 2. The applicant considers these results to be anomalous because such low individual results were not seen during testing at the 24-month time point for batch 0274, or during any timepoint at the proposed storage conditions for the other stability batches. The dissolution results are acceptable.

The stability data provided support the proposed shelf-life of 24 months at or below 25°C.

Biopharmaceutical data:

30. The applicant should justify why they have submitted a biostudy comparing the new products with the European innovator products and not the NZ innovator products.

The current European formulation of Eltroxin was registered in New Zealand from 08/04/1981 to 08/05/1992. In 1992 the formulation of the tablets was changed to the currently approved formulation. The bioavailability of the current New Zealand product was supported by dissolution data rather than a bioequivalence study. Therefore, the European product is considered the preferred reference product rather than the current New Zealand innovator product.

31. The applicant should confirm whether the reference product is controlled to dissolution specifications prior to distribution and, if so, provide details of these specifications.

The applicant states that the reference product (current European formulation) is periodically monitored and batches comply with a limit of [redacted]. Details of the dissolution test method used have not been provided. Given that this information is of limited benefit, further information will not be requested.

32. The applicant should justify the discriminatory nature of the comparative dissolution test performed in pH 1 medium without surfactant between the European and NZ innovator products. The applicant should also justify why the in-house dissolution method used for release specification testing was not used to compare the European and NZ innovator products.

The dissolution conditions used for comparative dissolution testing between the European and current New Zealand products were based on the monograph for levothyroxine tablets in earlier editions of the USP (prior to USP 24). The applicant states that the solubility of levothyroxine sodium was also taken into consideration; it is higher at pH 1 than in less acidic medium.

Dissolution method development was progressed as part of the reformulation development work; therefore the method proposed for release of the reformulated tablets was not available for the comparative testing of the innovator products.

The applicant also states that addition of 0.2 % SDS has no significant influence on levothyroxine dissolution rates and that the aim of the addition of 0.2 % SDS to the medium (as applied in USP 24 First Supplement) is to prevent levothyroxine sodium adsorption on filters. A dissolution rate comparison for the reference product used in the biostudy (batch 2707) shows that the rate of dissolution was not significantly affected by the addition of 0.2 % sodium dodecyl sulphate.

The above justification is acceptable.

33. The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparisons of the European and NZ innovator products.

Evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparisons of the European and NZ innovator products has not been provided. However, this is no longer necessary as the European formulation was approved in NZ from 08/04/1981 to 08/05/1992.

34. The applicant should confirm the temperature of the dissolution system used to compare the European and the NZ products.

The temperature of the dissolution system used to compare the European and the NZ products was 37°C. This is acceptable.

35. The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products.

The requested information has not been provided (refer to question 34).

The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products. As detailed in the initial evaluation report, in order for similarity calculations using similarity factor f2 to be valid the following must apply:

- ***At least two data points must be less than or equal to 85 % and no more than one data point should be above 85 % (if more than one data point above 85 % is used, false similarities may be concluded).***
- ***If mean data is used, the % coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %.***

36. The applicant should provide further dissolution profile comparisons for the 100 mcg reference (European formulation) and test products (new formulation) at pH 4.5 and 6.8.

Dissolution profile comparisons have been provided for the 100 mcg reference (European formulation) and test products (new formulation) at pH 4.5 and pH 6.8. The results are presented in Figures 1 and 2.
The 100 mcg reformulated tablets were slower to dissolve than the 100 mcg European product. The applicant states that this is because of the different characteristics of the excipients in each formulation. The current European formulation is lactose-based and the major excipients are largely soluble, whereas the reformulated tablets contain largely insoluble excipients (in aqueous media). Given that the typical Tmax published in the literature for thyroxine is 2 to 4 hours, it appears that dissolution is not the rate-limiting step in the absorption of levothyroxine from a tablet formulation. Therefore it is unlikely that the differences in dissolution observed at pH 4.5 and 6.8 between the 100 mcg reformulated tablets and the 100 mcg European tablets will result in significant differences in bioavailability.

Figure 1:

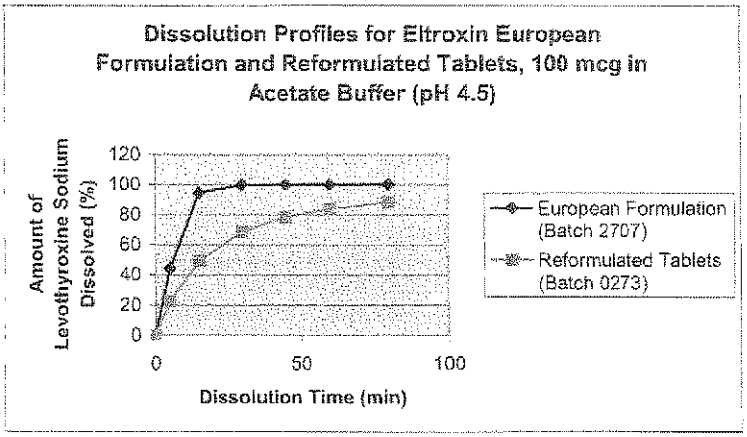
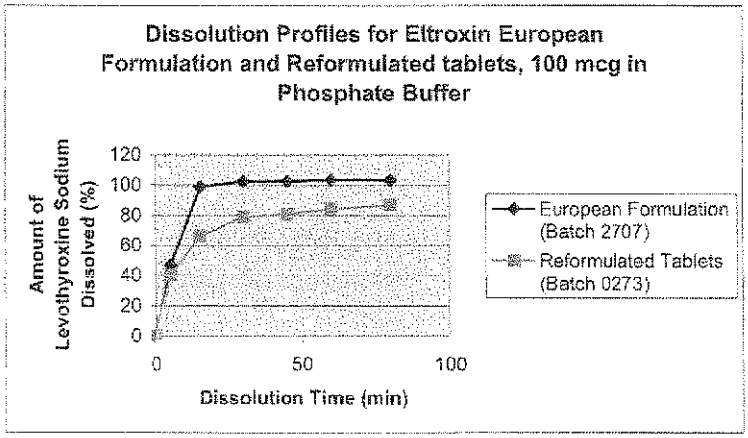


Figure 2:



37. Dissolution profile comparisons should be provided for the 50 µg tablets (European formulation versus reformulated tablets) using the proposed in-house dissolution test method [redacted] and pH 4.5 and 6.8.

Dissolution profile comparisons have been provided for the 50 mcg European formulation and the 50 mcg reformulated tablets using the proposed in-house dissolution test method, acetate buffer (pH 4.5) and phosphate buffer (pH 6.8). A paddle speed of [redacted] was used for all testing. The results are presented in Figures 3, 4 and 5.

The results show that dissolution of the 50 mcg reformulated tablets and 50 mcg European tablets are similar in the dissolution system proposed for testing of the reformulated tablets at release and expiry. In more basic media (pH 4.5 and 6.8) dissolution of the 50 mcg reformulated tablets was slower than for the 50 mcg European tablets. For the reasons discussed in Question 37, it is unlikely that the differences in dissolution observed at pH 4.5

and 6.8 between the 50 mcg reformulated tablets and the 100 mcg European tablets will result in significant differences in bioavailability.

