Expert Review of Medsafe's pre-licensing assessment and pharmacovigilance activities for a new formulation of Eltroxin® 50 mcg and 100 mcg Tablets

Conducted by the UK Medicines and Healthcare products Regulatory Agency for the New Zealand Ministry of Health

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Executive Summary

In March 2004 GlaxoSmithKline (GSK) submitted a New Medicines Application to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) in support of a new formulation for Eltroxin® 50 mcg and 100 mcg Tablets (NZ "New Eltroxin") to replace the existing product (NZ "Old Eltroxin"). The application was approved and the product was launched in June 2007. Subsequently, the Centre for Adverse Reactions Monitoring (CARM) received an increase in adverse reaction reports associated with the new formulation.

The New Zealand Ministry of Health has commissioned the UK Medicines and Healthcare products Regulatory Agency (MHRA) to provide an independent expert opinion on whether Medsafe applied appropriate regulatory standards when handling the application seeking approval for the new formulation of Eltroxin, and subsequently reacted appropriately to the large volume of adverse events relating to the reformulated product.

This Expert Review contains an evaluation of Medsafe's pre-licensing assessment of the quality and bioequivalence data that were submitted with the New Medicines Application for NZ New Eltroxin and an evaluation of the pharmacovigilance activities. Suggestions are included on future investigations for NZ New Eltroxin and measures that could be taken to reduce the possibility of this situation occurring in the future when patients are transferred to a new brand or a new formulation of a prescription medicine.

Quality

Adverse event reports were received soon after launch – a total of 39 between October 2007 and May 2008 with significant increases following media attention to 1309 reports between June 2008 and October 2008. Given the timing of the reports, soon after product launch, the adverse events are unlikely to be caused by loss of potency arising from stability issues. This is supported by the stability data for the NZ New Eltroxin formulation which showed satisfactory assay and related substances levels in stability studies with no significant trends on storage.

Medsafe's assessment of the quality dossier is considered appropriate at the time of approval. Some suggestions for future investigations have been put forward in the light of this review following subsequently reported adverse events, as summarised below.

The reported adverse events are unlikely to be attributed to any variability in the active substance since a single supplier (Sandoz GmbH) has been used to manufacture all Eltroxin products marketed in New Zealand. Medsafe may wish to confirm which grade of levothyroxine is actually employed and what measures are taken to ensure particle size is adequately controlled on receipt and storage.

The change in formulation excipients coupled with the new [redacted] manufacturing process for NZ New Eltroxin, whilst justifiable from a stability perspective, may have been a contributory factor for the adverse effects. However, no firm conclusion can be drawn. Differences between dissolution profiles of NZ New Eltroxin and the reference formulation NZ 81 Eltroxin (European Eltroxin) at higher pHs (indicative of the fed state) may merit investigation.

The Finished Product Specification of NZ New Eltroxin is satisfactory and complies with standards in place at the time of assessment. Medsafe may wish to review the potency limits in light of recent regulatory action taken by the FDA to tighten potency limits.

Other considerations

NZ New Eltroxin Marketed in Europe: According to the reports provided by Medsafe, the NZ New Eltroxin formulation has been approved in both Germany and Denmark. A review of

the assessment reports of the respective countries may provide additional information to assist Medsafe in their investigation.

GMP Inspection: It is unclear if the adverse effects are related to specific batches of the product. If this is the case, there may be underlying quality concerns with respect to GMP and Medsafe may wish to request the applicant to investigate these.

Bioequivalence

A single fasted biostudy, the design of which was consistent with contemporaneous FDA guidelines, was submitted to support the change in Eltroxin formulation (to NZ New Eltroxin) and demonstrated bioequivalence between formulations. Fed biostudy data were not provided nor advocated by FDA guidelines. However, *in vitro* data suggest that a fed study may have been most sensitive to detect product differences.

Contrary to FDA guidelines no dose-proportionality data were submitted (approval was sought for two dose strengths, 50 and 100 mcg) although *in vitro* data supported a waiver of the requirement for such data. Conversely dose-range scale differences between the NZ New Eltroxin and NZ Old Eltroxin suggest that clinical evaluation of the 50 mcg dose may have been prudent although a dose-proportionality study designed in accordance with FDA guidelines would have been unlikely to preclude approval of the new formulation.

Finally use of the European Eltroxin formulation as reference product in the biostudy is considered questionable given that in the event of product approval patients would be switching between NZ Old Eltroxin and NZ New Eltroxin formulations. However, the difficulties faced by Medsafe in ensuring continued drug supply from the country's single levothyroxine supplier in 2005/6 are recognised.

In conclusion Medsafe's clinical risk:benefit assessment of reformulated NZ New Eltroxin in 2005/6 is considered appropriate and consistent with contemporaneous regulatory standards. Some areas in which a different approach could have been taken have been identified.

Pharmacovigilance

Medsafe have clear systems in place to effectively monitor the safety of medicines and have demonstrated an approach to the pharmacovigilance handling of the Eltroxin issue that was appropriate and that would be consistent with that of many regulatory agencies.

With the benefit of hindsight and a retrospective understanding of the issues, points for consideration have been identified that could possibly strengthen existing procedures.

It is suggested that Medsafe may wish to review the medicines legislation around the requirements for a Risk Management Plan in order to evaluate the role of such a document at the outset of risk assessment prior to the launch of new formulations or chemical entities.

Medsafe may like to investigate the value of employing a statistical tool to aid signal generation and to clarify signal prioritisation. Once the signal criteria are established, there should be a standardised procedure in place for action and communication.

Medsafe may like to evaluate the possibility of more frequent or ad hoc Medicines Adverse Reactions Committee (MARC) meetings to allow real time discussion of key emerging safety issues and to reach agreement on appropriate regulatory action and communication.

Finally, Medsafe may like to review the current Adverse Drug Reaction (ADR) reporting forms so that the forms adequately capture the data required when evaluating the impact of any future brand switch problem.

1 Introduction

In March 2004 GlaxoSmithKline (GSK) submitted a New Medicines Application to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) in support of a new formulation for Eltroxin® 50 mcg and 100 mcg Tablets (NZ "New Eltroxin") to replace the existing product (NZ "Old Eltroxin"). The application was approved and the product was launched in June 2007. Subsequently, the Centre for Adverse Reactions Monitoring (CARM) received an increase in adverse reaction reports associated with the new formulation.

The New Zealand Ministry of Health has commissioned the UK Medicines and Healthcare products Regulatory Agency (MHRA) to provide an independent expert opinion on whether Medsafe applied appropriate regulatory standards when handling the application seeking approval for the new formulation of Eltroxin, and subsequently reacted appropriately to the large volume of adverse events relating to the reformulated product.

This Expert Review contains an evaluation of Medsafe's pre-licensing assessment of the quality and bioequivalence data that were submitted with the New Medicines Application for NZ New Eltroxin (Sections 2 and 3 respectively) and an evaluation of the pharmacovigilance activities (Section 4). Suggestions are included on future investigations for NZ New Eltroxin (Section 5) and measures that could be taken to reduce the possibility of this situation occurring in the future when patients are transferred to a new brand or a new formulation of a prescription medicine (Section 6).

2 Quality review

This section reviews Medsafe's Quality Assessment of the dossier submitted by GSK for NZ New Eltroxin, determines whether appropriate regulatory standards were applied and offers proposals for further investigation.

2.1 Background

GSK has implemented a series of formulation changes for Eltroxin 50 mcg and 100 mcg Tablets resulting in different products being marketed in New Zealand over the years:-

- NZ 81 Eltroxin: marketed between April 1981 and May 1992; this is the same formulation as the currently approved "European Eltroxin" formulation (as marketed in the UK);
- NZ Old Eltroxin: marketed between1992 and June 2007;
- NZ New Eltroxin: marketed from June 2007 to present; according to reports provided by Medsafe, this formulation has been approved in both Germany and Denmark.

Table 2-1 provides a qualitative comparison of the various Eltroxin formulations that have been marketed in New Zealand (see Bioequivalence Review, Section 3 for further discussion).