Figure 3:

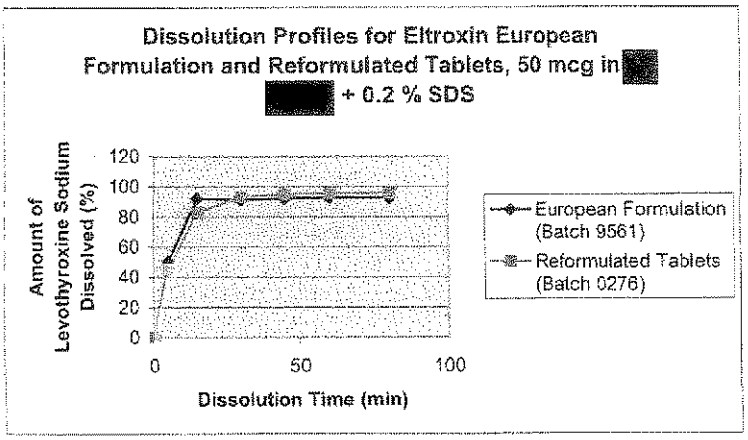


Figure 4:

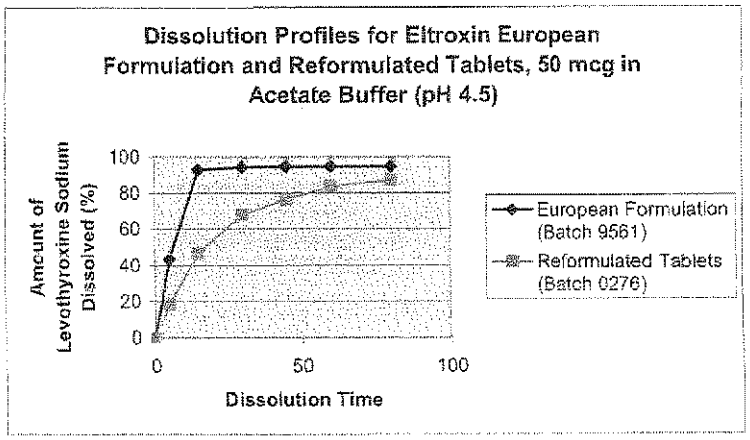
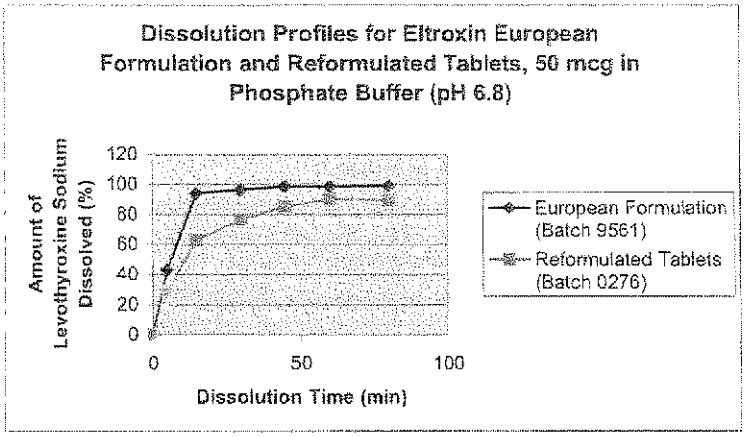


Figure 5:



38. The applicant should justify the absence of a biostudy comparing both strengths of the new products with both strengths of the reference products given that the reference products are not direct scales.

The justification provided by the applicant is that the 50 mcg and 100 mcg reformulated tablets are direct scales and have similar dissolution profiles in media of varying pH (ph 1, 2, 4.5 and 6.8).

39. Given that the absorption of levothyroxine is altered when it is administered with food, the applicant should justify why it is not necessary to perform a biostudy in non-fasting subjects.

Given that the bioequivalence study to support the reformulation was performed in accordance with FDA guidance and that the dosing advice provided by GSK for Eltroxin tablets recommends that the tablets are taken on an empty stomach. It is not considered necessary to perform a biostudy in non-fasting subjects.

40. The applicant should provide full details of the biostudy assay methods that were used, including details of the internal standards.

The plasma samples were analysed for total and free thyroxine (TT4 and FT4), total and free tri-iodothyronine (TT3 and FT3) and thyroxine stimulating hormone (TSH) using a commercial assay kit (AXSYM Total T4, Free T4, Total F3, Free T3 and hTSH Ultrasensitive II).

Details of the assay methods have been provided. Internal standards were provided with the assay kit. This is acceptable.

41. The applicant should confirm that the validation data were generated at the site used for assaying the actual study samples.

GlaxoSmithKline have confirmed that the validation data was generated at the site that assayed the study samples (W & T Laboratory, Berlin, Germany).

42. Validation reports should be provided from W & T Laboratory to demonstrate that the assay methods used to measure both total and free levothyroxine and tri-iodothyronine are validated for specificity, linearity, precision, accuracy, recovery and stability.

Validation data for the assay methods has been provided from W & T Laboratory. The methods have been validated for precision, accuracy, linearity and stability of solutions. Specificity and sensitivity testing was performed by the manufacturer of the testing kits and not at W & T Laboratory. The validation data provided is acceptable.

43. Quality control information relating to the sample assays should be provided including concentrations of daily calibration standards, the criteria for accepting assay results and the concentration of QC (seeded control) samples.

Concentrations of the calibration standards have been detailed (refer to Table 12) and are acceptable. The AxSYM instrumentation is calibrated once without further calibration unless the internal quality controls are out of range or a reagent kit with a new lot number is used. This is acceptable.

Table 12: Summary of calibration standard concentrations.

Method	Range of Calibration Standard Concentrations
FT3	0 - 46.08 pmol / L
FT4	0 - 77.22 pmol / L
T3	0 – 12.29 nmol / L
T4	0 – 308.88 nmol / L
TSH	0 – 100.00 mU / L

The assays were controlled by the use of internal quality controls. Assay results have to fall within the range defined by the internal quality controls to be acceptable. The concentrations of the quality control samples are provided in Table 13.

Table 13: Concentration of the quality control samples.

Method	Biorad Lot Number	Target	Range of accuracy
FT3	40131	3.30 pmol / L	2.60 – 3.90 pmol / L
	40132	10.00 pmol / L	8.00 – 12.00 pmol / L
FT4	40131	4.70 pmol / L	3.80 – 5.70 pmol / L
	40132	12.00 pmol / L	9.00 – 14.00 pmol / L
T3	40131	1.34 nmol / L	1.08 – 1.61 nmol / L
	40132	2.90 nmol / L	2.30 – 3.50 nmol / L
T4	40131	41.00 nmol / L	31.16 – 50.84 nmol / L
	40132	89.00 nmol / L	67.64 – 110.36 nmol / L
TSH	40131	0.43 mU / L	0.34 – 0.52 mU / L
	40132	5.00 mU / L	4.00 – 6.10 mU / L

The quality control sample assay data confirm that the study samples remained stable and that the assay data are reliable.

44. **The applicant should provide pharmacokinetic parameters and statistical analyses based on the results adjusted for baseline endogenous T4 concentrations, or justify why this is not necessary.**

GlaxoSmithKline has performed a statistical analysis of data that has been corrected for pre-dose values of levothyroxine T4. Pre-dose samples were collected for levothyroxine at the time points of –30, -15 and 0 hours. To correct for the values, the average of these three measurements was subtracted from each of the post-dose T4 measurements. Isolated samples with a negative value (n = 21 of >2000 samples) were omitted from the pharmacokinetic analysis. ***The applicant states that these calculations are provided in Appendix 13; however, the results have not been provided (a second copy of the GMP certificate was provided instead). The statistical calculations for the data adjusted for baseline endogenous T4 concentrations should be provided.***

The applicant states that following the correction for pre-dose levels of T4, bioequivalence was demonstrated between the two Eltroxin formulations as the 90 % confidence limits for Cmax and AUC_{0-t} of FT4 and TT4 were within the acceptable range (0.80 – 1.25). It is also stated that the Tmax values were similar for the two formulations.

45. **This application has been submitted for approval under the Intermediate Risk Stream. However, the biostudy provided does not meet Medsafe Intermediate Risk Stream criteria for demonstration of bioequivalence, as the reference product used is not the New Zealand innovator product. Therefore, further information is required as detailed below:**

    Please provide either a bioequivalence study comparing the reformulated products and the New Zealand innovator products, or a bioequivalence study comparing the European innovator products and the New Zealand innovator products. Alternatively, clinical data supporting the safety and efficacy of the European formulation, or the new formulation should be submitted via the High Risk Medicine Stream.

Since the initial evaluation of this new medicine application, it has become apparent that the European formulation (same formulation as the reference product) was approved in New Zealand from 08/04/1981 to 08/05/1992. In 1992 the formulation of the tablets was changed from the European formulation to the currently approved formulation based on dissolution data (comparative dissolution testing between the European formulation and the currently approved formulation in the same dissolution system was not performed at this time). Although the European formulation and the currently approved formulation have not been shown to be bioequivalent, they have similar dissolution profiles in media at pH 1, 4.5 and 6.8. Furthermore, the fact that the European formulation was approved in New Zealand from 08/04/1981 to 08/05/1992 provides evidence to support the safety and efficacy of the European formulation. It should also be noted that both the European product and the current New Zealand innovator product are marketed by the same company based on the same clinical data.

In summary, the use of the European product as the reference product in the biostudy is appropriate, and demonstration of bioequivalence to this product implies a demonstration of safety and efficacy.

Comments:

A public meeting co-sponsored by the Food and Drug Administration and the American Thyroid Association, The Endocrine Society, and the American Association of Clinical Endocrinologists was held in Washington, DC on Monday the 23rd of May 2005 to discuss

levothyroxine sodium therapeutic equivalence. Details of presentations from this meeting are available at http://www.fda.gov/cder/meeting/levothyroxinePresentations.htm and the minutes at http://www.fda.gov/cder/meeting/LevothyroxineTranscript20050523.pdf. A concern raised at the meeting was whether the acceptance criteria (90 % confidence interval within an 80 – 125 % acceptance range) for bioequivalence are too wide, given that levothyroxine is a narrow therapeutic index drug. This may need to be considered by the Generics SubCommittee.

It was also apparent from the minutes of this meeting that in addition to analysing the results for levothyroxine unadjusted for baseline, the FDA routinely request that applicants perform a baseline correction prior to analysing the results for levothyroxine in bioequivalence studies.

Results after baseline correction will be requested as supporting data given the controversy over the importance of baseline correction.

Assessment:

1. **The finished product manufacturer should routinely test each batch of active ingredient for assay and related substances as well as identity and specific rotation.**
2. **Evidence should be provided to support the acceptability of reduced testing of the active ingredient by the finished product manufacturer. Such evidence may include but not be limited to information regarding any auditing of the active ingredient manufacturer that is performed by the finished product manufacturer, GMP certification for the active ingredient manufacturing site and Certificates of Analysis issued by the finished product manufacturer for batches of active ingredient.**
3. Certificates of Analysis issued by the finished product manufacturer for three batches of the finished product have been provided. However, these detail results transposed from the supplier's Certificate of Analysis and are not representative of testing performed by the finished product manufacturer. **Certificates of Analysis issued by the finished product manufacturer for three batches of active ingredient representative of testing performed at the finished product manufacturing site should be provided.**
4. The following statement has been included in the revised data sheet: "Due to a lack of data to support the use of crushing tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow tablets." **It is recommended that this statement is amended to read, "Due to a lack of data to support the use of crushing or halving tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow whole tablets."**
5. **Further evidence should be provided to support the proposed shelf-life specification for HDPhDB (NMT 2.5 %). Such evidence may include but not be limited to safety / toxicological data relating to batch G03102 of the European innovator product and further impurity data for two batches of the 100 mcg strength of the European innovator product and three batches of the 50 mcg strength of the European innovator product.**
6. **The applicant should explain why Certificates of Analysis were not issued for batches 0274, 0275, 0276, 0271, 0272 and 0273 of the reformulated products.**
7. **The applicant should commit to placing at least one production scale batch of each strength of the finished product annually on stability trials.**
8. **The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products. As detailed in the initial evaluation report, in order for similarity calculations using similarity factor f2 to be valid the following must apply:**

At least two data points must be less than or equal to 85 % and no more than one data point should be above 85 % (if more than one data point above 85 % is used, false similarities may be concluded).

If mean data is used, the % coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %.

9. GlaxoSmithKline has performed a statistical analysis of data that has been corrected for pre-dose values of levothyroxine T4. The applicant states that these calculations are provided in Appendix 13; however, the results have not been provided (a second copy of the GMP certificate was provided instead). The statistical calculations for the data adjusted for baseline endogenous T4 concentrations should be provided.

Further correspondence

Because the sponsor's first response was incomplete or inadequate, further information was requested via email on the 16th of January 2006:

1.Please provide assurance that the finished product manufacturer will routinely test each batch of active ingredient for assay and related substances, as well as identity and specific rotation.

2.Please provide evidence to support the acceptability of reduced testing of the active ingredient by the finished product manufacturer. Such evidence may include, but not be limited to, information regarding any auditing of the active ingredient manufacturer that is performed by the finished product manufacturer, GMP certification for the active ingredient manufacturing site and Certificates of Analysis issued by the finished product manufacturer for batches of active ingredient.

3.Certificates of Analysis issued by the finished product manufacturer for three batches of the finished product have been provided. However, these detail results transposed from the supplier's Certificate of Analysis and are not representative of testing performed by the finished product manufacturer. Please provide Certificates of Analysis issued by the finished product manufacturer for three batches of active ingredient representative of testing performed at the finished product manufacturing site.

4.The following statement has been included in the revised data sheet: "Due to a lack of data to support the use of crushing tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow tablets." Please consider amending this statement to read: "Due to a lack of data to support the use of crushing or halving tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow whole tablets."

5.Please provide further evidence to support the proposed shelf-life specification for HDPhDB (NMT 2.5 %). Such evidence may include, but not be limited to, safety / toxicological data relating to batch G03102 of the European innovator product and further impurity data for two batches of the 100 mcg strength of the European innovator product and three batches of the 50 mcg strength of the European innovator product.

6.Please explain why Certificates of Analysis were not issued for batches 0274, 0275, 0276, 0271, 0272 and 0273 of the reformulated products.

7.Please commit to placing at least one production scale batch of each strength of the finished product annually on stability trials.

8.Please provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products. As detailed in the initial evaluation report, in order for similarity calculations using similarity factor f2 to be valid the following must apply:

- At least two data points must be less than or equal to 85 % and no more than one data point should be above 85 % (if more than one data point above 85 % is used, false similarities may be concluded).
- If mean data is used, the % coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %.

9.A statistical analysis of data corrected for pre-dose values of levothyroxine T4 has been performed. It is stated that these calculations are provided in Appendix 13 of the most

recently submitted information; however, the results have not been provided (a second copy of the GMP certificate was provided instead). Please provide the statistical calculations for the data adjusted for baseline endogenous T4 concentrations.

Resolution of Issues

Date: 06/04/2006

Evaluator: Jacqui Watt

Sponsor's responses to issues raised in the initial assessment

The sponsor responded to the request for information on 27/01/2006.

The responses received and the evaluator's assessment of the responses are outlined below.

1. **The finished product manufacturer should routinely test each batch of active ingredient for assay and related substances as well as identity and specific rotation.**

   The applicant has confirmed that the finished product manufacturer will routinely test each batch of active ingredient for assay, related substances, loss on drying and colour of solution as well as identity and specific rotation. This is acceptable.

2. **Evidence should be provided to support the acceptability of reduced testing of the active ingredient by the finished product manufacturer. Such evidence may include but not be limited to information regarding any auditing of the active ingredient manufacturer that is performed by the finished product manufacturer, GMP certification for the active ingredient manufacturing site and Certificates of Analysis issued by the finished product manufacturer for batches of active ingredient.**

   The applicant has confirmed that all materials purchased from a new supplier are subject to full specification testing by GlaxoSmithKline (GSK) to ensure compliance with the specification until reliability of supply is established.

   Reliability of supply is established once the following criteria are met:

   - Specifications and related methods have been agreed between the supplier and the receiver.
   - Suppliers of materials considered critical for quality have been audited.
   - Any quality history or background information available to GSK regarding the supplier has been reviewed.
   - The materials have been evaluated with regard to their intended use.

   The approval status of a supplier is periodically reviewed and documented. For suppliers with acceptable performance, an assessment or supplier audit is performed at least every four years. If the audit results are acceptable, the material may be considered for certification (which allows acceptance based on the Certificate of Analysis with reduced testing). Full testing is performed on three consecutive receipts in-house or by an approved outside laboratory to verify the results obtained by the supplier. If the results are acceptable, the supplier will be certified. The verification is repeated on one batch annually to maintain the certification.

   Further information specifically relating to the proposed active ingredient manufacturing site (Sandoz GmbH, Schaftenau Plant, Biochemiestrasse 10, A-6336 Langkampfen, Tyrol, AUSTRIA) has been provided as follows:

   - A summary of a GSK audit of the site. The audit was performed on the 29th of September 2004. The site was found to be GMP compliant.
   - A GMP certificate issued by the Austrian Federal Ministry of Health and Women, dated the 29th of September 2005 attesting to the sites compliance with GMP standards.