Table 2-1: Qualitative comparison of New Zealand Eltroxin formulations

Component	NZ 81 Eltroxin (same as European Eltroxin)	NZ Old Eltroxin	NZ New Eltroxin
Active ingredient	Levothyroxine sodium	Levothyroxine sodium	Levothyroxine sodium
Excipients	Magnesium stearate	Magnesium stearate	Magnesium stearate
	Lactose monohydrate	Lactose monohydrate	Microcrystalline cellulose
	Maize starch	Maize starch	Pre-gelatinized maize starch
	Powdered Acacia	Acacia	Purified talc
	Sodium citrate	-	Silicon dioxide (Colloidal anhydrous silica)
	Purified water (removed during processing)	-	-

2.2 Quality dossier (Module 3) evaluation

2.2.1 Active substance

The active substance used to manufacture all the Eltroxin products described in Table 2-1 is sourced from Sandoz GmbH (Schaftenau Plant, Biochemiestrasse 10, Langkampfen, Tyrol, Austria). Therefore the reported adverse events are unlikely to be attributed to any variability in the quality of the active substance. GSK stated that the active substance for NZ New Eltroxin is supplied with reference to a Certificate of Suitability R0-CEP 1998-141-Rev 02; this was omitted from the dossier but its attached for ease of review in Annex 2. Two particle size

grades of levothyroxine sodium (material code 460 187 and 460 132) may be supplied under the CEP as shown below:

Test for particle size distribution by [redacted]

Material code 460 187:

Mean particle size x (50.3)	not more than [redacted]
80%	Particle size between [redacted]

Material code 460 132:

Mean particle size x (50.3)	[redacted]
90% (upper limit)	Particle size between [redacted]

GSK apparently utilise fine [redacted] material with 90% undersize [$D_{0.9}$] particle size [redacted] however this information is not declared in the manufacturer's active substance specification. Different grades might influence the homogeneity of the granulation and hence the final quality attributes of the finished product. Medsafe may wish to confirm which grade of levothyroxine is employed and what control measures are taken to ensure that the particle size is controlled on receipt and on storage.

MHRA conclusion: The reported adverse events are unlikely to be attributed to any variability in the quality of the active substance since a single supplier (Sandoz GmbH) has been used to manufacture all the Eltroxin products marketed in New Zealand. As particle size is a critical attribute, Medsafe may wish to confirm which grade of levothyroxine is actually employed and what control measures are in place to ensure the particle size is adequately controlled on receipt and on storage.

2.2.2 Pharmaceutical development

GSK states that the rationale for the reformulation to NZ New Eltroxin was to improve product stability (levothyroxine is unstable in the presence of light, heat, air and humidity). A further driver may have been the desire to rationalise global formulations since the proposed NZ New Eltroxin product had (according to Medsafe) already been approved in Germany and Denmark. The reformulation to NZ New Eltroxin offers the following advantages:

- NZ Old Eltroxin is manufactured by [redacted]
- microcrystalline cellulose introduced in the NZ New Eltroxin acts as a [redacted] which might enhance stability;
- [redacted] is a more efficient manufacturing process than [redacted]

The [redacted] formulation of NZ New Eltroxin required new functional excipients (fillers, disintegrants and lubrication system). i.e. the excipients used for NZ Old Eltroxin did not have the required properties. Sample Certificates of Analysis for the new excipients were not provided. However, these are extensively used by the pharmaceutical industry for solid dosage forms and acceptable standards were applied.

Appropriate interaction studies were conducted for the active substance, excipients and packaging confirming their suitability for the new formulation. Long term stability data for finished product (3 production scale batches for each strength stored at 25°C/60%RH for up to 2 years) demonstrated a satisfactory stability profile for the reformulated product with no apparent trends in the data.

The dissolution test is in line with Test 1 given in the relevant USP tablet monograph, which includes the use of a surfactant.

Medsafe questioned the addition of the surfactant SDS (sodium dodecyl sulphate) added to the [redacted] dissolution medium [redacted] GSK's explanation that the addition of SDS had no significant influence on levothyroxine dissolution rates and was added to prevent levothyroxine adsorption on the apparatus filters was accepted. On review of the pharmaceutical development and response data provided, suitable evidence to justify the addition of SDS to the dissolution medium has been provided. However, it is not clear why the surfactant was not added to all the dissolution media (pHs 1.0, 4.5 and 6.8).

Dissolution profiles of NZ New Eltroxin and the reference product NZ 81 Eltroxin (European Eltroxin) used in the bioequivalence studies are presented in the Bioequivalence Review, Section 3. Comparative dissolution profiles show dissolution similarity between both strengths of the test and reference products under acidic conditions. However, it is noted that dissolution similarity between test and reference products is not seen at pHs 4.5 and 6.8. In the interests of better understanding of the drug product, Medsafe may consider requesting further information and clarification concerning the biopharmaceutical effect of these differences. This is because there is a concern that in some cases a reduced bioavailability could be possible in patients with a high gastric pH in the fasted stated. It is known that the solubility of levothyroxine sodium is pH dependant, with better solubility seen in acidic or alkaline conditions.

MHRA conclusion: The rationale for reformulating to NZ New Eltroxin to enable manufacture by [redacted] process is, at face value, scientifically sound. Stability data provided in the excipient compatibility and finished product studies were entirety satisfactory and no significant trends were observed in the data. The dissolution test is considered acceptable, but differences seen between test and reference products at higher pHs raise a concern that in some cases, a reduced bioavailability could be possible in patients with a high gastric pH, in the fasted stated. This may merit further investigation.

2.2.3 Manufacturing process validation

It is notable that the [redacted] method, as applied to NZ Old Eltroxin, is more commonly used by solid dosage manufacturers, particularly if lacking expertise in [redacted] That GSK has the appropriate know-how would be apparent from the GMP inspection of the manufacturing site. The [redacted] process outlined for NZ New Eltroxin is considered acceptable. Extensive process validation data were generated for production-scale batches aimed at demonstrating homogeneity of the blending and compression processes. Satisfactory data were presented for: 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 with in-process controls: uniformity of weight, crushing strength, disintegration and friability. The process validation studies complied with Note for Guidance on Process Validation (CPMP/QWP/848/96).

MHRA conclusion: The change in the manufacturing method from [redacted] (NZ Old Eltroxin) to [redacted] (NZ New Eltroxin) was fully validated achieving homogeneity throughout the process and a robust product. Whilst justifiable from a stability perspective, the change in formulation excipients coupled with the new [redacted] process may (with hindsight) have contributed to the adverse effects. However, no firm conclusions can be drawn.

2.2.4 Finished Product Specification

The scope of the Finished Product Specification (Annex 1) is considered in line with current regulatory requirements and in line with the relevant BP monograph and is considered acceptable.

The release and shelf life Finished Product Specification of the NZ New Eltroxin is considered satisfactory with appropriate controls applied including assay, dissolution, content uniformity and related substances (Annex 1). The impurity profile of the NZ New Eltroxin lists additional related substances compared to NZ Old Eltroxin. These impurities came to light following the introduction of an improved analytical detection method. It is noteworthy that with the exception of HDPhDB acid (4-[(4-hydroxy-3,5-diiodophenyl)oxy]-3,5-diiodobenzoic acid), the named impurities comply with ICH Guidelines (ICH Topic Q 3 B (R2) [NfG on Impurities in New Drug Products (CPMP/ICH/2738/99)]). HDPhDB acid (shelf-life control limit: NMT 2.5%) being an existing impurity is considered toxicologically qualified. Since the impurity profile of NZ New Eltroxin is unchanged compared to previous formulations, this is not implicated in the adverse events reported.

However, it should be noted that the relevant USP monograph has recently been revised to tighten the potency limits from 90-110% to 95-105% at shelf life. This is due to FDA regulatory action to mandate the tighter limits, following safety concerns by health care professionals and patients that the potency of the drug may deteriorate prior to its expiration date.

It should be noted that the BP monograph is under review but no decision regarding potency limits has been made. It is acknowledged that tightening the limits would have an impact on the shelf life of the drug product and hence marketability and availability of the drug product.

MHRA conclusion: Acceptable and justified control limits for all tests listed in the Finished Product Specification of the NZ New Eltroxin have been applied. Medsafe may wish to review the potency limits in light of recent regulatory action taken by the FDA.

2.2.5 Other considerations

NZ New Eltroxin Marketed in Europe: According to the reports provided by Medsafe, the NZ New Eltroxin formulation has been approved in both Germany and Denmark. A review of the assessment reports of the respective countries may provide additional information to assist Medsafe in their investigation.

GMP Inspection: It is unclear if the adverse effects are related to specific batches of the product. If this is the case, there may be underlying quality concerns with respect to GMP and Medsafe may wish to request the applicant to investigate these.

3 Bioequivalence review

This section reviews Medsafe's assessment of the bioequivalence data submitted by GSK for NZ New Eltroxin, determines whether appropriate regulatory standards were applied and offers proposals for further investigation.

3.1 Summary of GSK data and Medsafe assessment

GSK submitted a single open-label, single-dose (6 x 100 mcg tablets), two-treatment, two-sequence bioequivalence study comparing test (NZ New Eltroxin) versus reference (European Eltroxin) formulations in 36 healthy volunteers in the fasted state. This single bioequivalence study in conjunction with the pharmaceutical data was intended to support both proposed dose strengths (50 mcg and 100 mcg) of the reformulated NZ New Eltroxin.

Standard pharmacokinetic (PK) parameters were calculated for (uncorrected) total T4 and total T3 (per FDA 2000 guidelines, the primary variables for determination of bioavailability) and analysis of variance was performed for log-transformed AUC_{0-t} and C_{max}. Geometric means and 90% confidence intervals of the geometric mean ratio (test / reference) were presented. PK parameters were also derived and statistical analyses performed for (uncorrected) free T4 and free T3. Subsequently, in response to questions from Medsafe, GSK also derived corrected data for total T4 and free 4, with correction by subtraction of the baseline value for each biochemical variable. The results of the various bioavailability comparisons are summarised below in Table 3-1.

Table 3-1: Summary table of test/reference geometric mean ratios (90% confidence intervals) for key pharmacokinetic parameters

Total T4	C_{max}	AUC_{0-t}
Non-corrected	94% (91-97%)	98% (96-101%)
Corrected	88% (82-95%)	96% (88-104%)
Total T3	C_{max}	AUC_{0-t}
Non-corrected	102% (96-108%)	99% (94-104%)
Corrected	n/a	n/a
free T4	C_{max}	AUC_{0-t}
Non-corrected	95% (91-98%)	97% (95-100%)
Corrected	90% (83-97%)	91% (83-100%)
free T3	C_{max}	AUC_{0-t}
Non-corrected	101% (97-106%)	100% (97-103%)
Corrected	n/a	n/a

On the basis of the above data, and GSK's responses to other key questions raised by Medsafe (discussed further under MHRA assessment), the clinical submission package was eventually considered approvable.

3.2 MHRA assessment of bioequivalence study and of Medsafe's review of the data

Key aspects of the data and the MHRA's consideration of Medsafe's assessment (where relevant) are presented below.

3.2.1 Study design

The study was designed in accordance with contemporaneous FDA guidelines[1] for a single-dose levothyroxine bioavailability study. Key aspects of study methodology recommended by FDA and adhered to within the study were assessment under fasting conditions, use of healthy volunteers, Total T4 and Total T3 as primary variables, non-correction for baseline endogenous substance levels and administration of 600 mcg supratherapeutic drug doses.

MHRA conclusion: Medsafe's assessment that the overall study design was in keeping with contemporary regulatory standards is considered appropriate.

3.2.2 Food effect

The single biostudy submitted was conducted under fasting conditions, as advocated by existing FDA guidance. Given a known food effect for levothyroxine, Medsafe queried the absence of fed data, subsequently accepting GSK's argument that the biostudy was conducted in accordance with guidelines and that the approved posology recommended tablet intake on an empty stomach.

MHRA conclusion: The rationale for provision of fasting data alone, in particular adherence to existing accepted FDA guidelines, may be considered appropriate. However, given that a food effect of up to approximately 50%[2] reduction in absorption is reported for levothyroxine, it may have been desirable to request bioavailability data in the fed state to provide assurance that both test and reference formulations were similarly affected by food intake.

This is considered supported by the available *in vitro* dissolution data. Dissolution profiles between test and reference formulations were most similar at pH 1 (i.e., under *in vitro* conditions most analogous to the fasted state) (Figure 1), where an f2 similarity factor greater than 50 was reported. Conversely, at pH 4.5 (i.e. under *in vitro* conditions similar to those seen with food intake)[3] and pH 6.8 (Figures 2 & 3), the dissolution curves clearly cannot be considered equivalent (f2 similarity factor values <50). Therefore, it is plausible that a fed study would have been more likely to differentiate between the test and reference formulations.

Overall, Medsafe's consideration of this issue may be considered consistent with contemporaneous guidelines. However, a valid rationale for requiring fed data existed and a fed study may have been more sensitive to detect product differences than a fasted study *in vivo*.

[1] FDA Guidance for Industry 2000: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing (Presented in Annex 3)

[2] Bach-Huynh et al, J Clin Endocrin Metab 2009 Jul 7. [Epub ahead of print] (Presented in Annex 4)

[3] Pearson DE & Hutton D. Structure and function on the stomach. In: Sadler MJ, Strain JJ, Caballero B (eds). Encyclopedia of Human Nutrition. Academic Press;1999;pp929-938 (Presented in Annex 5)

Figure 1. Dissolution Profiles for Eltroxin European Formulation and Reformulated Tablets, 50 mcg in [redacted] + 0.2 % SDS (Sodium Dodecyl Sulphate)

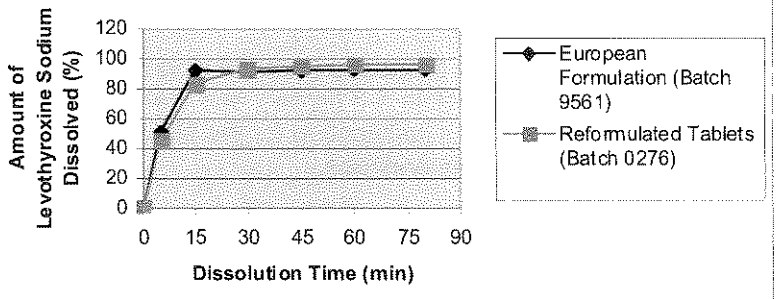


Figure 2. Dissolution Profiles for Eltroxin European Formulation and Reformulated Tablets, 50 mcg in Acetate Buffer (pH 4.5)

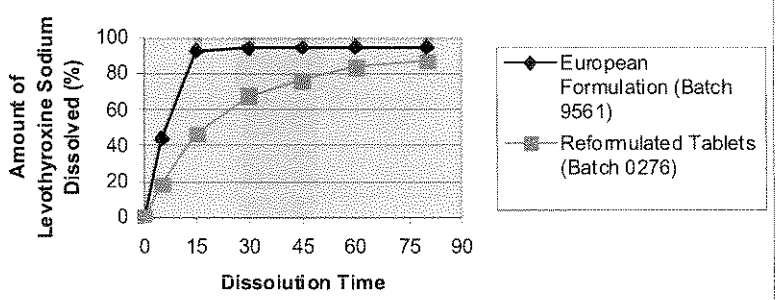
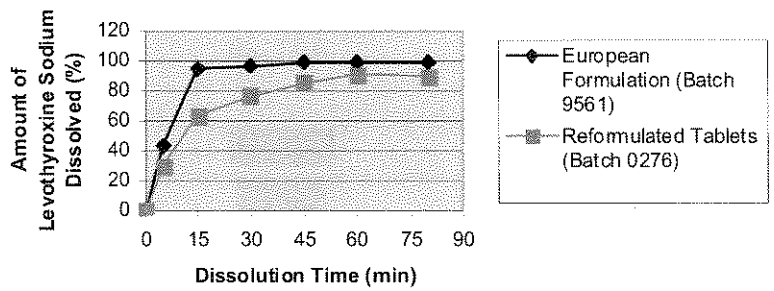


Figure 3. Dissolution Profiles for Eltroxin European Formulation and Reformulated Tablets, 50 mcg in Phosphate Buffer (pH 6.8)



3.2.3 Waiver of the requirement for a biostudy evaluating the 50 mcg presentation of the test formulation

The single biostudy submitted compared 100 mcg presentations of test and reference formulations. However, GSK also sought approval for a lower dose 50 mcg presentation. Existing FDA guidance recommended that a dose-proportionality study of the test formulation be conducted over the range of presentations. This would require comparing the bioavailability

of 600 mcg doses of the test formulation administered as six 100 mcg tablets versus twelve 50 mcg tablets.