- Certificates of Analysis issued by the finished product manufacturer for three batches of active ingredient have been provided. The Certificates are representative of testing performed at the finished product manufacturing site. The results indicate that all three batches comply with the EP monograph for levothyroxine sodium.

The evidence provided supports the proposed reduced testing regimen for the active ingredient.

A summary of the active ingredient specifications and test methods applied by the finished product manufacturer should be provided. The summary should detail the frequency of testing for each of the tests.

3. Certificates of Analysis issued by the finished product manufacturer for three batches of the finished product have been provided. However, these detail results transposed from the supplier's Certificate of Analysis and are not representative of testing performed by the finished product manufacturer. **Certificates of Analysis issued by the finished product manufacturer for three batches of active ingredient representative of testing performed at the finished product manufacturing site should be provided.**

   As discussed above Certificates of Analysis representative of testing by the finished product manufacturer have been provided for three batches of active ingredient. The results indicate that all three batches complied with the EP monograph for levothyroxine sodium. The company will be asked to include testing for iodide content, related substances by liquid chromatography and residual solvents by gas chromatography when performing full testing for batches of the active ingredient.

4. The following statement has been included in the revised data sheet: "Due to a lack of data to support the use of crushing tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow tablets." **It is recommended that this statement is amended to read, "Due to a lack of data to support the use of crushing or halving tablets, it is recommended that thyroxine tablets are only prescribed to patients who are able to swallow whole tablets."**

   The proposed datasheet has been updated to include the requested statement. This is acceptable.

5. **Further evidence should be provided to support the proposed shelf-life specification for HDPhDB (NMT 2.5 %). Such evidence may include but not be limited to safety / toxicological data relating to batch G03102 of the European innovator product and further impurity data for two batches of the 100 mcg strength of the European innovator product and three batches of the 50 mcg strength of the European innovator product.**

   Impurity data for two further batches of each strength of the European innovator product has been provided. The batches were tested for HDPhDB content at the end of the shelf life (duration of storage and storage conditions were not provided), and the results are presented in Table 1 (bold text).

Table 1: HDPhDB content of Eltroxin tablets

Product	Strength	Batch Number	Storage details	HDPhDB content (%)
Current New Zealand innovator product	50 mcg	2H511 (Manufactured 08/2002)	36 months at room temperature	0.56
		2G427 (Manufactured 07/2002)	36 months at room temperature	0.58
		2F529 (Manufactured 07/2002)	36 months at room temperature	0.54
	100 mcg	2G487 (Manufactured 07/2002)	36 months at room temperature	0.55
		2G406 (Manufactured 07/2002)	36 months at room temperature	0.56
		2E486 (Manufactured 07/2002)	36 months at room temperature	0.57
European innovator product	50 mcg	**2297**	**End of shelf life (no further details provided)**	**1.92**
		7963	**End of shelf life (no further details provided)**	**1.23**
	100 mcg	G03102	34 months at 25°C / 60 % RH	3.0
		2508	**End of shelf life (no further details provided)**	**0.95**
		2707	**End of shelf life (no further details provided)**	**0.66**
Reformulated products	50 mcg	0276 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
		0275 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
		0274 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
	100 mcg	0273 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.2
		0272 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.2
		0271 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.3

The date of manufacture and details of storage should be provided for batches 2297, 7963, 2508 and 2707 of the European innovator product that were tested for HDPhDB content. The date of manufacture for batch G03102 of the European innovator product should also be provided.

The applicant should explain why there is such a difference between HDPhDB content in the tablets currently registered in NZ and the reformulated tablets and European tablets.

The applicant should provide details of the HDPhDB limits approved by European regulatory bodies for the European formulated tablets as well as the HDPhDB limit approved by Germany for the reformulated tablets.

Any batch data indicating HDPhDB content of further batches of the European tablets would be appreciated.

6. **The applicant should explain why Certificates of Analysis were not issued for batches 0274, 0275, 0276, 0271, 0272 and 0273 of the reformulated products.**

   The applicant has explained that Certificates of Analysis were not provided for the above batches as the tablets from these batches had not been imprinted with the commercial image.

   Certificates of Analysis for batches 0274, 0275, 0276, 0271, 0272 and 0273 have now been provided. The results are considered acceptable.

7. **The applicant should commit to placing at least one production scale batch of each strength of the finished product annually on stability trials.**

   A commitment to placing at least one production scale batch of each strength of the finished product on annual stability trials has been provided. This is acceptable.

8. **The applicant should provide evidence that the similarity calculations using similarity factor f2 are valid for the dissolution comparison of the reference (European formulation) and test (new formulation) products. As detailed in the initial evaluation report, in order for similarity calculations using similarity factor f2 to be valid the following must apply:**

   At least two data points must be less than or equal to 85 % and no more than one data point should be above 85 % (if more than one data point above 85 % is used, false similarities may be concluded).

   If mean data is used, the % coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20 %, and at other time points should not be more than 10 %.

   The similarity factor f2 has been recalculated based on the three earliest time points for each profile (5, 15 and 30 minutes).

   The first two time points for the reformulated tablets are below 85 % while only the values for the first time point are below 85 % for the current European formulation. The similarity factor obtained is equal to 50.3, indicating equivalence of the formulations.

   The results suggest that the reformulated tablets may be slower to dissolve than the European formulated tablets at the earlier time points (5, 15, and 30 minutes). However, given that the results of the bioequivalence study indicate that the two formulations are bioequivalent, any difference in dissolution rate at the earlier time points does not appear to be of clinical concern.

   Coefficients of variation have been calculated for the dissolution data used for the dissolution comparison of the reference (European formulation) and test (new formulation) products. The results are acceptable.

9. GlaxoSmithKline has performed a statistical analysis of data that has been corrected for pre-dose values of levothyroxine T4. The applicant states that these calculations are provided in Appendix 13; however, the results have not been provided (a second copy of the GMP certificate was provided instead). The statistical calculations for the data adjusted for baseline endogenous T4 concentrations should be provided.

The results of the statistical analysis of the data corrected for pre-dose values of levothyroxine (T4) have been provided and are presented in Table 2.

Table 2: Results of statistical calculations for data adjusted for baseline endogenous levothyroxine (T4) concentrations.

		Free Unchanged drug (FT4):		
		T_{max} (h)	C_{max} (pmol/L)	AUC_t (pmol.h/L)
Treatment				
A: (Reference)			12.80	294.85
B: (Test product)			11.49	269.39
Statistical analysis:		***(median diff.)***	***(ratio)***	***(ratio)***
B/A:	*Estimate*	0.49	*90 %*	*91 %*
	90 % CI	(0.03-0.75)	*83-97 %*	*83-100 %*
		Total Unchanged drug (TT4):		
		T_{max} (h)	C_{max} (nmol/L)	AUC_t (nmol.h/L)
Treatment				
A: (Reference)			84.89	2055.25
B: (Test product)			74.99	1968.51
Statistical analysis:		***(median diff.)***	***(ratio)***	***(ratio)***
B/A:	*Estimate*	0.5	*88 %*	*96 %*
	90 % CI	(0.00-1.00)	*82-95 %*	*88-104 %*

The 90 % confidence intervals for C_{max} and AUC_{0-t} of FT4 and TT4 were within the 80-125 % acceptance range.

Assessment:

1. A summary of the active ingredient specifications and test methods applied by the finished product manufacturer should be provided. The summary should detail the frequency of testing for each of the tests.
2. The date of manufacture and details of storage should be provided for batches 2297, 7963, 2508 and 2707 of the European innovator product that were tested for HDPhDB content. The date of manufacture for batch G03102 of the European innovator product should also be provided.
3. The applicant should explain why there is such a difference between HDPhDB content in the tablets currently registered in NZ and the reformulated tablets and European tablets.
4. The applicant should provide details of the HDPhDB limits approved by European regulatory bodies for the European formulated tablets as well as the HDPhDB limit approved by Germany for the reformulated tablets.
5. Any batch data indicating HDPhDB content of further batches of the European tablets would be appreciated.

An email requesting the above information was sent to the applicant on the 6th of April 2006.

Resolution of Issues

Date: 02/06/2006

Evaluator: Jacqui Watt

Sponsor's responses to issues raised in the initial assessment

The sponsor responded to the request for further information on the 28th of April 2006.