Adopting a different approach to this issue, Medsafe queried the lack of a test versus reference 50 mcg tablet study as the reference 50 mcg and 100 mcg tablets were not direct scaled versions of one another (see Table 3-2 below).

Medsafe subsequently accepted GSK's response that the proposed (test) 50 mcg and 100 mcg tablets were direct pharmaceutical scales (see Table 3-3 below), and that they had very similar dissolution profiles at pH 1, 4.5 and 6.8. GSK's justification for the biowaiver is considered to be in line with current EU guidance on bioequivalence.

Table 3-2: Composition of European Eltroxin formulation (or NZ 81 Eltroxin) Bioequivalence Reference Product

Composition	European Eltroxin (mg/tablet)	
	50 mcg	100 mcg
Levothyroxine sodium	0.056	0.112
Lactose monohydrate	[redacted]	[redacted]
Maize starch	[redacted]	[redacted]
Sodium citrate	[redacted]	[redacted]
Acacia powder, spray dried	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]
Total	[redacted]	[redacted]

The two strengths are not direct scaled versions of one another.

Table 3-3: Composition of NZ New Eltroxin formulation Bioequivalence Test Product

Composition	NZ New Eltroxin (mg/tablet)	
	50 mcg	100 mcg
Triturate Levothyroxine sodium	0.05563	0.11126
Cellulose, microcrystalline	[redacted]	[redacted]
Other components Cellulose, microcrystalline	[redacted]	[redacted]
Starch, pregelatinised	[redacted]	[redacted]
Talc	[redacted]	[redacted]
Silica, colloidal anhydrous	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]
Total	[redacted]	[redacted]

The two strengths are direct scaled versions of one another.

MHRA conclusion: The rationale for non-performance of a study evaluating the 50 mcg tablet strength is coherent, and one routinely used (and accepted) to justify biowaivers of certain table strengths. On that basis the approach taken by Medsafe may be considered appropriate. Conversely it may be argued that FDA guidelines were not strictly adhered to since there are scale differences between test and reference 50 mcg and 100 mcg products. Thus a 50 mcg strength test/reference study may have been prudent since patients would ultimately 'switch' between, and not only within, formulations. However, it should also be stated that had GSK performed the test/test dose-proportionality study recommended by FDA guidelines it is very plausible based on *in vitro* data that bioequivalence would have been demonstrated.

Overall, the approach taken by Medsafe can be considered appropriate, although an alternative approach would have been justified.

3.2.4 Use of European Eltroxin as the reference formulation in the biostudy

The use of European Eltroxin as the comparator in the biostudy was queried by Medsafe. The argument put forward by GSK in their response and accepted by Medsafe was that the European formulation was identical to that approved in New Zealand from 1981 to 1992 (NZ 81 Eltroxin) and that, as the formulation change in New Zealand in 1992 (to NZ Old Eltroxin) had been based on *in vitro* data alone, the EU formulation was therefore the 'preferred' reference product. Further to recent correspondence between MHRA and Medsafe, it appears that a complicating issue at the time was that GSK were ceasing production of the NZ Old Eltroxin formulation which was the only registered levothyroxine product available in the country in 2005/6.

MHRA conclusion: Given the inevitable switching between the formulations NZ Old Eltroxin and NZ New Eltroxin amongst patients on existing levothyroxine treatment it is clear that a biostudy comparing these two formulations would have been the most appropriate study to conduct/request. GSK's explanation for using the European Eltroxin formulation as a biostudy comparator is not considered valid. However, in mitigation it is recognised that Medsafe had to act to ensure continued product availability and also that as New Zealand is a relatively small pharmaceutical market in global terms the agency's negotiation with GSK may have been difficult.

3.3 Overall MHRA conclusion on biostudy

The single fasted biostudy submitted by GSK to support the change in formulation to NZ New Eltroxin was consistent with contemporaneous FDA guidelines. Of note the latter did not advocate provision of fed study data. Nonetheless, fed biostudy data may have been desirable with *in vitro* data suggesting that a fed study may have been more sensitive to detect product differences.

The FDA guidelines did advocate provision of a dose-proportionality study, which was not provided by GSK. Medsafe accepted non-provision of data for the 50 mcg tablet on grounds that are widely used to justify dose strength waivers. Although this decision may be disputed on the grounds of scale differences between 50 mcg and 50 mcg new and old (NZ 81 Eltroxin) formulations it is noted that had a dose-proportionality study been conducted per FDA guidelines it would have been unlikely to preclude approval of the new formulation.

Regarding the use of the European Eltroxin formulation as reference product in the biostudy, this is considered questionable. However, the difficulties faced by the agency in ensuring continued drug supply from the country's single levothyroxine supplier at that time are recognised.

In conclusion Medsafe's clinical risk:benefit assessment of reformulated NZ New Eltroxin conducted in 2005/6 is considered appropriate, although some areas in which a different approach could have been taken have been identified.

4 Pharmacovigilance review

4.1 Risk minimisation prior to the launch of the new formulation of Eltroxin

At the time of the introduction of the NZ New Eltroxin to the market, it was recognised by Medsafe and GSK that due to pharmacokinetic variability between patients there may be some patients who could experience a change in clinical effect when switched to different drug product brands or formulations. This advice along with the recommendation for 'dose adjustments and monitoring of thyroid hormone level' was communicated to prescribers in a Dear Healthcare Professional communication from GSK.

As part of the risk minimisation measures for the new formulation two further letters were sent by GSK to healthcare professionals (in June 2007 and June 2008) detailing the new tablet appearance and dosing instructions required for those patients who required 25 mcg, 75 mcg or 125 mcg doses.

It appears that, for several reasons, some healthcare professionals did not receive the initial and possibly the subsequent communications. This resulted in the Minister of Health receiving several complaints that information had not been issued. It remains largely unclear why some healthcare professionals reported a lack of information necessary to inform their clinical decision making.

MHRA conclusion

Medsafe ensured that GSK issued communications to healthcare professionals about the launch of NZ New Eltroxin. However, the Dear Healthcare Professional communications representing the first risk minimisation opportunity could have been strengthened. The advice to monitor thyroid hormone levels and adjust dose is one of the key messages and this could have been given greater prominence.

Letters sent by the pharmaceutical industry are an appropriate and widely used means of getting messages to healthcare professionals, however it is accepted that not all healthcare professionals will receive or take note of these communications. No one form of communication can be expected to reach everyone.

Given the differences between the old and new formulations (different excipients, change in tablet size and colour, lack of score line leading to the need for alternate day dosing), it may have been appropriate, prior to the launch of NZ New Eltroxin, for Medsafe to have considered what additional communications may have been necessary. Options could have included: use of the Medsafe website; early engagement with physicians and patient support groups to gather any feedback or concerns prior to the new formulation launch; formulary advice updates to provide information about switching and recommendations for monitoring and dose adjustment along with similar advice targeted at patients that pharmacists could distribute at the launch of the new formulation and a 'flash' on the packaging to highlight the new formulation and advice for patients to discuss the changes with their doctor.

It is possible that a multi-stranded communication strategy could have prevented some of the loss of public confidence by better informing prescribers and patients of what to expect with the new product.

Currently the medicines legislation in New Zealand does not require submission of a Risk Management Plan as part of the dossier for a new licence application or a change to an existing medicine. Risk Management Plans provide a framework for careful prospective consideration and documentation of all risk minimisation activities required for safe use of a new product.

4.2 Adverse events associated with the new formulation of Eltroxin

Prior to the launch of the NZ New Eltroxin and since 1973, the Centre for Adverse Reactions Monitoring (CARM) had received 14 adverse drug reaction reports where thyroxine was the suspect drug. The first adverse event report associated with the use of the NZ New Eltroxin was received in October 2007. A total of 39 reports were received between October 2007 and May 2008.