The responses received and the evaluator's assessment of the responses is as follows:

1. **A summary of the active ingredient specifications and test methods applied by the finished product manufacturer should be provided. The summary should detail the frequency of testing for each of the tests.**

   The applicant has confirmed that the finished product manufacturer will test batches of active ingredient according to the following testing regimen.

   Table 1: Finished product manufacturer's proposed testing regimen for batches of the active ingredient.

Test	Limit	Frequency of Testing
Characteristics	Almost white to slightly brownish-yellow powder	Routine
Identity		
• Optical rotation	+16° - +20°	Routine
• FTIR	Positive	Routine
• Test for sodium	Positive	Routine
Appearance of solution	Not more intensely coloured than reference solution BY3	1 batch per year
Optical rotation	+16° - +20°	Routine
Related substances by HPLC		
• Liothyronine	NMT 1.0 %	1 batch per year
• Other related substances	NMT 1.0 %	1 batch per year
Loss on drying	6.0 – 12.0 %	1 batch per year
Assay by HPLC	97.0 – 102.0 %	1 batch per year

   The test methods and specifications are those of the EP monograph for levothyroxine sodium.

   Previously the applicant stated that the finished product manufacturer would routinely test each batch of active ingredient for assay, related substances, loss on drying and colour of solution as well as identity. However, it is now proposed that the tests for appearance of solution, assay, related substances and loss on drying will be performed on only one batch per year.

   The following justification has been provided for the proposed reduced testing regimen:

Full testing is performed on three consecutive batches in-house or by an approved outside laboratory to verify the results obtained by the supplier. Once a supplier is certified, batches are accepted on the supplier's Certificate of Analysis, although identity testing is performed for every batch.

Suppliers with an acceptable performance are assessed or audited at least every four years.

The following evidence of GMP has been provided in relation to the proposed active ingredient manufacturing site (Sandoz GmbH, Schaftenau Plant. Biochemiestrasse 10, A-6336 Langkampfen, Tyrol, AUSTRIA):

- A summary of a GSK audit of the site. The audit was performed on the 29th of September 2004. The site was found to be GMP compliant.
- A GMP certificate issued by the Austrian Federal Ministry of Health and Women, dated the 29th of September 2005 attesting to the sites compliance with GMP standards.

The above justification supports the proposed reduced testing regimen for appearance of solution and loss on drying; however Medsafe would still expect that the finished product manufacturer would test every batch of active ingredient for assay and related substances. ***The finished product manufacturer should test every batch of active ingredient for assay and related substances.***

2. **The date of manufacture and details of storage should be provided for batches 2297, 7963, 2508 and 2707 of the European innovator product that were tested for HDPhDB content. The date of manufacture for batch G03102 of the European innovator product should also be provided.**

The date of manufacture and details of storage have been provided for batches 2297, 7963, 2508 and 2707 of the European innovator product. This information is detailed in Table 2.

Batches 2297, 7963, 2508 and 2707 were all manufactured at the proposed finished product manufacturing site (Bad Oldesloe). Batch G03102 was manufactured at a different manufacturing site (Poznan) and the date that this batch was manufactured has not been provided.

Table 2: HDPhDB content of Eltroxin tablets

Product	Strength	Batch Number	Storage details	HDPhDB content (%)
Current New Zealand innovator product	50 mcg	2H511 (Manufactured 08/2002)	36 months at room temperature	0.56
		2G427 (Manufactured 07/2002)	36 months at room temperature	0.58
		2F529 (Manufactured 07/2002)	36 months at room temperature	0.54
	100 mcg	2G487 (Manufactured 07/2002)	36 months at room temperature	0.55
		2G406 (Manufactured 07/2002)	36 months at room temperature	0.56
		2E486 (Manufactured 07/2002)	36 months at room temperature	0.57
European innovator product	50 mcg	2297 (Manufactured at Bad Oldesloe, 03/09/2002)	36 months at room temperature	1.92
		7963 (Manufactured at Bad Oldesloe, 10/04/2001)	36 months, 25°C/60%RH	1.23
	100 mcg	**G03102 (Manufactured at Poznan, manufacturing date not specified)**	34 months at 25°C / 60 % RH	3.0
		2508 (Manufactured at Bad Oldesloe, 02/09/2002)	36 months at room temperature	0.95
		2707 (Manufactured at Bad Oldesloe, 23/08/2002)	36 months at room temperature	0.66
Reformulated products	50 mcg	0276 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
		0275 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
		0274 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.8
	100 mcg	0273 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.2
		0272 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.2
		0271 (Manufactured November 2001)	24 months at 25°C / 60 % RH	1.3

3. **The applicant should explain why there is such a difference between HDPhDB content in the tablets currently registered in NZ and the reformulated tablets and European tablets.**

The applicant states that degradation of levothyroxine sodium in tablets occurs mainly due to reactions affecting the aliphatic side chain of the molecule resulting in the formation of tetrac and HDPhDB acid. They also state that the rate of levothyroxine sodium degradation and actual contribution of particular processes of degradation of levothyroxine sodium in the aliphatic chain and its content depends strongly on the amounts of various excipients in a formulation. Therefore, since the reformulated Eltroxin tablets, the European tablets and the tablets currently registered in New Zealand differ in respect to the content of excipients, differences between the degradation profiles observed for these three formulations can be expected.

The applicant also states that HDPhDB acid is not detected by the registered methods for the tablets that are currently marketed in New Zealand, therefore no comprehensive data is available. They also state that as both the European Originator tablets and the tablets currently registered in New Zealand are due to be superseded by the Reformulated Tablets which contain a limit for HDPhDB acid it is considered that the specification for the Reformulated Tablets provides an improvement in quality over the existing formulation.

It is correct that the currently registered related substance test method for Eltroxin tablets does not detect HDPhDB acid; however, this is not a sufficient argument to support the proposed expiry limit for HDPhDB acid content of NMT 2.5 % for the reformulated tablets.

The applicant should provide details of the HDPhDB limits approved by European regulatory bodies for the European formulated tablets as well as the HDPhDB limit approved by Germany for the reformulated tablets.

The reformulated tablets have been approved by BfArM in Germany. The expiry specifications for related substances in Table 3 have been approved by [redacted]

The expiry specifications for related substances in Table 3 have also been approved by [redacted] It was not stated whether [redacted] has approved these specifications for the Reformulated Tablets or the European formulated tablets.

It is unclear whether [redacted] has approved the Reformulated tablets or approved the HDPhDB limit of 2.5 % for the European formulated tablets. The applicant should confirm whether [redacted] have approved the Reformulated tablets.

The proposed expiry specifications for the reformulated are tablets are the same as those approved in [redacted] except that the proposed limit for total impurities has been reduced from NMT 6 % to NMT 5 %.

Table 3: Proposed related substance expiry specifications

Drug-related impurities content (%w/w)	
Liothyronine sodium	Not greater than 1.0
Tetraiodothyroacetic acid (tetrac)	Not greater than 1.0
HDPhDB	Not greater than 2.5
Any unspecified impurity	Not greater than 1.0
Total	Not greater than 6.0

4. **Any batch data indicating HDPhDB content of further batches of the European tablets would be appreciated.**

   The applicant has advised that no further batch data is currently available; however further samples are due to undergo analysis soon. The samples are from one batch of Eltroxin 100 mg tablets after 24 months of storage in 25°C/60 % RH, one batch of Eltroxin 100 mg tablets after 29 months of storage at 25°C/60 % RH, one batch of Eltroxin 50 mg tablets after 24 months of storage at 25°C/60 % RH and one batch of Eltroxin 50 mg tablets after 29 months of storage at 25°C/60 % RH.

   Results of HDPhDB testing for further batches of the European tablets should be submitted to Medsafe when these are available.

Summary of information provided to support the proposed expiry specification for HDPhDB content (Not greater than 2.5 %).

The proposed expiry specification for HDPhDB content is NMT 2.5 %. This limit has been approved by [redacted]

The proposed limit has been established based on the HDPhDB content of batches of the European innovator product (0.66 – 3.0 % after storage at room temperature or 25°C / 60 % RH for 34 – 36 months). The shelf-life for the European innovator product is 36 months.

The European formulation is registered for marketing in Holland, Denmark, Poland, the Czech Republic and Lithuania and was registered in New Zealand from 08/04/1981 to 08/05/1992.

An expert statement written by GlaxoSmithKline's Safety Assessment Division states that safe and efficacious use of the European formulation has been demonstrated over many years of clinical usage, representing millions of patient years of exposure since 1962 (e.g. approximately 1.9 million patient years of exposure to Eltroxin worldwide during 1997 and 1998, based on available sales volume data and assuming a standard daily dose of levothyroxine sodium of 100 mcg). A copy of the expert report is attached to this evaluation report.

The company also state that the structure of HDPhDB acid has been analysed using the DEREK (Deductive Estimation of Risk for Existing Knowledge) SAR application, which is an industry accepted standard for the *in silico* prediction of genotoxic liability. The analysis revealed no structural features that would give cause for concern with regards to potential for genotoxicity.

A comparison of HDPhDB content for batches of the current New Zealand innovator product, the European innovator product and the reformulated products is presented in Table 2. The proposed limit for HDPhDB content is more than four times higher than that contained in batches of the current New Zealand innovator product. This difference is likely to be

explained by the different excipients contained in the formulations of the current New Zealand innovator products and the reformulated products.

Comments

The primary objective of the reformulation is to improve the stability of the finished products. Based on the fact that the reformulated tablets contain significantly more HDPhDB acid than the currently approved tablets after storage for a shorter period of time, it would appear that the primary objective has not been met. The applicant will be asked to comment on this.

Assessment:

1. **The finished product manufacturer should test every batch of active ingredient for assay and related substances.**
2. **It is unclear whether [redacted] has approved the Reformulated tablets or approved the HDPhDB limit of 2.5 % for the European formulated tablets. The applicant should confirm whether [redacted] have approved the Reformulated tablets.**
3. **Results of HDPhDB testing for further batches of the European tablets should be submitted to Medsafe when these are available.**
4. **The primary objective of the reformulation is to improve the stability of the finished products. Based on the fact that the reformulated tablets contain significantly more HDPhDB acid than the currently approved tablets after storage for a shorter period of time, it would appear that the primary objective has not been met. The applicant will be asked to comment on this.**

An email requesting the above information was sent to the applicant on the 2nd of June 2006.

Resolution of Issues

Date: 26/06/2006

Evaluator: Jacqui Watt

Sponsor's responses to issues raised in the initial assessment

The sponsor responded to the request for further information on the 16th of June 2006.

The responses received and the evaluator's assessment of the responses is as follows:

1. **The finished product manufacturer should test every batch of active ingredient for assay and related substances.**

   The applicant restated the proposed testing regimen and also stated that all manufacture at GSK facilities is performed under conditions of cGMP.

   The applicant has replied that they will test the next 30 batches of active ingredient for assay and related substances. After this time, the previously proposed annual testing will be instituted. The proposed active ingredient testing regimen is outlined in Table 1.

   Table 1: Finished product manufacturer's proposed testing regimen for the next 30 batches of the active ingredient.

Test	Limit	Frequency of Testing
Characteristics	Almost white to slightly brownish-yellow powder	Routine
Identity • Optical rotation • FTIR • Test for sodium	 +16° - +20° Positive Positive	 Routine Routine Routine
Optical rotation	+16° - +20°	Routine
Related substances by HPLC • Liothyronine • Other related substances	 NMT 1.0 % NMT 1.0 %	 Next 30 batches then 1 batch per year
Assay by HPLC	97.0 – 102.0 %	Next 30 batches then 1 batch per year

The finished product manufacturer ensures the quality of the active ingredient by fully testing three consecutive batches and one batch per year thereafter. All other batches are tested for identity and are accepted based on the supplier's Certificate of Analysis. The finished product manufacturer also assesses or audits the supplier at least every four years. GSK has also stated that they will test the next 30 batches of active ingredient for assay and related substances before switching to the proposed regimen of fully testing one batch per year.

The proposed active ingredient manufacturer is the same as that currently approved for the New Zealand innovator product.

The proposed reduced testing regimen for the active ingredient is considered acceptable.

2. **It is unclear whether [redacted] has approved the Reformulated tablets or approved the HDPhDB limit of 2.5 % for the European formulated tablets. The applicant should confirm whether [redacted] have approved the Reformulated tablets.**

   GSK have confirmed that the reformulated tablets (50 mcg and 100 mcg) were approved in Denmark in February 2006. The Danish Medicines Agency has approved the reformulated tablets with a limit of [redacted] for HDPhDB acid.

3. **Results of HDPhDB testing for further batches of the European tablets should be submitted to Medsafe when these are available.**

   The applicant states that further data will be provided when it is available.

4. **The primary objective of the reformulation is to improve the stability of the finished products. Based on the fact that the reformulated tablets contain significantly more HDPhDB acid than the currently approved tablets after storage for a shorter period of time, it would appear that the primary objective has not been met. The applicant will be asked to comment on this.**

   The applicant states that the stability of the reformulated product, as a whole, is superior to the stability of the currently approved tablet formulation in New Zealand. It is stated that levels of total impurities observed are lower in the case of the reformulated tablets although levels of HDPhDB acid are higher. A comparison of total impurity content and HDPhDB acid content for one batch of reformulated tablets (100 mcg) and two batches of the currently registered New Zealand formulation has been provided and is presented in Table 2.

   Table 2: Total impurity content and HDPhDB acid content for batches of Eltroxin 100 mcg tablets after storage for the duration of the product shelf life.

Tablets	Batch	Duration of storage	HDPhDB acid (%)	Total impurities (%)
Reformulated tablets 100 mcg	0271	24 months	1.3	3.1
Currently registered New Zealand tablets 100 mcg	2G487	36 months	0.55	4.59
Currently registered New Zealand tablets 100 mcg	2G406	36 months	0.56	4.01

   It is difficult to compare the overall stability of the reformulated tablets and the currently registered New Zealand tablets from the data provided as the batches were stored for different lengths of time and data was only provided for two batches of the 100 mcg strength of the currently registered New Zealand product.

   The applicant has reiterated that overall the products have been reformulated with the primary objective of improving stability. A secondary objective has been to provide a single formulation to replace the multiple variants of existing Eltroxin formulations which currently exist in markets around the world.

   GSK accept that the formulation currently marketed in Europe has a different stability profile than the tablet formulation currently marketed in New Zealand. GSK state that the primary motivation in the case of New Zealand has been to seek to register a single tablet formulation world-wide with a tighter specification and product specific, fully validated

analytical methodology which represents an improvement on the currently registered formulation in terms of quality and stability throughout the storage period.

GSK state that the reformulation exercise represents a significant opportunity to improve on the registration in light of the experience of nearly forty years of manufacturing since the New Zealand formulation was approved in the 1960s. The currently approved impurity specifications for Eltroxin tablets include a specification for liothyronine sodium but not total impurities or any other impurities. Furthermore the currently approved test method for related substances is not capable of detecting tetrac or HDPhDB acid.

The new analytical methodology for related substance testing has been fully validated for the reformulated tablets; however it has not been validated for the currently marketed New Zealand formulation. GSK state that although levels of HDPhDB acid appear to be higher in the reformulated batches at the end of the shelf life, it should be borne in mind that the methods have not fully validated for the current New Zealand formulation. In a previous response (September 2005), GSK stated that even though the methods have not been validated for testing the current formulations, they considered it acceptable to use them for comparative analysis of the old and proposed formulations.

Given that the currently approved New Zealand innovator product is controlled for liothyronine sodium content, but not for any other impurities or total impurities, the proposed impurity specifications for the reformulated tablets are an improvement. In light of the fact that there is no other replacement product for currently marketed formulation, the proposed limit for HDPhDB acid is considered acceptable.