This issue was first highlighted at the Medicines Adverse Reactions Committee (MARC) meeting in May 2008 and was stated to be an emerging issue. MARC was provided with very high level information on the nature of the reports received in the Quarterly CARM report and also informed of the communications issued by the Marketing Authorisation Holder. MARC was informed that CARM would continue to investigate the issue in association with Medsafe and report back to MARC as necessary.

In June 2008 there was significant media attention and an increase in the number of reports in association with NZ New Eltroxin such that 1309 reports were received between June 2008 and October 2008. The absolute impact of the media activity is uncertain but from the pattern of reporting it can be estimated to be significant.

The largest number of reports was received in September 2008 probably in response to lobbying by pressure groups. Further to this there was the development by a healthcare professional of a "tick box" Adverse Drug Reaction (ADR) form which was given to patients to complete encouraging them to send it to CARM. The form that was distributed contained a list of reactions that may have been experienced by patients and it is feasible that such activity not only elicited reporting but may have "suggested' symptoms to patients. It is believed that the "tick box" reports contributed to a significant proportion of reports received, however since the form was posted on the internet and sent to CARM independently by reporters the true impact is difficult to ascertain.

The adverse event reports prior to the media event were described as mostly involving symptoms that could be attributed to thyroid dysfunction. After the media attention the number of reports concerned with eye symptoms increased. There was also an increase in reporting of events that could be related to an allergic reaction. The adverse events reported were largely subjective with extensive narrative describing symptoms from several different organ classes. The adverse event reports largely impacted on the quality of life of the patients who sent in the reports.

Hypothyroid symptoms accounted for 53% of all reports received. In 92 reports patients reported improvement on discontinuing the new formulation especially in those patients reporting hypersensitivity and GI symptoms.

After the media attention in June 2008 there was a significant rise in the number of reports describing the following events: alopecia (42), arthralgia (108), confusion (114), depression (151), headache (485), hypertension (45), lethargy (210), memory loss (84), palpitations (126), myalgia (190), weight increase (205).

Of the serious adverse events, 5 of the 8 resulting in hospitalisation described symptoms that could be attributed to the thyrotoxic state. The occurrence of excess levels of thyroxine in some cases may possibly have been related to confusion with the dosing regimen of the NZ New Eltroxin, patients taking a mixture of the two formulations, patients switching between brands frequently and self adjustment of Eltroxin dose with inadequate monitoring of thyroid function.

However, the initial investigation by Medsafe concluded that patients who switched to alternate day dosing did not experience a disproportionate increase in reports of suspected ADRs. For example, the CARM report shows that of the 451 reports received up until the end

of August that included information on dose, 82% were from patients taking whole tablets daily as opposed to a combination regimen. Therefore, only 18% of the total number of adverse drug reaction reports could have been attributed to difficulties in compliance with the alternate day dosing regimen.

An alternative brand was introduced to the market in November 2008. It is noted that once the alternative brand became available the number of reports received declined, however, the lobbying by pressure groups also appeared to have decreased at this time and it is not clear how these two factors influenced reporting. However, until February 2009 the reporting rate of adverse events was still greater than prior to the launch of the NZ New Eltroxin.

MHRA conclusion

There appears to be no clear single reason why so many adverse events associated with Eltroxin were reported to CARM between October 2007 and October 2008.

There are several possible explanations all of which may have contributed:

- A number of healthcare professionals reported they did not receive the communications advising to monitor thyroid function and adjust the dose of Eltroxin as necessary and therefore ADRs relating to inappropriate dosing may have occurred.
- The new formulation was markedly different in appearance to the old formulation and a scored 50 mcg tablet was not available leading to the potential for alternate day dosing errors for patients prescribed 75 and 125 mcg doses.
- There was an intense period of media interest and lobbying for ADR reports to be sent to CARM. The impact of the 'tick box' form for Eltroxin ADRs cannot be adequately assessed unless the reports can be analysed to try to determine how many were prompted by the form posted on the internet.
- There was a misinterpretation of the new formulation by some healthcare professionals and some members of the public in New Zealand who may have erroneously believed that the new formulation was generic (which may have led to negative perceptions in some cases).

4.3 Signal detection/evaluation

The first adverse reaction associated with the new formulation of Eltroxin was received in October 2007. Between October 2007 and May 2008 a total of 39 reports were received, which equates to an average of approximately 5 reports per month. Given that only 14 reports associated with thyroxine had been received since 1973 it is queried at what point the significant increase in the rate of reporting of adverse events associated with Eltroxin could and should have been raised as a signal.

We are aware that Medsafe and CARM have regular weekly meetings to discuss reports received by CARM. However, it is not clear what other procedures are in place regarding signal detection and whether any statistical tools CARM and Medsafe use to detect an increasing frequency of a suspected ADR (eg disproportionality analysis which is used to determine whether the number of reports received for a particular drug or drug/reaction combination are greater than would be expected).

From the data and information presented to us it is unclear at what point the accumulating reports with the NZ New Eltroxin were first considered by either CARM or Medsafe to be an emerging signal and what priority was given to the further review of this potential signal/issue.

The emerging issue with the new Eltroxin formulation was first presented to the MARC in May 2008. MARC was informed that the reports received described diverse reactions, some suggesting a change in therapeutic effect, while others described a range of apparently

unrelated events and that the problems appeared to have resolved when the patients returned to their previous formulation. By May 2008, 39 adverse event reports had been received by CARM although only 13 were presented at the May 2008 meeting of the MARC. MARC currently meets quarterly and it is unclear how Medsafe could/would seek independent expert advice on important safety issues outside these times.

MHRA conclusion

Medsafe has a well established interaction with CARM over the review and analysis of suspected ADR reports. Real-time monitoring of emerging safety data is extremely important in order to detect potential safety issues in a timely manner. In this respect it is essential to ensure that review of emerging safety data including ADR reports is systematic and conducted on a regular basis. There needs to be agreed, clear, pre-defined criteria that would trigger a signal and lead to the review of reports and consideration of possible regulatory action in accordance with agreed timelines which are proportionate to the risk.

The timescale for evaluation of an emerging safety issue needs to reflect amongst other things the strength of the evidence and also the public health impact of the issue. However, in situations like this where the scale of the public health issue was given gravitas by the public perception there needs to be the capacity to react to the changing/emerging picture and to re-visit the original priority to determine whether this still accurately reflects the current situation.

The ability to seek timely independent expert advice is key to effective risk management. The possibility of more frequent or ad hoc MARC meetings for any similar emerging safety issues should be considered. The ability to seek the advice of an independent expert committee in a timely manner should help to gain the confidence and trust of the public and healthcare professionals that all appropriate and necessary action is being taken with regards to an emerging safety issue.

4.4 Risk management

In June 2008, following consultation with specialist endocrinologists, Medsafe issued advice to healthcare professionals to monitor patients and adjust the dose of the new formulation of Eltroxin if necessary.

In addition, an article was published in the Best Practices Journal (August 2008) providing further information on the Eltroxin formulation change. Information published in the journal encouraged reporters to include a greater depth of data with any ADR report. Healthcare professionals were asked to provide pre and post formulation changes in thyroid function tests, information about the dose change and timing of administration, confirmation that the patient was not splitting the tablets and the date the patient was changed to the new formulation. Unfortunately, this attempt at improving the quality of data in the ADR reports met with limited success.

MHRA conclusion

The communication issued by Medsafe in June 2008 coupled with the communication in the Best Practices Journal was a valuable way to ensure that healthcare professionals were informed about the issue and provided with information to support their prescribing decisions and discussions with patients. The communication could also have emphasised Medsafe's commitment to real-time monitoring of emerging safety data.

Proactive and effective communication in the early stages of an emerging issue and continued and regular updates are useful in managing issues where there is significant public concern.

The media have great potential influence on the public's perception of an issue and it is important that they are provided with the necessary facts and interpretation to maximise the

opportunity for a balanced report. It is unclear what, if any, engagement with experts in the field of media and public relations was undertaken at the peak time of media interest. Also a timely media appearance by a member of the agency detailing the agency's action plan for handling the issue may have helped maintain public confidence at a time when there was negative media attention around the product.

5 Suggestions for future investigations / measures for Eltroxin / levothyroxine

5.1 Quality

1. Medsafe may wish to confirm which particle size grade of levothyroxine is employed and what control measures are taken to ensure the particle size is adequately controlled on receipt and on storage.
2. The dissolution test is considered acceptable, but differences seen between test and reference products at higher pHs raise a concern that in some cases, a reduced bioavailability could be possible in patients with a high gastric pH, in the fasted state. This may merit further investigation.
3. *NZ New Eltroxin Marketed in Europe:* According to the reports provided by Medsafe, the NZ New Eltroxin formulation has been approved in both Germany and Denmark. A review of the assessment reports of the respective countries may provide additional information to assist Medsafe in their investigation.
4. *GMP Inspection:* It is unclear if the adverse effects are related to specific batches of the product. If this is the case, there may be underlying quality concerns with respect to GMP and Medsafe may wish to request the applicant to investigate these.
5. The potency limits may be reviewed in light of recent FDA action, although not related to stability.

5.2 Bioequivalence

1. It is suggested that the currently available data (for TT4 PK parameters) be reanalysed with TT4 incorporated as a covariate in the statistical model in accordance with Walter-Sack et al's publication[4] which indicated that this approach could substantially reduce the dependency of TT4 on age, season and thyroid volume and also reduce residual variability. Given the requisite length of washout periods in thyroxine studies (approximately 5 weeks in the Eltroxin biostudy) such an approach appears particularly relevant. It may simply be that this approach increases the reliability of the point estimates previously observed. However, in view of the slightly lesser bioavailability of test versus reference formulations noted in the baseline-subtraction corrected analyses, the results of this alternative analytical approach would be of interest.

5.3 Future measures to reduce adverse incidents arising from new levothyroxine / Eltroxin formulations

1. *Instructions for administration:* Given the known food effect on the bioavailability of levothyroxine, it may now be prudent to review the clarity and suitability of current advice to physicians and patients in the drug product literature, regarding administration and avoiding a risk of a food interaction. This could be supported by appropriate readability studies.
2. *Levothyroxine stability issue*: Levothyroxine sodium drug products are known to degrade on storage, in acknowledging this shelf life assay limits are typically 90-110% (see BP 2009 monograph).

   However, it should be noted that the FDA is now mandating that levothyroxine sodium drug products have tightened potency shelf life specifications of 95% to 105%, following

[4] Walter-Sack et al, Clin Pharmacokinet 2004;43(14):1037-1053 (Presented in Annex 6)

concerns by healthcare professionals and patients that the potency of the drug may deteriorate prior to its expiration date. The USP monograph has recently been revised with assay limits of 95-105%.

The relevant BP Expert Advisory Group is currently reviewing the tablet monograph for Levothyroxine Tablets BP and is considering tightening the upper assay limit from 110% to 105%.

It is suggested that Medsafe may wish to review the required potency limits.

5.4 Pharmacovigilance

1. It is considered important to investigate fully the reasons why healthcare professionals did not receive information prior to the introduction of the new formulation of Eltroxin to the market.
2. It is considered important that GSK is approached to discuss the possibility of introducing a 25 mcg tablet of Eltroxin to the market especially in view of the serious adverse events associated with the hyperthyroid state and possible contribution to these of alternate day dosing confusion.

6 Suggestions for future measures concerning introduction of new brands and formulations

This section considers measures that could be taken to reduce the possibility of the situation that arose with NZ New Eltroxin occurring in the future when patients are transferred to a new brand or a new formulation of a prescription medicine.

6.1 Quality

The particle size grade of the active substance used and whether it is micronized might be critical factors in tablet formulations. Suitable control measures should be in place to ensure the particle size is adequately controlled on receipt and on storage.

Dissolution profiles of test and reference products at ranges of pHs should be known. This arises from a concern that in some cases, reduced bioavailability could be possible in patients with a high gastric pH, in the fasted state.

6.2 Measures for future bioequivalence studies

6.2.1 Critical dose / narrow therapeutic index drugs

Although there is no consensus definition of the drugs which may fall into these categories several drugs including thyroxine have been discussed in these terms. For such drugs it may be prudent to require a more substantial level of clinical evidence to demonstrate equivalence between formulations, to allow less extrapolation from the pharmaceutical data and to consider worst case scenarios irrespective of Summary of Product Characteristics (SPC) recommendations / warnings such as intake on an empty stomach. In the case of Eltroxin a biostudy comparing test and reference 50 mcg formulations and fed biostudy data would have been of interest for these reasons.

6.2.2 Reference product

It is important that formulations between which patients will switch in the post-market experience are those which are directly compared in biostudies. By way of illustration consider three drug formulations, A, B and C. A and B are bioequivalent, with a B:A point estimate ratio for AUC of 0.8. B and C are bioequivalent with a C:B point estimate ratio for AUC of 0.8. However C and A are clearly non-equivalent with C providing approximately 36% less drug exposure than A.

6.3 Pharmacovigilance

Given the history of public concern over brand switches in New Zealand, it is suggested that Medsafe can anticipate a similar problem in the future when a new formulation or brand of a prescription product with a narrow therapeutic index is to be launched and prepare a strategy to deal with this before the product is launched.

Medsafe may wish to consider engagement with relevant patient and professional groups early in the approval process to obtain feedback as to the feasibility and practicality of proposed risk minimisation measures.

Proactive effective communication emphasising the recommendations for prescribers is key to risk management and should be initiated as early as possible. Involvement of key professional bodies and patient groups on the content and means of such communications should help increase the effectiveness of such communications.

Timely formulary updates, patient information leaflet updates, flashes on new packs of medicine highlighting the changes, and proactive press releases on the Medsafe website could all help to manage such situations in future.

Currently the medicines legislation in New Zealand does not require submission of a Risk Management Plan as part of the dossier for a new licence application or a change to an existing medicine. Risk Management Plans provide a framework for structured discussion with pharmaceutical companies about management of any known or possible risks.

The ability for real-time monitoring of emerging safety data and the capacity to seek timely expert advice is key to effective pharmacovigilance. Medsafe and CARM may wish to consider the feasibility and usefulness of formal statistical tools to aid signal detection. It may also be appropriate to investigate the possibility of a risk based approach to signal detection with more frequent analysis of adverse event reports associated with a new brand or formulation to enable early detection of any evolving problems.

MARC currently meets quarterly and it is unclear how Medsafe seeks independent expert advice on important safety issues outside these times. The possibility of more frequent MARC meetings when an emerging safety issue is detected may be considered. The ability to seek advice from an independent expert committee in a timely manner may help to gain the confidence and trust of the public and healthcare professionals that all appropriate and necessary action is being taken with regards to an emerging safety issue.

Medsafe may wish to strengthen the current pharmacovigilance provisions by considering the following:

1. A review of the medicines legislation around the requirements for a Risk Management Plan
2. Introduction of a statistical tool to aid signal generation and agreement between CARM and MARC of clear predefined criteria for signals and also introduction of a clear consistent approach to signal prioritisation.
3. The possibility of more frequent or ad hoc MARC meetings to allow real time discussion of key emerging safety issues and to reach agreement on appropriate regulatory action and communication.
4. A review of the current ADR reporting forms so that the forms adequately capture the data required when anticipating the impact of any future brand switch problem.

Annex 1: Finished product specification (shelf life) for NZ Old Eltroxin and NZ New Eltroxin

Extracted from Medsafe website: http://www.medsafe.govt.nz/hot/Alerts/EltroxinInfo.asp

Test	Acceptance criteria		Comment
	Old formulation	**New formulation**	
Description	50 mcg tablet: A white, ¼", biconvex tablet, with a bisecting breakline on one face and "50" inscribed above the breakline. The othe face is plain.	50 mcg tablet: White to off-white, round, biconvex tablets imprinted GS 11E on one face and 50 on the other.	Standard requirement for pharmaceutical products.
	100 mcg tablet: A yellow, ¼", biconvex tablet, with a bisecting breakline on one face and "100" inscribed above the breakline. The othe face is plain.	100 mcg tablet: White to off-white, round, biconvex tablets imprinted GS 21C on one face and 100 on the other.	
Identification of levothyroxine sodium			
By HPLC	No specification	The retention time of the principal peak in the sample chromatogram corresponds with that of the principal peak in the levothyroxine sodium reference material chromatogram.	Standard requirement for pharmaceutical products.
By UV	No specification	The spectrum of the sample is concordant with that of the levothyroxine sodium reference material.	