Further to discussion with [redacted] and [redacted] from the Pharmacovigilence team, the following information was requested by email on the 30th of June 2006:

1. **Please provide details regarding the proposed transition protocol for the switch from the currently registered formulation to the new formulation. The transition protocol should include an outline of the proposed time frames with regard to the distribution of the notification letter, commencement of supply of the new formulation and cessation of supply of the current formulation. Prior to marketing of the new formulation Medsafe will require notification of the date when GSK will stop supplying wholesalers with the current formulation and start supplying the new formulation.**

   GSK have provided assurance that Medsafe will be notified of the date of ceasing supply of the current formulation and commencement of supply of the new formulation of Eltroxin tablets.
   It is currently anticipated that the new formulation will be supplied to the New Zealand market in March 2007. Until that time the current formulation of Eltroxin tablets will continue to be supplied. [redacted] phoned on Monday the 4th of September 2006 to advise that manufacture of the currently approved Eltroxin formulation will cease at the end of 2006 and that stocks of the current formulation are likely to run out in March 2007. GSK intends to communicate the change in formulation to health professionals early in 2007 before commencing the supply of new formulation in New Zealand.

2. **Please provide a copy of the notification letter that will be sent to health professionals and specify who the letter will be sent to. The notification letter will need to include monitoring recommendations.**

   A copy of the proposed notification letter to healthcare professionals has been provided. ***The proposed letter has been discussed with*** [redacted] ***and*** [redacted]

[redacted] ***and recommendations for changes to the letter will be sent to GSK (refer to amended letter on file).***

GSK intend to send this letter to general practitioners and specialists (including endocrinologists). ***The notification letter must also be sent to pharmacists.***

3. **Due to concerns regarding the clinical consequences of the formulation change please label the packaging for the reformulated products with the words "New Formulation" for an appropriate period of time to ensure that the different formulations are easily distinguishable. Please provide copies of the "New Formulation" labelling and details of the site where the additional labelling will be performed. If overlabelling is performed by a site other than the finished product manufacturer, a GMP certificate or packing licence will need to be submitted for that site.**

GSK have advised that they intend to label the new formulation with the words "New Formulation" for the first batches of product to be supplied to New Zealand. Revised bottle labelling for each strength of the finished product (although the labels for the 50 mg tablets were unreadable) has been provided with a corresponding declaration and checklists.
GSK will be asked how many batches will be labelled with the words "New Formulation" and the expected time frame that these "specially" labelled batches will be on the New Zealand market.

It was noted that the proposed labelling indicates that the tablets comply with the USP monograph for Levothyyroxine Sodium Tablets; however this is not the case, therefore this statement must be removed. ***Given that the reformulated tablets are not tested using USP test methods, please remove the reference to the USP on the proposed labelling for both strengths of the finished product.***

4. **Please provide a copy of the currently proposed shelf life specifications that include the revised total impurity limit.**

A copy of the finished product shelf life specifications has been provided; however, the limit for total impurities is NMT 6.0 % rather than NMT 5.0 % (see response dated 19/10/2005). ***A copy of the currently proposed shelf life specifications that include the revised total impurity limit will be requested once more.***

An updated copy of the proposed finished product release specifications has also been provided with tightened limits for assay (96-105 %).

The following further two questions were also asked:

4. **Please provide the T4 AUC and Cmax data for each individual subject for the biostudy results adjusted for baseline T4 concentrations.**

Baseline samples were collected for levothyroxine at the time points of -30, -15 and 0 hours. To correct for baseline concentrations, the average of these three measurements was subtracted from each of the post-dose T4 measurements. A summary of the investigators' results and the results calculated by the evaluator are presented in the table below. Given that there is a 6 % difference in assay (levothyroxine) between the reference and test products, the normalized estimates were calculated for C_{max} and AUC (refer to Table 1 below).

Based on the normalized results, the 90 % confidence interval for C_{max} was 77.2 – 89.4 %. This result is not within the usually accepted limits of 80 – 125 % and is therefore a concern, particularly given that levothyroxine is considered to have a narrow therapeutic index.

Table 1: A comparison of the investigators' pharmacokinetic parameters versus recalculated parameters for study RES11116 (corrected for baseline concentrations)

Comment: Values are in pmol.h/L not nanograms

Total Unchanged drug (TT4):						
	T_{max} (~~h~~ min)	T_{max} (~~h~~ min)	C_{max} (~~nmol/L~~ pmol/L)	C_{max} (~~nmol/L~~ pmol/L)	AUC (~~nmol.h/L~~ pmol.h/L)	AUC (~~nmol.h/L~~ pmol.h/L)
Treatment						
A: (Reference)		151.75 ± 112.51		89.44 ± 28.33		131594.69 ± 45548.55
B: (Test product)		180.97 ± 102.95		78.9 ± 25.72		124764.83 ± 41268.95
Statistical analysis:		***(median diff.)***	***(ratio)***	***(ratio)***	***(ratio)***	***(ratio)***
B/A: *Estimate*		*30*	*88 %*	*88.3 %*	*96 %*	*95.8 %*
90% CI		*0.00 to 60.00*	*82-95 %*	*82.1-95.1 %*	*88-104 %*	*88.1-104.2 %*
Normalised estimate				***83.1 %***		***90.1 %***
Normalised 90% CI				***77.2-89.4 %***		***82.8-98.0 %***
Power				***100 %***		***100 %***

When the results for levothyroxine were adjusted for baseline endogenous concentrations, the 90 % confidence intervals for C_{max} and AUC were 77.2 – 89.4 % and 82.8 – 98.0 % respectively. The result for C_{max} was not within the usually accepted range of 80 – 125 % and the results for both Cmax and AUC suggest that the test product may be less bioavailable than the reference product.

The significance of the above results is controversial. Walter-Sack et al, 2004 performed a pooled analysis of eight identically designed trials with 396 drug exposures to levothyroxine sodium and considered result with and without baseline adjustment. It was found that a simple subtraction of baseline endogenous levels prior to manipulation of the data increased the random error and may have overcorrected for baseline values. However, it was also found that even with the administration of doses greater than or equal to 600 mcg, AUC values for total levothyroxine were closely associated with baseline levothyroxine concentrations. Furthermore, if baseline levothyroxine was ignored, log AUC crossover differences depended on season, age and thyroid volume. The authors concluded that while the primary outcome of levothyroxine bioavailability studies should be log total AUC, the usual four-way ANOVA model should be supplemented by baseline total levothyroxine as a covariate to minimize the influence of potential sources of bias and to reduce residual variation as much as possible.

Given the uncertainty regarding the interpretation of results after baseline adjustment and the fact that the new formulation needs to be approved to ensure continuity of supply when the old formulation is discontinued, it is not considered necessary to discuss the results after baseline adjustment further.

Reference: Walter-Sack I, Clanget C, Ding R, Goeggelmann C, Hinke V, Lang M, Pfeilschifter J, Tayrouz Y and Wegscheider K. Assessment of Levothyroxine Sodium Bioavailability.

Recommendations for an Improved Methodology Based on the Pooled Analysis of Eight Identically Designed Trials with 396 Drug Exposures. Clinical Pharmacokinetics. 2004; 43 (14): 1037 – 1053.

5. **The proposed data sheet implies that the reformulated tablets are tested using the test methods described in the BP monograph for levothyroxine tablets. Given that this is not the case, please revise the wording "Thyroxine Tablets BP 50 mcg, 100 mcg" to read "Thyroxine (BP) Tablets 50 mcg, 100 mcg" or "Thyroxine Tablets 50 mcg, 100 mcg" and remove the statement "Eltroxin tablets comply with the specification for Thyroxine Tablets BP".**

   The data sheet has been revised as requested.

Assessment:

1. **The proposed letter has been discussed with [redacted] and [redacted] and recommendations for changes to the letter will be sent to GSK (refer to amended letter on file).**

2. **The notification letter must be sent to pharmacists as well as general practitioners and specialists (including endocrinologists).**

3. **GSK will be asked how many batches will be labelled with the words "New Formulation" and the expected time frame that these "specially" labelled batches will be on the New Zealand market.**

4. **Given that the reformulated tablets are not tested using USP test methods, the reference to the USP on the proposed labelling for both strengths of the finished product must be removed.**

5. **A copy of the currently proposed shelf life specifications that include the revised total impurity limit of NMT 5.0 % must be provided.**

The above information was requested by email on the 12th of September 2006.

Resolution of Issues

Date: 16/10/2006

Evaluator: Jacqui Watt

Sponsor's responses to issues raised in the initial assessment

The sponsor responded to the request for further information on the 15th of September 2006.