Levothyroxine sodium content (% label claim)	90.0 - 110.0	90.0 - 105.0	Standard requirement for pharmaceutical products. The upper limit for assay (levothyroxine) is tighter for the new formulation than the old formulation.
Drug-related impurities content (%) **Liothyronine sodium** **Tetrac*** **HDPhDB acid**** **Any unspecified impurity** **Total**	 ≤ 2.0 No specification No specification No specification No specification	 ≤ 1.0 ≤ 1.0 ≤ 2.5 ≤ 1.0 ≤ 5.0	The specification for impurities is significantly improved for the new formulation compared to that for the old formulation. GSK developed an improved test method capable of detecting impurities that the old method was unable to detect. The new method is used to test the new formulation. The limit for liothyronine sodium is tighter for the new formulation and the content of tetrac, HDPhDB acid, unspecified impurities and total impurities is controlled. Testing of the old formulation using the new test method indicates that the old formulation also contained tetrac, HDPhDB acid and unspecified impurities. The acceptance criteria for impurities were found to be acceptable based on: ICH Guideline, Impurities In New Drug Products, Q3B(R), (refer to www.ich.org/LOB/media/MEDIA421.pdf for the current version of this guideline), and the impurity content of the old formulation of Eltroxin tablets and Eltroxin tablets marketed in Europe.
Loss on drying at 105°C (%w/w)	No specification	3.0 - 6.5	Surrogate test for water content (permitted by ICH guideline Q6A).
Hardness	2.5 to 5.0 Kp	No specification	Hardness is not included in the specification for the new formulation as hardness testing is performed as an in-process control during manufacture. This is acceptable and is supported by ICH guideline Q6A.
Friability (performed only when hardness fails)	≤ 1.0 %	No specification	Tablet friability is not included in the specification for the new formulation as friability testing is performed as an in-process control during manufacture. This is acceptable and is supported by ICH guideline Q6A.
Dissolution (% levothyroxine sodium released)	55 % dissolution at 80 minutes	70 % dissolution in 45 minutes	Standard pharmacopoeial requirement for tablets.
Microbial limits test:			Standard pharmacopoeial requirement for tablets. The acceptance criteria applied for the new

			formulation are those specified in the European Pharmacopoeia.
Total viable aerobic count (cfu/mL)			
Bacteria	No specification	Not more than 10^3	
Fungi	No specification	Not more than 10^2	
E. coli	No specification	Absent from 1 g	
Packaging components	To be inspected	No specification	It is not currently a standard requirement to include this type of specification in the shelf-life specifications as packaging materials are controlled during the manufacturing process.

* tetraiodothyroacetic acid

**4-[(4-hydroxy-3,5-diiodophenyl)oxy]-3,5-diiodobenzoic acid

Annex 2: European Certificate of Suitability for Levothyroxine Sodium supplied by Sandoz GmbH

Note: the current certificate version is R1-CEP 1998-141- Rev04 however the supplemental tests listed below are unchanged.

edqm

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

European Directorate for the Quality of Medicines
Certification Unit

Certificate No. R1-CEP 1998-141-Rev 02

Name of the substance:
LEVOTHYROXINE SODIUM
Code 460 187 - Code 460 132

Name of holder:
SANDOZ GMBH
Biochemiestrasse 10
A - 6250 Kundl, Tyrol

Site of production:
SANDOZ GMBH
Schaftenau Plant
Biochemiestrasse 10
A - 6336 Langkampfen, Tyrol

THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE
R1-CEP 1998-141-REV 01

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site of production mentioned above, A - 6336 Langkampfen, Tyrol, we certify that the quality of the substance is suitably controlled by the current version of the monograph LEVOTHYROXINE SODIUM no. 0401 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

— Test for iodide	[redacted]	(Annex 1)
— Test for related substances by liquid chromatography		(Annex 2)
O-(4-hydroxy-3,5-diiodophenyl)-thyroxine	[redacted]	
O-(methyl-tetraiodothyroethylamine)		
Monochlorotriiodothyronine sodium		
Triiodothyroacetic acid		
Tetraiodothyroacetic acid		
Any other detectable impurity*	not more than 0.10%	
Total impurities (except liothyronine sodium)*	not more than 1.0%	

* and other than those mentioned in the monograph

Postal Address: 226 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - E-mail: certification@pheur.org

— Test for residual solvents by gas chromatography (Annex 3)
Ethanol [redacted]

— Test for particle size distribution by microscopy (Annex 4)
Material code 460 187:
Mean particle size x (50.3) [redacted]
90% Particle size between [redacted]
Material code 460 132:
Mean particle size x (50.3) [redacted]
90% (upper limit) Particle size between [redacted]

The submitted dossier must be updated every five years or after any significant modification of the manufacturing method that may alter the quality, safety or efficacy of the product or require changing the specifications of the monograph.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (93) 5 as amended] for a period of five years starting from 12 April 2004. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has 51 lines and four annexes, the first of 1 page, the second of 7 pages, the third of 4 pages and the fourth of 2 pages.

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 19 August 2005

Annex 3: Literature Reference 1

FDA Guidance for Industry 2000: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

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 (CDER)

December 2000
Clinical Medical

Guidance for Industry

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573

Internet at http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2000
Clinical Medical

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GUIDANCE FOR INDUSTRY[1]

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) for levothyroxine sodium tablets who wish to conduct in vivo pharmacokinetic and bioavailability studies and in vitro dissolution testing for their products. Information from these studies would generally be submitted in section 6 of an NDA. Sponsors who wish to use approaches other than those recommended in this guidance should discuss their plans with the FDA prior to preparing an NDA.

II. BACKGROUND

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine. Thyroid hormones affect protein, lipid, and carbohydrate metabolism, growth, and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart.

The production of levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secretes thyroid stimulating hormone-releasing hormone (TSH-RH), which stimulates the anterior pituitary to produce thyroid stimulating-hormone (TSH). TSH then stimulates the thyroid gland to produce levothyroxine

[1] This guidance has been prepared by the Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics, which operates under the direction of the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). The guidance has also been reviewed by the Guidances Technical Committee of the Biopharmaceutics Coordinating Committee, as well as the Division of Metabolic and Endocrine Drug Products in CDER.

(T_4) and triiodothyronine (T_3). T_4 is subsequently converted to the highly active T_3 in the peripheral tissues. High levels of T_4 inhibit the production of TSH and (to a lesser degree) TSH-RH. This effect in turn decreases the further production of T_4 (Farwell 1996).

Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function such as cretinism, myxedema, nontoxic goiter, or hypothyroidism. The diminished or absent thyroid function may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine sodium may also be used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

Levothyroxine sodium is a compound with a narrow therapeutic range. If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on another product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestation of hyperthyroidism such as cardiac pain, palpitation, or cardiac arrhythmia. In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous. Hyperthyroidism is a known risk factor for osteoporosis (Paul et al. 1988). To minimize the risk of osteoporosis, it is advisable that levothyroxine sodium be titrated to the lowest effective dose. Because of the risks associated with over- or under-treatment with levothyroxine sodium, it is critical that patients have available to them products that are consistent in potency and bioavailability.

It is a challenge to determine the bioavailability of levothyroxine sodium products because levothyroxine is naturally present in minute quantities in the blood, with the total levels reaching 5.0-12.0 μg/dl and free (or unbound) levels reaching 0.8-2.7 ng/dl in a healthy adult. To assess the bioavailability of levothyroxine sodium after a single dose, several times the normal dose should be given to raise the levels of the drug significantly above baseline to allow measurement. Furthermore, levothyroxine has a long half-life of 6 to 9 days, and therefore, a long washout period is necessary between treatments.