The responses received and the evaluator's assessment of the responses is as follows:

1. **The proposed letter has been discussed with [redacted] and [redacted] and recommendations for changes to the letter will be sent to GSK (refer to amended letter on file).**

   GSK has amended the letter as requested and it is considered acceptable by both myself and [redacted]

2. **The notification letter must be sent to pharmacists as well as general practitioners and specialists (including endocrinologists).**

   Assurance has been provided that the notification letter will be sent to pharmacists, general practitioners and specialists (including endocrinologists).

3. **GSK will be asked how many batches will be labelled with the words "New Formulation" and the expected time frame that these "specially" labelled batches will be on the New Zealand market.**

   It is proposed that the new formulation available as labelled with the words "New Formulation" will be available for at least 6 months. Based on current estimates it is anticipated that a 6 month supply period to the New Zealand market will be possible by 1 batch each of both strengths. This is acceptable.

4. **Given that the reformulated tablets are not tested using USP test methods, the reference to the USP on the proposed labelling for both strengths of the finished product must be removed.**

   The proposed labelling has been revised and is considered acceptable.

5. **A copy of the currently proposed shelf life specifications that include the revised total impurity limit of NMT 5.0 % must be provided.**

   A copy of the revised shelf life specifications has been provided.

   A further copy of the proposed release specifications was also provided; however, the limits for assay were 95 – 105 % rather than 96 – 105 %. The previously submitted limits for assay at release were 96 – 105 %.

   [redacted] confirmed over the telephone on the 19th of October 2006 that the proposed assay limits for levothyroxine sodium at release are 96 – 105 %. This is acceptable.

Evaluator's Final Conclusions and Recommendations

Summary:

This application is for the approval of a new formulation of the currently approved Eltroxin tablets that will be manufactured at a new manufacturing site. The new formulation has been approved in Denmark (Danish Medicines Agency) and Germany (BfArM).

An application to register the new formulation has not been submitted to the Therapeutic Goods Administration in Australia.

a. Suitability for distribution in New Zealand

A number of deficiencies in the application and the supporting data relating to the composition, manufacture, quality control, stability and bioavailability of this product were identified during the evaluation. The majority of these issues have now been resolved.

Although bioequivalence has not been established with the formulation currently marketed in New Zealand and there is still some concern regarding the quantity of HDPhDB acid contained in the reformulated tablets, Eltroxin is the only levothyroxine product available on the New Zealand market and the current formulation is to be discontinued at the end of 2006 (stock is likely to last until March 2007). Therefore approval of both the 50 mcg and 100 mcg strengths of the reformulated tablets will need to be granted to ensure continuity of supply for the thousands of New Zealanders who need this medicine.

b. Shelf life

The stability data submitted support a maximum shelf life for the unopened product of 24 months stored at or below 25°C.

GSK has made a commitment to perform a formal stability study for three batches of the levothyroxine sodium triturate stored in the proposed packaging for 6 months at 25°C / 60 % RH.

c. Bioequivalence

Bioequivalence with the New Zealand innovator product has not been demonstrated. Instead a bioequivalence study comparing the 100 mcg strength of the European product (currently registered for marketing in Holland, Poland, Czech Republic and Lithuania) and the 100 mcg strength of the reformulated product has been provided.

Although the reference product is different to the currently approved New Zealand product in terms of qualitative and quantitative composition, the bioequivalence study is considered relevant as the reference product was registered and marketed in New Zealand from 08/04/1981 to 08/05/1992. The currently registered Eltroxin formulation was approved in New Zealand in 1992 based on dissolution comparisons with the European formulation (reference product) rather than a bioequivalence study.

The results of the study are considered to be reliable and consistent with published pharmacokinetic data for the medicine.

The bioequivalence study results for levothyroxine (T4) (unadjusted for endogenous concentrations) and tri-iodothyronine (T3) demonstrate that the new formulation (test product) and the European formulation (reference product) are bioequivalent (when bioequivalence is defined as geometric means and 90 % confidence intervals of the geometric mean ratio (test/reference) for AUC and C_{max} within the range 0.8- 1.25 and no significant difference in relation to Tmax).

Given that a single bioequivalence study was submitted testing the 100 mcg strength of the reformulated tablets, a biowaiver is required to support the approval of the 50 mcg strength. The reformulated products do not meet the FDA or WHO criteria for a biowaiver as levothyroxine sodium is considered to have a narrow therapeutic index, levothyroxine sodium fits the BCS Class 3 criteria due to low permeability and the reformulated tablets do not dissolve ≥ 85 % in 15 minutes or less at pH 1.2, 4.5 and 6.8. Furthermore, the 50 mcg and 100 mcg strengths of both the European reference product and Eltroxin tablets currently registered in New Zealand are not direct scales. Therefore, a biowaiver would not normally be granted.

d. Recommendation

Approval of this product under Section 21 of the Medicines Act 1981 for distribution in New Zealand for the requested indications should be considered at a management level as levothyroxine sodium has a narrow therapeutic index and bioequivalence with the New Zealand innovator product has not been established for either strength of the reformulated tablet.

e. Additional comments

The bioavailability of the reformulated tablets in relation to the formulation that is currently marketed in New Zealand is unclear. Therefore, a notification letter is to be sent to health professionals in New Zealand (general practitioners, specialists (including endocrinologists) and pharmacists) early in 2007. The notification letter (see attached) advises of the change in formulation and makes the following recommendations:

- Advise patients that from March 2007 onwards, their Eltroxin tablets may look different.
- Eltroxin tablets, in common with all levothyroxine sodium products, have a narrow therapeutic index and therefore prescribers should be vigilant for symptoms suggestive of adverse reactions or loss of clinical control in patients using the new Eltroxin tablets. Dose adjustments and monitoring of thyroid hormone levels may be necessary.
- Ask patients to promptly report any changes in their clinical condition.

GSK have also provided assurance that the packaging for the new formulation will be labelled accordingly with the words "New Formulation" for the first 6 months of marketing.

Attachments to Evaluation Report

1. Therapeutic Product Database Reports
2. Product formulation and ingredient quality standard details from the dossier
3. Manufacturing process and in process controls
4. Release and shelf life specifications for the finished product
5. Comparative dissolution data comparing the dissolution conditions used for specification and stability testing.
6. Batch analytical data for the finished product
7. Bioequivalence data from the application dossier:
   - Comparative formulation details for European reference and New Zealand innovator products
   - Comparative dissolution data for reference and trial products in both tabular and graphical form
   - Demographic data
   - Randomisation table
   - Tabulated individual and mean concentration vs. time data
   - Graphs of mean plasma profiles in bioequivalence study
   - Tabulated individual and mean pharmacokinetic parameters
   - Investigators' statistical analyses of the pharmacokinetic data
8. Evaluator's check calculations of pharmacokinetic parameters and statistical analyses of bioavailability/bioequivalence data
9. Draft data sheet for the new product.
10. Approved data sheet for the corresponding innovator product as published on Medsafe's web site.
11. A copy of the proposed notification letter for health professionals.
12. Copies of relevant published pharmacokinetic data for the innovator product.
13. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 2000 Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.
14. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research 1997 Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms.
15. Therapeutic Products Directorate, Health Product and Food Branch, Health Canada – Expert Advisory Committee on Bioavailability and Bioequivalence. Record of Proceedings from a teleconference on April 16, 2003.
16. Blakesley V, Awni W, Locke C, Ludden T, Granneman GR, Braverman LE 2004 Are Bioequivalence Studies of Levothyroxine Sodium Formulations in Euthyroid Volunteers Reliable? Thyroid Vol 14, Number 3, pages 191-200.

17. Walter-Sack I, Clanget C, Ding R, Goeggelmann C, Hinke V, Lang M, Pfeilschifter J, Tayrouz Y and Wegscheider K. Assessment of Levothyroxine Sodium Bioavailability. Recommendations for an Improved Methodology Based on the Pooled Analysis of Eight Identically Designed Trials with 396 Drug Exposures. Clinical Pharmacokinetics. 2004; 43 (14): 1037 – 1053.

18. Hennessey JV. Limitations of Current Bioequivalence Standards. Joint Public Meeting on Equivalence of Levothyroxine Sodium Products. Monday, May 23, 2005. Washington, DC. [Power Point Presentation]. Accessed from http://www.fda.gov/cder/meeting/levothyroxinePresentations.htm on 05/12/2005.

19. Expert Report on impurity HDPhDB