III. PHARMACOKINETIC AND BIOAVAILABILITY STUDIES IN VIVO

Information on the pharmacokinetics (absorption, distribution, metabolism, and excretion) of levothyroxine sodium can be obtained from the literature and/or from original studies. If the studies cited have used levothyroxine sodium formulations other than the formulation intended for marketing, the submission should contain information identifying how those formulations differ from the to-be-marketed formulation.

For sponsors who have a product on the market, we recommend that in vivo bioavailability studies be conducted using the formulation(s) already on the market, assuming that the sponsor intends to keep marketing the formulation(s). The tablets used in the study should be made from a full-scale production batch and should meet all compendial requirements. The formulations used should demonstrate sufficient stability for the length of the study. Stability evaluations should be made for the bio-batch prior

to and after the study. All dissolution, potency, and content uniformity data should be submitted to the NDA for review.

For sponsors who do not have a levothyroxine sodium formulation on the market, the usual approaches to developing pilot-scale batches for bioavailability studies apply.[2]

A. Inclusion Criteria

For each pharmacokinetic and bioavailability study outlined below, at least 24 volunteers should complete the trial. The subjects should be healthy volunteers, 18 to 50 years of age and within 15 percent of ideal body weight for their height and build. Sponsors should attempt to enroll an equal number of men and women, if possible. Volunteers recruited for the study should have an acceptable medical history, physical examination, and clinical laboratory tests. All thyroid function tests should be within normal limits. Volunteers with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to levothyroxine sodium should be excluded. Female volunteers should be given a pregnancy test prior to beginning the study. Pregnant women should be excluded from the study. Written informed consent should be obtained from all volunteers before they are accepted into the study.

B. Single-Dose Bioavailability Study

Objective: To determine the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference (oral solution) under fasting conditions.

Design: The study is a single-dose, two-treatment, two-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strength and Dose: A multiple of the highest tablet strength to achieve a total dose of 600 μg should be given to detect T_4 above baseline levels.

Procedure: Following a 10-hour overnight fast, volunteers should be administered a single dose of levothyroxine sodium orally with 240-mL water. The treatments should be as follows:

Treatment 1: Multiples of the highest strength of levothyroxine sodium tablets to be marketed.

Treatment 2: Levothyroxine sodium as an oral solution at an equivalent dose with treatment 1. The intravenous formulation can be used as a convenient source of an oral levothyroxine solution.

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[2] See *Q1A Stability Testing of New Drug Substances and Products* (59 FR 48754, September 1994).

Volunteers should remain fasted for 4 hours after dosing, with water only allowed after the first hour. Volunteers should be served standardized meals according to the schedule throughout the study.

Blood Sampling: Blood samples should be drawn at -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, and 48 hours post dose.

Data Analysis: Individual and mean plasma/serum concentration-time profiles of total (bound + free) T_4 and T_3 should be included in the report. The plasma/serum profiles and pharmacokinetic measures should be presented without the adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study. The following pharmacokinetic measures should be computed:

- Area under the plasma/serum concentration-time curve from time 0 to the last measurable time point (AUC_{0-t})
- Peak concentration (C_{max})
- Time to peak concentration (T_{max})

Analysis of variance (ANOVA) should be performed for both log-transformed AUC_{0-t} and C_{max} using the SAS General Linear Models (GLM) procedure. The oral solution should be used as the reference formulation. The geometric means and 90 percent confidence intervals of the geometric mean ratio (test/reference) in AUC_{0-t} and C_{max} should be presented as evidence of bioavailability.

C. Dosage-Form Proportionality Study

Objective: To determine the dosage-form proportionality among the to-be-marketed tablet strengths of levothyroxine sodium.[3]

Design: The recommended study is a single-dose, three-treatment, six-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strengths and Dose: Three strengths of tablets should be studied that represent the low, middle, and high strength of the formulations to be marketed. Generally, the middle strength studied is the 100-µg tablet. A multiple of each tablet strength should be given to detect T_4 above baseline levels. The total dose given for each treatment in the study will usually be 600 µg and should be the same dose for each treatment.

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[3] Available strengths of levothyroxine sodium tablets from many manufacturers include 25, 50, 75, 88, 100, 112, 125, 137, 150, 200 and 300 µg.

Procedure: Following a 10-hour overnight fast, volunteers should be given a single dose of levothyroxine sodium orally with 240-mL water. The treatments consisting of equal doses of levothyroxine should be as follows:

Treatment 1: Multiples of the representative low strength tablets (usually 50 μg).

Treatment 2: Multiples of the representative mid-strength tablets. This is normally the 100-μg tablet, and should be considered as the reference for this study.

Treatment 3: Multiples of the representative high strength tablets (usually 300 μg).

Volunteers should fast for an additional 4 hours after dosing, with only water allowed after the first hour. Volunteers should be served standardized meals throughout the study according to the schedule.

Blood Sampling: The blood sampling schedule for this study should be identical to that recommended for the bioavailability study.

Data Analysis: Individual and mean plasma/serum concentration-time profiles of total (bound + free) T_4 and T_3 should be included in the report. The plasma/serum profiles and pharmacokinetic measures should be presented without adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study.

The pharmacokinetic measures, including AUC_{0-t}, C_{max} and T_{max}, should be computed for both total T_4 and T_3. For the assessment of proportionality between strengths, both log-transformed AUC_{0-t} and C_{max} should be analyzed with ANOVA using the SAS GLM procedure. The geometric means and 90 percent confidence intervals of the geometric mean ratio of AUC_{0-t} and C_{max} should be presented for each pairwise comparison. Dosage-form proportionality is demonstrated if the 90 percent confidence intervals fall within the 80-125 percent range.

For both single-dose bioavailability and dosage-form proportionality studies, the assessment of bioavailability should be based on the measurement of total (bound + free) T_4 and total T_3 levels. The determination of free T_4 and T_3 is not necessary. However, if sufficiently precise and accurate assays are available for free T_4 and T_3, these moieties can be measured as well. Statistical analyses of free T_4 and T_3 should then be performed, with the results used as supportive data. If free T_4 and T_3 are measured, the assays used should be based on the immuno-extraction (two-step) method, rather than the labeled analog (one-step) method. Levels of TSH should be measured as part of the volunteer-screening process as well as post-study examination. These TSH data should be reported in the NDA.

IV. DISSOLUTION TESTING IN VITRO

Dissolution studies can be performed using an appropriate method developed by a sponsor[4] or the current USP method. For each tablet strength to be marketed, multi-point dissolution studies should be performed on three production-sized batches using 12 tablets per batch. The time points used should be 10, 20, 30, 45, 60, 80, 100, and 120 minutes, or until 80 percent of the labeled claim is dissolved, so that a complete profile may be obtained. Dissolution testing should include lots used in the bioavailability studies.

V. FORMULATION

The composition of the formulation for each tablet strength of levothyroxine sodium to be marketed should be provided in the NDA.

VI. BIOWAIVER

For tablet strengths not studied in the dosage-form proportionality study (see section III. C), the sponsor should request biowaivers and provide appropriate formulation information as well as in vitro dissolution data as covered under 21 CFR 320.22(d)(2). Specifically, all of the following conditions should be met:

1. The dosage-form proportionality study among the to-be-marketed tablet strengths of levothyroxine sodium (low, medium, and high strengths) has been found acceptable, and proportionality has been shown among the strengths included in the study (also see section III. C. *Data Analysis).*

2. For tablet strengths to be covered under the waiver request, they should differ only in the amount of levothyroxine sodium and filler needed to maintain the tablet weights.

3. Multi-point dissolution profiles are similar across tablet strengths using an f2 test. If both test and reference products dissolve 85 percent or more of the label amount of the drug in • 15 minutes, the f2 test is not necessary.[4] The dissolution method as well as dissolution data have been found acceptable by the Agency.

Sponsors whose products do not meet the above conditions should contact the Division of Pharmaceutical Evaluation II for further guidance.

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[4] See FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997).

VII. ASSAY VALIDATION

Assays used for both in vivo and in vitro studies should be fully validated, reproducible, precise, accurate, specific, stable, and linear. If commercial kits are used, they should be validated in-house at the analytical site where the assay for the study is performed. Please note that the validation data from the kit manufacturer alone is insufficient.

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Annex 4: Literature Reference 2

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Annex 6: Literature Reference 4

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